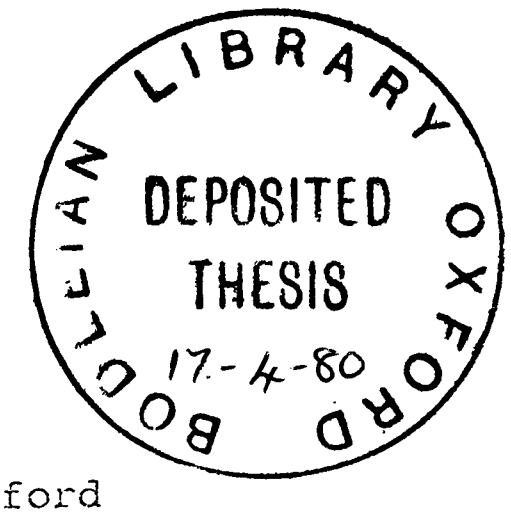
SYNTHESIS AND SOLUTION

CHEMISTRY OF FUNCTIONAL SURFACTANTS

by

Colin George Griggs, B.Sc. (C.N.A.A.)

Thesis presented for the degree of Doctor of Philosophy



University of Oxford Michaelmas Term 1979

DECLARATION

I declare that this thesis is of my own composition, that the work of which it is a record has been carried out by myself, unless otherwise acknowledged, and has not been submitted in any previous application for a higher degree, in this or any other university.

The thesis describes the results of research carried out in the Dyson Perrins Laboratory, University of Oxford and the Research Department of Procter and Gamble, Longbenton, Newcastle between October 1975 and September 1978.

ACKNOWLEDGEMENTS

I am pleased to express my thanks to my supervisor Dr. John M. Brown, whose practical expertise, ideas and encouragement were given so freely during my research studies at Oxford.

Thanks are due to various members of the Dyson Perrins Laboratory; to G. Procter and Dr. R. Aplin for mass spectra; to Mrs. A. Rivers for infra-red spectra; to Dr. F. Strauss and staff for microanalysis. Special thanks are expressed to Mrs. E. McGuiness, Lady E. Richards and Miss T. Jackson for the patient recording of many excellent n.m.r. spectra.

I would like to express thanks to many colleagues in Oxford, whether Part II, postgraduate, postdoctoral or sabbatical, for helpful discussions. In particular I wish to thank D. Parker, B. Murrer, J. Darwent, R. Elliott, Drs. M.C. Grossel, J. Lynn, H. Molinari and P.A. Chaloner for helpful discussions, criticism and often sympathy whilst indulging in alcoholic pursuits. Special thanks go to I. Field for his help and advice in simulating n.m.r. spectra and proving to me that perhaps the computer is a wonderful machine after all.

I am grateful to Miss Paula Nielsen for her skill and patience in typing the thesis. I wish to

particularly thank my wife Janet for her encouragement and patience during the early months of our marriage whilst completing this thesis.

I am grateful to the S.R.C. for provision of a C.A.S.E. award in collaboration with the Procter and Gamble Research Department, Longbenton, Newcastle.

Dedicated to my parents,

George and Doreen Griggs

ABSTRACT

Title:- "Synthesis and solution chemistry of functional surfactants"

Candidate:- Colin George Griggs, B.Sc. (C.N.A.A.)

College:- The Queen's College

Degree:- Doctor of Philosophy

Term of submission:- Michaelmas Term 1979

A number of synthetic approaches to preparing a metal-binding surfactant, containing the α-dioxime moiety, are described. Both linear and convergent synthetic methods have been unsuccessful in the preparation of a target surfactant. While the preparation of such a target molecule was not realised, some simple long chain α-dioximes have however been prepared in the course of investigating various synthetic methods. Microemulsion phenomena of these simple α-dioximes in aqueous surfactant micelles have been investigated by ultrasonic techniques, with the kinetics associated with such a process being determined. The kinetics of such α-dioximes in a co-micellar environment with nickel ions has been investigated under various conditions e.g. pH, surfactant concentration, and are reported.

In order to prepare chiral functionalised long-chain surfactants of known configuration via "directed resolution" of diasteromeric amides obtained from racemic lactones, the alkylation of lactone enolates has been investigated. Only the enolate of γ-butyrolactone has been satisfactorily alkylated with long-chain electrophiles. Numerous attempts to alkylate the enolate of ε-caprolactone have been uniformly unsuccessful. Through optimisation of conditions a viable synthesis to α-alkylated derivatives of γ-butyrolactone has been found. "Directed resolution" of diastereomeric amides, prepared from the racemic γ-butyrolactone derivatives, have resulted in the isolation of optically pure lactones.

Investigation of potential protecting groups for the α-diketone moiety in a functional surfactant

/...

synthesis resulted in the preparation of a 9,10-dimethyl substituted 1,4,5,8-tetraoxadecalin in a model study. Analysis of the AA' BB' multiplet couplings provided unambiguous evidence that the structure of this bicyclic molecule has the cis-configuration. Activation parameters for the ring inversion process between enantiomeric forms were obtained by line shape analysis of the variable temperature ^{1}H- and ^{13}C-n.m.r. spectra.

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INTRODUCTION

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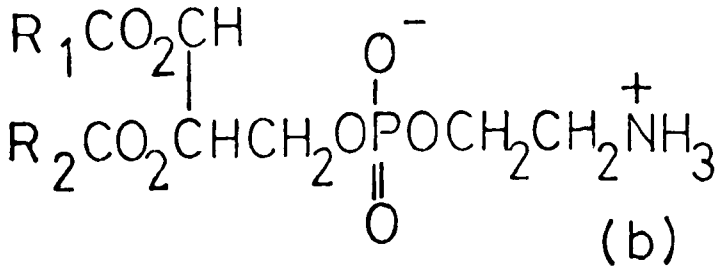
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1.1 Surfactants and associated species

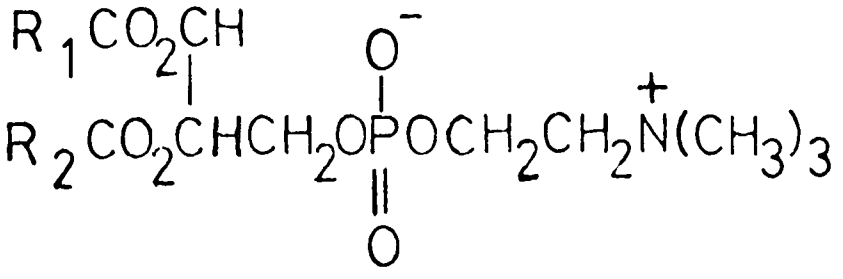
Surfactants, whether natural or synthetic, contain one or more ionic or polar hydrophilic groups and an apolar hydrophobic organic residue, usually an n-alkyl group, and can interact with both water and non-polar organic substrates[1] e.g. benzene, hexane, cyclohexane. In 1936, G. S. Hartley introduced the term "amphipathy" to describe the unusual properties exhibited by aqueous solutions of surfactant molecules.[2] This amphipathic property is the simultaneous presence in the same molecule of both sympathy and antipathy for water.

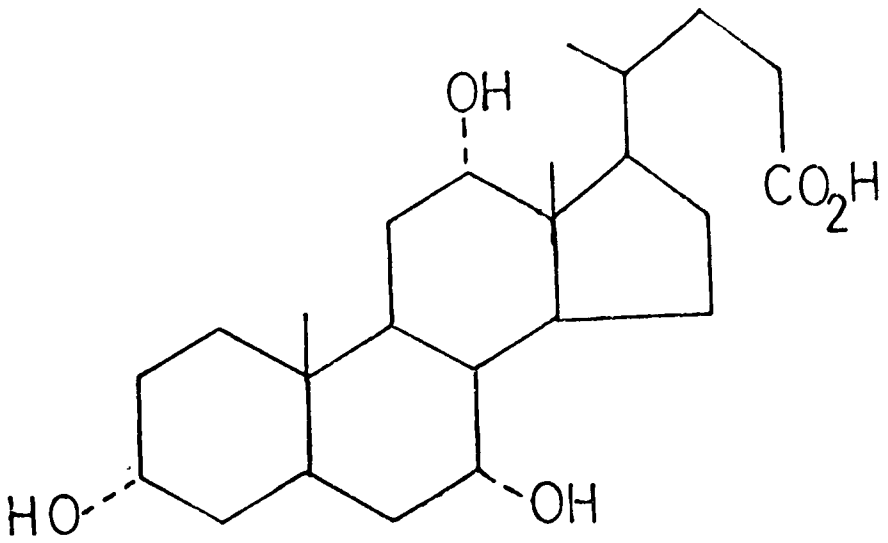
Naturally occurring amphiphiles include simple lipids e.g. carboxylic acid esters, complex lipids e.g. fatty acid esters containing phosphorus, nitrogen bases, and/or sugars, and bile acids e.g. cholic and deoxycholic acids. Many of these amphiphiles play important roles in transport and membrane phenomena *in vivo* since a great many biological processes occur on or involve amphipathic surfaces. Examples of some naturally occurring surfactants are shown in Figure 1(a)-(e)

(a) α-phosphatidyl ethanolamine

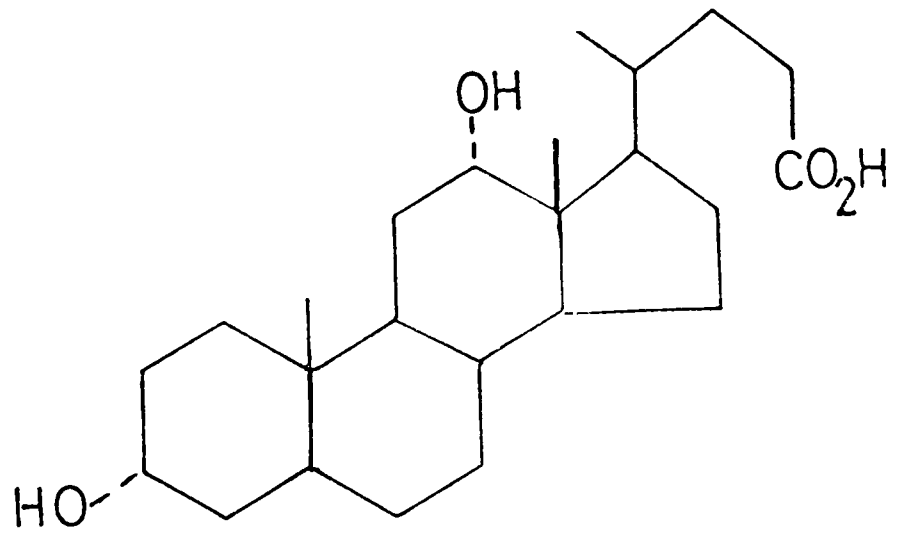


(b) α-phosphatidyl choline

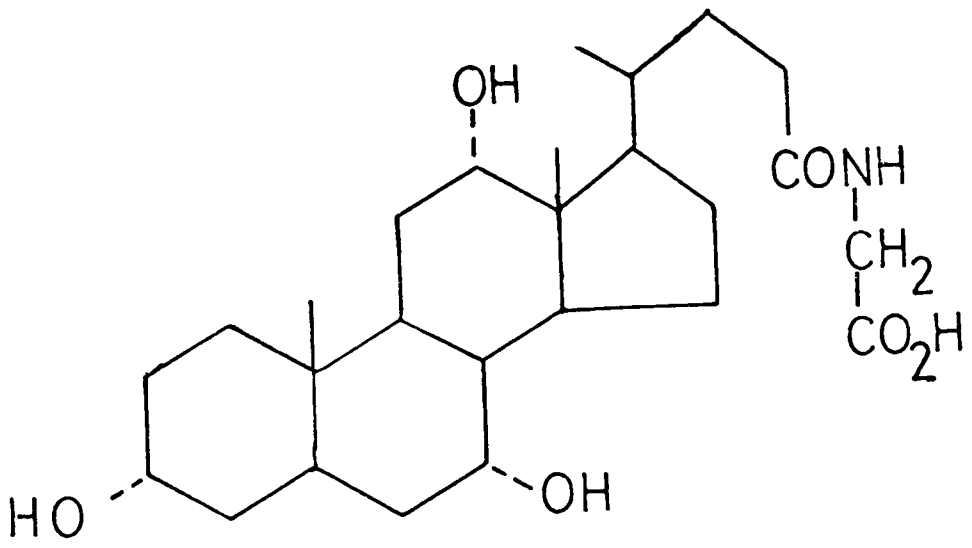




(c) Cholic acid



(d) Deoxycholic acid



(e) Glycocholic acid

Figure 1. Examples of naturally occurring surfactants (R_1 and R_2 are hydrocarbon chains of more than twelve carbon atoms)

Surfactant	Structure
<u>Cationic</u>	
Decylammonium bromide	$CH_3(CH_2)_9\overset{+}{N}H_3Br^-$
Hexadecyltrimethyl-ammonium bromide (CTAB)	$CH_3(CH_2)_{15}\overset{+}{N}(CH_3)_3Br^-$
Hexadecylpyridinium iodide	$CH_3(CH_2)_{15}\overset{+}{N}C_5H_5I^-$
<u>Anionic</u>	
Sodium dodecyl sulphate (SDS)	$CH_3(CH_2)_{11}SO_4^-Na^+$
Potassium dodecanoate	$CH_3(CH_2)_{10}CO_2^-K^+$
<u>Zwitterionic</u>	
3-(Dimethyldodecyl-ammonium)-propane-1-sulphate	$CH_3(CH_2)_{11}\overset{+}{N}(CH_3)_2(CH_2)_3SO_3^-$
<u>N</u>,<u>N</u>,N-Dodecyldimethyl-glycine	$CH_3(CH_2)_{11}\overset{+}{N}(CH_3)_2CH_2CO_2^-$
<u>Non-ionic</u>	
Polyoxyethylene(3)-dodecanol	$CH_3(CH_2)_9O(CH_2CH_2O)_3H$
<u>N</u>,<u>N</u>-Dimethyldodecyl amine oxide	$CH_3(CH_2)_{11}\overset{\downarrow O}{N}(CH_3)_2$

Table 1. <u>Examples of synthetic surfactants</u>

Synthetic surfactants, used extensively in industry e.g. for cleaning and solubilisation of materials, are often composed of a straight chain of carbon atoms, usually 8-18 in number, attached to a polar group, which may be cationic, anionic, zwitterionic or non-ionic in nature.[3-6] Typical examples of synthetic surfactants are shown in Table 1. As can be seen great structural variation is possible within this general class of molecules, since both the length of the hydrophobic hydrocarbon chain and the nature of the hydrophilic head group, as well as its position along the carbon backbone, may be varied.

1.2 Surfactants in water

In aqueous solutions, surfactants form aggregates or surface layers to minimise the interaction of hydrophobic functionalities with water. This phenomenon has come to be known as "hydrophobic bonding".[7,8] When a polar molecule is transferred from an apolar solvent e.g. hexane, to water the transfer is accompanied by a decrease in entropy of hydration (e.g. for methane = $-77\ Jmol^{-1}K^{-1}$). This observation led to the suggestion that inert solutes promote structuring of the neighbouring water molecules i.e. the "iceberg effect".[9,10] Consequently hydrophobic bonding, or the association of apolar molecules, as shown in Figure 2, could be regarded as a partial reversal of the thermodynamically unfavourable process of solution.[7]

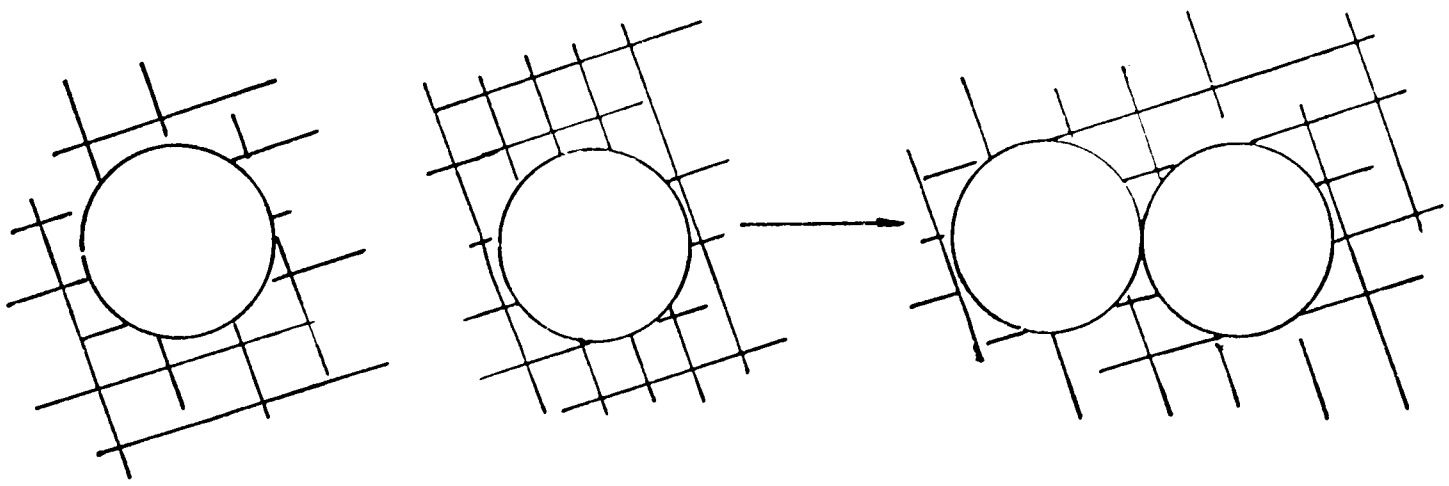
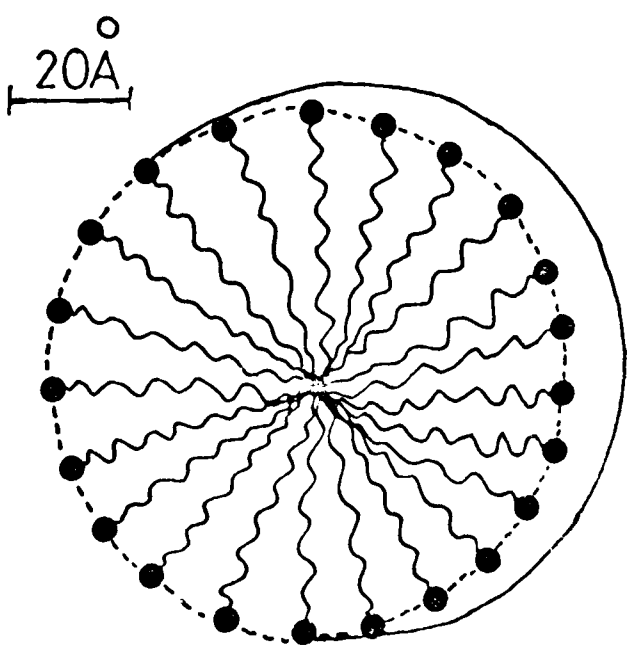


Figure 2. Association of apolar molecules in water by the hydrophobic effect

Such reasoning has been extended to the association of more complex molecules in which one of the requirements is the presence of substantial apolar residues in an aqueous environment. Thus the reversible aggregation of molecules or ions with long apolar chains or aromatic groups, as present in surfactants, lipids, glycerides and dyestuffs, is believed to depend mainly on the phenomenon of hydrophobic association. In such a way complex aggregates e.g. micelles, bimolecular layers and lamellar structures, can exist as shown in Figure 3, depending on the nature of the aggregating species.[11,12]



Spherical micelle
m.w. ≃ 2×10^4

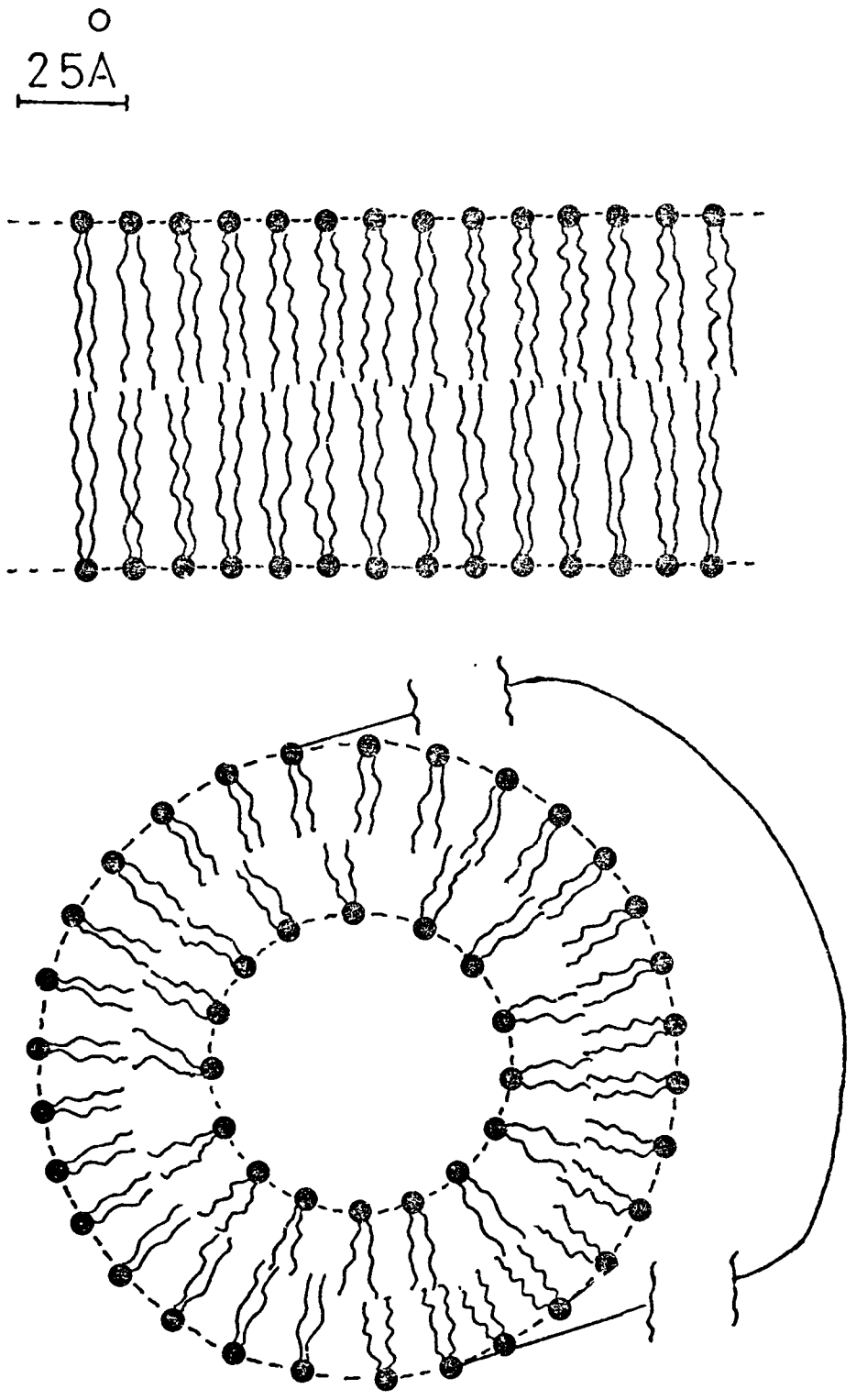


Figure 3. Examples of surfactant aggregation in water

With increasing concentration, surfactants may associate to give aggregates of varying structure as follows:

(a) they absorb at an air-water or oil-water interface so that the apolar functionalities populate the air or oil phase, whilst the polar groups are retained in the aqueous environment

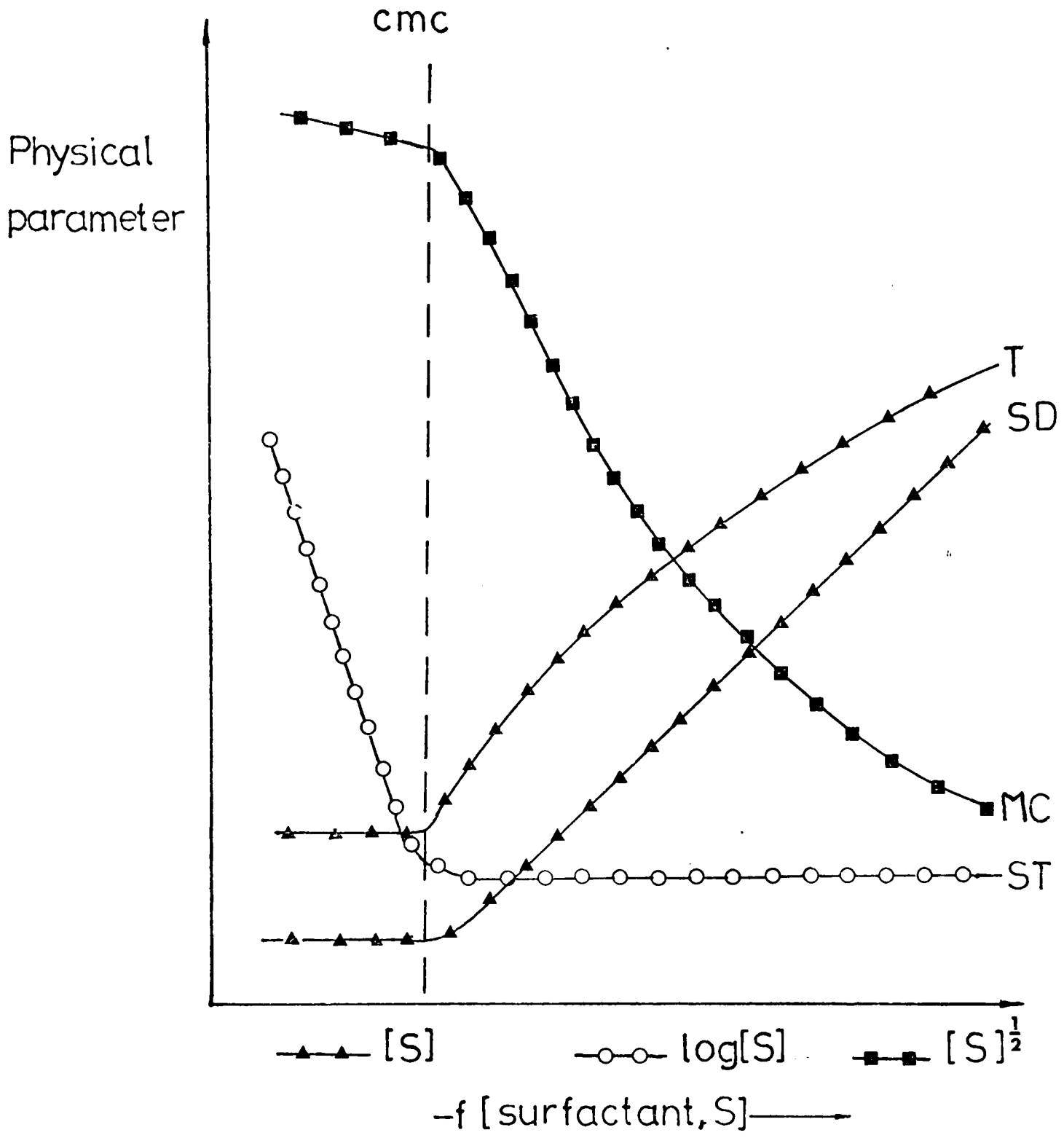


Figure 4. Some typical variations in physical properties of an ionic surfactant in aqueous solution[11] (T=turbidity, SD=solubilisation of a water insoluble dye, MC= molar conductivity, ST= surface tension)

(b) in dilute solution, micelles are formed which are almost spherical and contain about 100 monomers

(c) in more concentrated solution large aggregates are formed, and phase changes may occur, the extreme case being formation of lyotropic liquid crystals or a viscous isotropic phase.

Consequently the segregation of hydrophilic and hydrophobic groupings in a surfactant micelle leads to the formation of interfaces between essentially apolar regions and water.

1.3 Experimental Aspects of Micelle Formation

1.3.1 Critical micelle concentration

Association of monomeric surfactants in water to form high molecular weight aggregates, known as micelles, is observed within a fairly narrow concentration range in dilute solutions.[13] Thus as the concentration of surfactant in an aqueous solution is increased many of the physical and chemical properties of the solution change abruptly, but continuously, over a narrow concentration range referred to as the critical micelle concentration (cmc). Some affected properties, as shown in Figure 4 for an ionic surfactant, can include conductivity, viscosity, surface tension and turbidity. This change in colligative properties is attributed to the formation of micelles with the concentration at which micelles become significant

being referred to as the cmc. Below the cmc the monomer concentration in solution is approximately equal to the total concentration of surfactant, whilst above the cmc the concentration of micelles increases linearly with surfactant concentration so that the monomer concentration remains approximately constant. Thus the cmc can be regarded as the maximum concentration of monomer surfactant, as shown schematically in Figure 5, assuming n is large in $nM \rightleftharpoons^{K} M^n$.

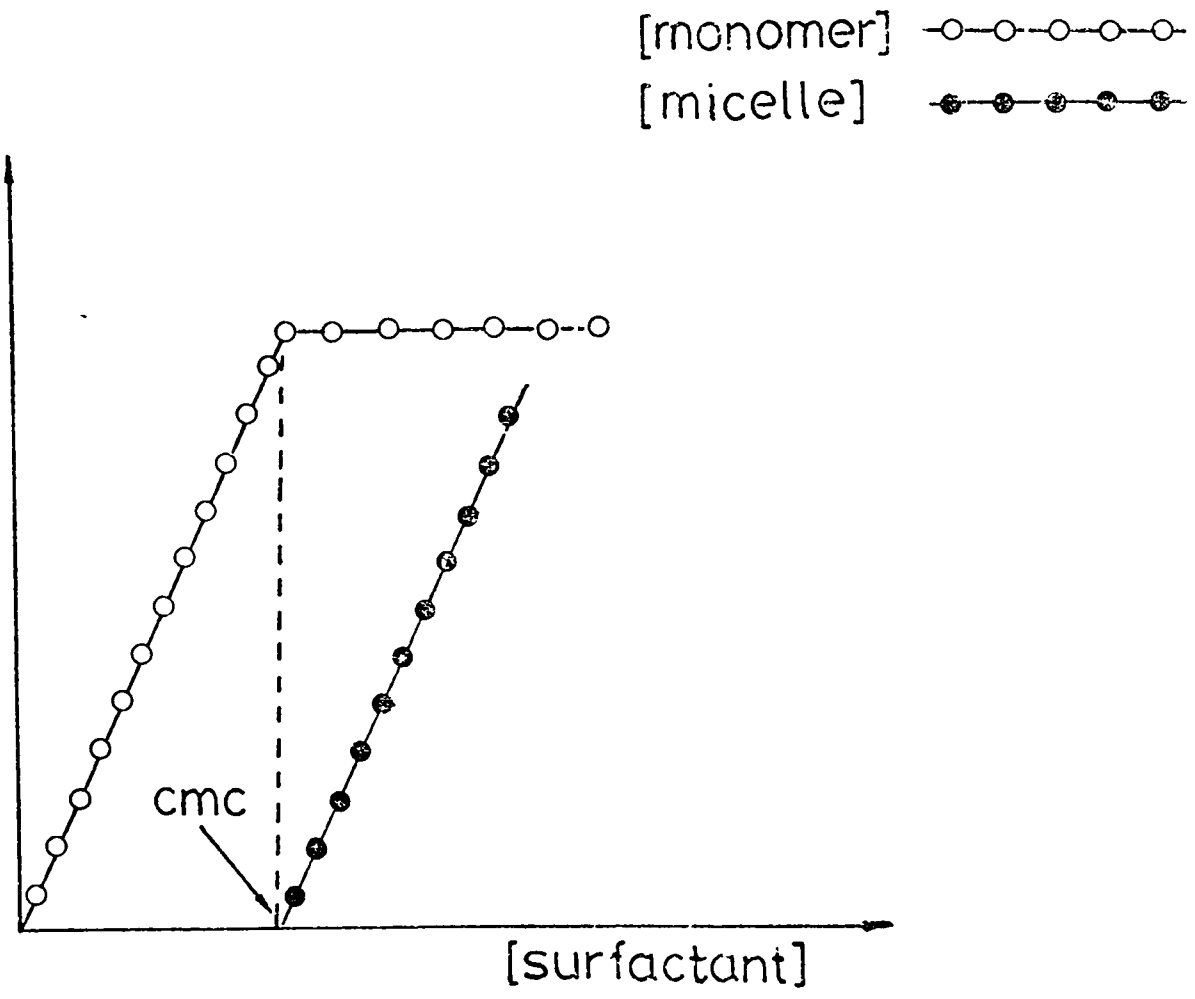


Figure 5. Possible variation of monomer concentration for an aqueous surfactant solution

Recent theoretical considerations of micelle formation[14,15] and e.s.r. experiments[16,17] suggest

that the interpretation of the cmc as the concentration at which aggregates first form is an oversimplification; Ruckenstein and Nagarajan[14,15] prefer to define a critical concentration. Below this concentration the size distribution for aggregates, S_n, is monotonic and decreasing, whereas above the cmc large aggregates becomes significant. These predictions are shown in Figure 6, and perhaps present a better insight into aggregation close to the cmc.

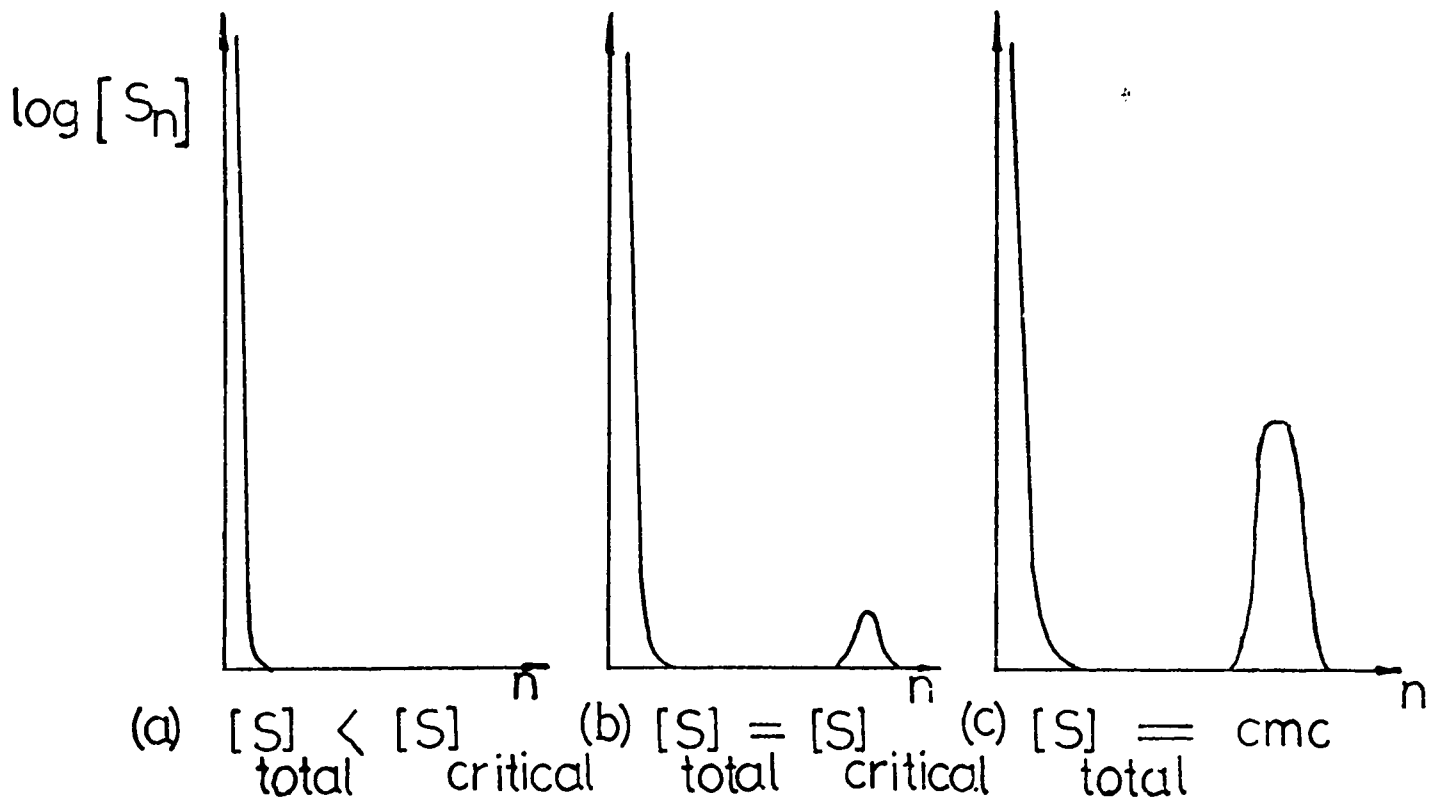


Figure 6. Variation in aggregation as a function of surfactant concentration, [S].

A variety of methods have been used for the determination of the cmc and these have been critically reviewed.[18] In a typical cmc determination some physical property of the solution is plotted as a function of

solute concentration. An apparent discontinuity results at the cmc, although curvature of the plot in the vicinity of the cmc nearly always occurs, as shown for the variation of surface tension in Figure 7.

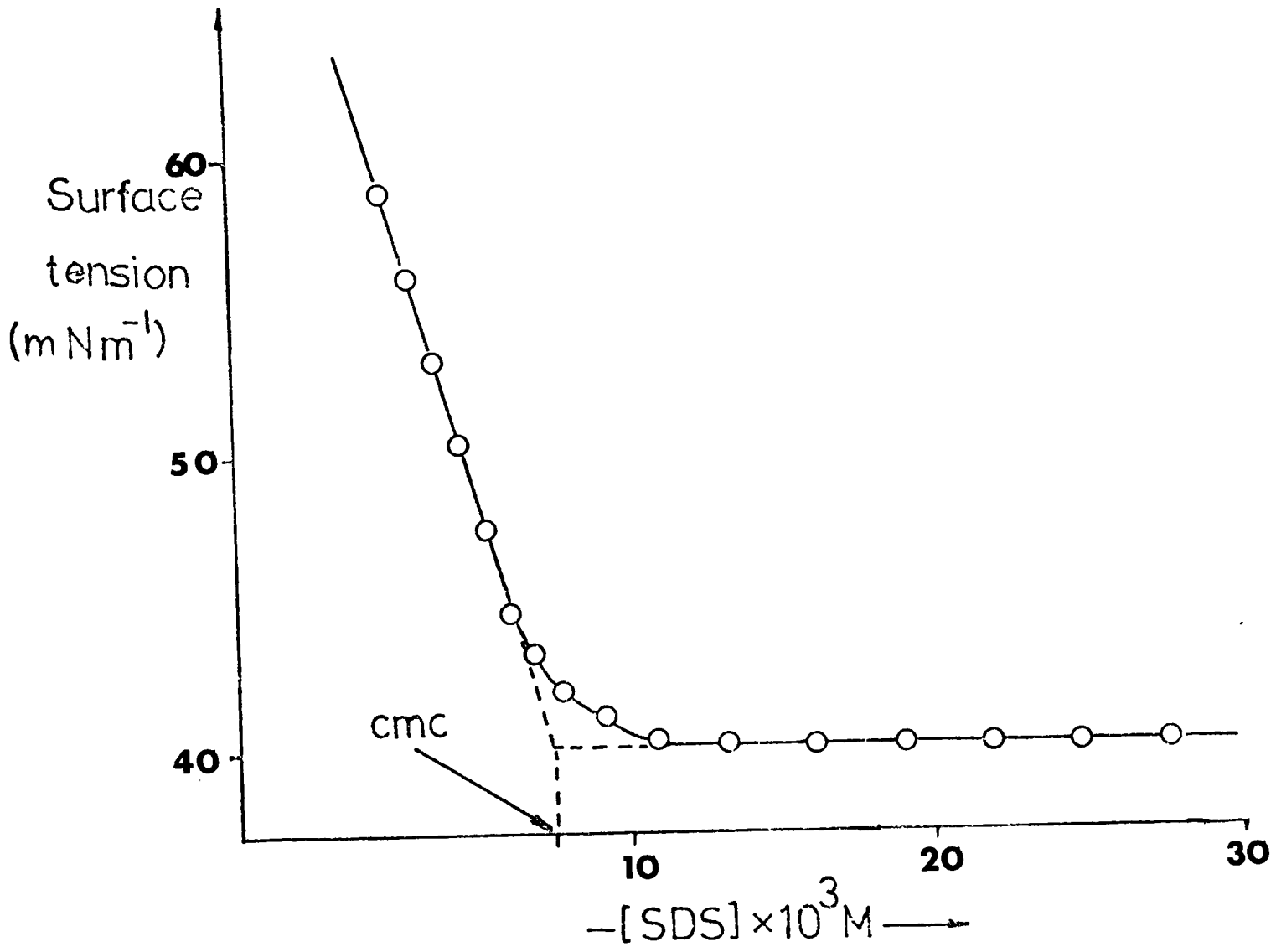


Figure 7. Variation of surface tension with surfactant concentration for sodium dodecyl sulphate (SDS) at 30°C

This slight curvature reflects the fact that the cmc is not a precise concentration per se, but an average of a narrow range of surfactant concentrations in which micelles form. Since the choice of the cmc value is never

Surfactant	cmc/M	Temperature/^{o}C
$\underline{n}$-$C_{10}H_{21}SO_4^-Na^+$	3.3×10^{-2}	30
$\underline{n}$-$C_{12}H_{25}SO_4^-Na^+$	8.4×10^{-3}	30
$(\underline{n}$-$C_{12}H_{25}SO_4^-)_2Mg^{2+}$	1.2×10^{-3}	30
$\underline{n}$-$C_{12}H_{25}SO_4^-NH_4^+$	7.2×10^{-3}	30
$\underline{n}$-$C_{12}H_{25}SO_4^-NMe_4^+$	5.0×10^{-3}	30
$(\underline{n}$-$C_{12}H_{25}SO_4^-)_2Co^{2+}$	1.2×10^{-3}	30
$\underline{n}$-$C_{14}H_{29}SO_4^-Na^+$	2.1×10^{-3}	30
$\underline{n}$-$C_{10}H_{21}\overset{+}{N}Me_3Cl^-$	6.5×10^{-2}	25
$\underline{n}$-$C_{12}H_{25}\overset{+}{N}Me_3F^-$	6.4×10^{-3}	30
$\underline{n}$-$C_{12}H_{25}\overset{+}{N}Me_3Cl^-$	2.3×10^{-2}	30
$\underline{n}$-$C_{12}H_{25}\overset{+}{N}Me_3Br^-$	1.5×10^{-2}	30
$\underline{n}$-$C_{12}H_{25}\overset{+}{N}Me_3BrO_3^-$	3.3×10^{-3}	30
$\underline{n}$-$C_{12}H_{25}\overset{+}{N}Me_3NO_3^-$	8.0×10^{-4}	30
$\underline{n}$-$C_{12}H_{25}\overset{+}{N}Me_3HCO_2^-$	6.0×10^{-3}	30
$\underline{n}$-$C_{16}H_{33}\overset{+}{N}Me_3Cl^-$	1.3×10^{-3}	30
$\underline{n}$-$C_{18}H_{37}\overset{+}{N}Me_3Cl^-$	4.0×10^{-3}	30
$\underline{n}$-$C_8H_{17}(OCH_2CH_2)_6OH$	9.9×10^{-3}	25
$\underline{n}$-$C_{10}H_{21}(OCH_2CH_2)_6OH$	9.0×10^{-4}	25
$\underline{n}$-$C_{12}H_{25}(OCH_2CH_2)_6OH$	8.7×10^{-5}	25
$\underline{n}$-$C_{14}H_{29}\overset{+}{N}Me_2O^-$	3.0×10^{-4}	25

Table 2. Critical micelle concentrations of selected surfactants in water[14]

unambiguous the value obtained depends both on the nature of the data and the manner in which they are plotted.[18] Since micelles are normally polydisperse, methods yielding a weight average e.g. light scattering, give higher cmc values than methods giving a number average e.g. dye solubilisation.[3] Some representative value of cmc's for a variety of simple surfactants are given in Table 2.

Comparison of the cmc's quoted demonstrates a number of important empirical correlations between different classes of surfactants:-

(a) non-ionic and zwitterionic surfactants have lower cmc's than comparable ionic species

(b) increasing the number of methylene groups in the alkyl chain lowers the cmc by a factor of $\simeq$ 2-3 per methylene group

(c) the effect of the counter-ion in ionic surfactant cmc's is dependent on its charge, size and hydration form.

In the above points the size and chemical nature of the non-polar side chain has the most important bearing on the cmc. It has been known for some time[19] that the variation of the cmc with chain length for a given homologous series can be represented by equation (1)

$$\log (\text{cmc}) = a - bn \qquad \text{equation (1)}$$

Surfactant	Temp./°C	a	b
Sodium carboxylates	20	2.41	0.341
Potassium carboxylates	25	1.92	0.290
Alkyl sulphonates	40	1.59	0.294
Alkyl sulphates	45	1.42	0.295
Alkylammonium chlorides	25	1.25	0.265
Alkyl glycoside	25	2.65	0.531
Alkyldimethylphosphine oxide	30	2.31	0.466
Alkyldimethylamine oxide	27	3.300	0.500

Table 3. Values of "a" and "b", defined in equation (1), for various surfactants[13]

where "a" and "b" are constants for a particular experimental condition and "n" is the number of carbon atoms in the n-alkyl side chain. Representative values of "a" and "b" are given in Table 3 for typical surfactants.[13]

The cmc can be affected by many variables besides the chain length, the most important of which are temperature[13,20,21] and pressure.[22-29] Surfactants can show a shallow minimum in the cmc as a function of temperature; in the case of an ionic surfactant this can be explained by opposing temperature dependencies of the head groups and the hydrophobic hydrocarbon chain interactions.[13] For non-ionics no satisfactory rationalisation exists and a minimum only occurs when a large head group is present[21] and at higher temperatures than exhibited by ionic surfactants. Pressure affects the cmc since micelle formation is accompanied by a volume change.[22,23] Compression of micelle solutions by an externally applied pressure inhibits micelle formation as a result of the greater volume of surfactants in the micellar state compared to the unassociated state. In the main, conductivity has been employed to monitor high pressure studies,[24-28] although recently absorption spectroscopy has been used.[29] The origin of this effect has been the object of considerable speculation and suggestions include solidification of the micellar interior,[25] compressibility of micelles and monomers,[26] and structuring of surrounding

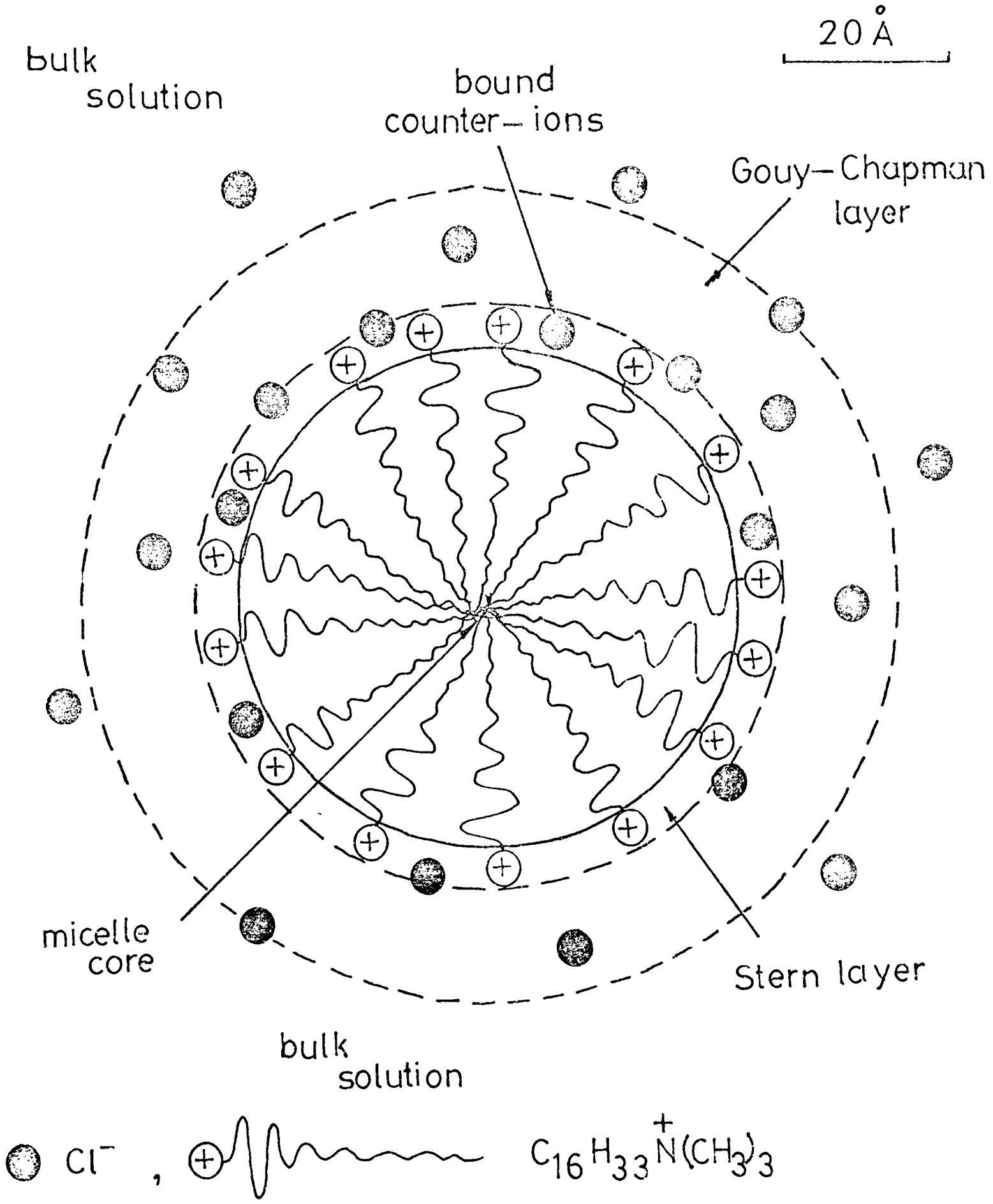


Figure 8. A two-dimensional schematic representation of an idealised spherical model of an ionic micelle

water molecules.[27,28]

Since water structuring promotes hydrophobic association and therefore micellisation, the addition of polar species e.g. low molecular alcohols and ketones, urea or guanidinium salts[18,30,31] disrupts such structuring and increases the cmc. Addition of hydrophobic solutes alter the cmc by virtue of their incorporation into the micelle, consequently affecting its size and structure.

1.3.2 Micellar size, shape and character

It has been previously assumed that micelles of synthetic surfactants close to their cmc in aqueous solution are spherical and monodisperse;[3,4] neither assumption is strictly accurate. Such assumptions do provide a good working model for the interpretation of much experimental data, although it is now accepted that micelles are often polydisperse and non-spherical.[32] The average number of monomer units in a micelle, the aggregation number, can range from 10 to 100 in the case of ionic surfactants[5] to greater than a 1000 for non-ionic surfactants.[6] For an ionic surfactant theoretical treatments based on the concept of a spherical micelle give an accurate approximation of the cmc within an order of magnitude. A two-dimensional representation for such a structure is shown in Figure 8 in the case of a long chain quaternary ammonium chloride. The hydrophobic part of the aggregate forms the core of the micelle, with the polar head

groups being located at the micelle-water interface in contact with and hydrated by a number of water molecules.

Many physical techniques have been used to probe the different environments within a micelle,[3,12,32] particularly with respect to the hydrophobic core and the Stern layer. The details of micellar structure depend upon the probe utilised however. Since micelles and monomers are rapidly equilibrating (see Section 1.3.4) there is a mixture of monomeric surfactants and micelles of various sizes and degrees of charge neutralisation by counter ions. Thus thermochemical and electrochemical measurements give a long, time-averaged picture, whereas n.m.r. spectroscopy gives a short, time-average ($t_{\frac{1}{2}} \simeq 10^{-2}$s) and electronic spectroscopy gives a picture on the time scale of molecular movement.

1.3.2.1 The Stern layer and counter-ion association

As shown in Figure 8, the charged head groups and the corresponding counter-ions of the micelle are located in a compact region, known as the Stern layer, which extends from the core's edge to within a few angstroms of the shear surface of the micelle. The compactness of the Stern layer is responsible for most of the reduction of net charge on the micelle, since 60-70% of the polar head groups are neutralised by incorporation of counter-ions. The binding of these counter-ions parallels their ion-pairing ability[34] and are contained in a 2-10Å layer.

Further counter-ions are weakly bound in the diffuse Gouy-Chapman layer, which may extend up to 100Å from the micelle surface.

The fraction of ions bound to the Stern layer can be expressed by equation (2) for an ionic micelle

$$mS^- + pX^+ \rightleftharpoons S_mX_p^{(m-p)-} \qquad \text{equation (2)}$$

where S^- is an anionic surfactant monomer, X^+ is an associated counterion, S_mX_p is the micelle subsequently formed and m>p. The quantity (m-p) corresponds to the residual charge on the micelle, since only a fraction, $p/_m$, is neutralised.

A number of techniques e.g. e.m.f.,[34] diffusion electrophoresis,[35] demonstrate that the counter-ions are tightly bound in the Stern layer and can migrate with the micelle under electrophoretic conditions. Nuclear and electron magnetic resonance[36-39] studies have yielded three main conclusions:-

(a) bound counter-ions are hydrated to much the same extent as their free counterparts,

(b) the mobility of bound counter-ions is restricted, but not dramatically so,

(c) specific interactions with the head group e.g. hydrogen bonding of water in the hydration shell of carboxylates, may be important.

1.3.2.2 The micellar interior

The micellar interior has been generally considered to have the properties of a liquid hydrocarbon into which the water does not penetrate.[3] Further investigations suggest that water is present, although its penetration does not extend beyond the third carbon in the hydrophobic chain.[40,41] However more recent data makes the situation ambiguous.[13,42] Results from fluorine magnetic resonance, using ω-fluorinated surfactants, by Muller et al.[43] and Henriksson[44] had been initially explained by a successively decreasing water exposure of the fluorine atoms with increasing distance from the polar functionality. Such a proposal, pointing towards water being present in the micelle, has been challenged by Cordes[45] who suggested that since the fluorinated hydrocarbon possesses a large dipole moment, water may be inadvertently drawn into the micellar core. Alternatively the fluorinated group may spend some time on the micellar surface,[45,46] as shown in Figure 9.

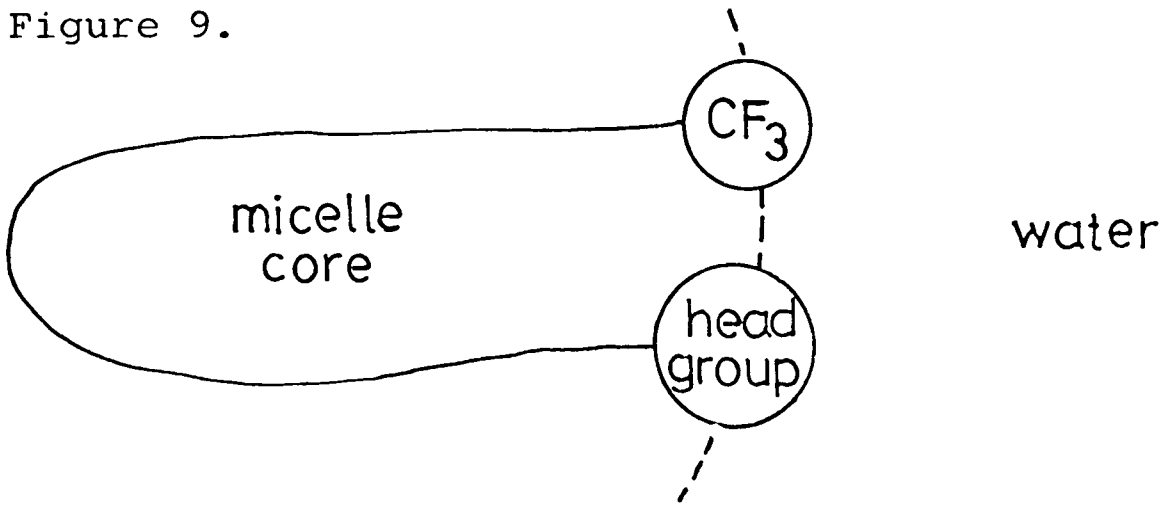


Figure 9. Possible interaction of a fluorinated surfactant with the bulk medium[46]

The techniques of photoluminescence[47,48] and fluorescence quenching[49], and magnetic resonance[50,51] have indicated that the viscosity of the micellar interior is higher than that of hydrocarbons. The core has been found to be similar to an ethanol-glycerol environment in terms of viscosity.[47-51]

1.3.2.3 Aggregation numbers.

An important parameter to consider is the aggregation number, N, i.e. the number of monomers in a micelle at a given concentration. Since the molecular weight of micelles is high (>15,000) the determination of N becomes a problem of colloid physical chemistry. Methods of estimating N can give different results depending whether a weight-average (N_W) or number-average (N_A) is calculated.[18,53] Such discrepancies indicate that in some micellar systems polydispersity exists,[54] with the ratio of the two averages being an indication of the range of the size distribution. The size distribution is narrow for small micelles, broadening with increasing aggregation number.[18]

Techniques used to determine aggregation numbers include light scattering,[55-59] sedimentation equilibria,[60-62] membrane osmometry,[63,64] magnetic resonance,[43] gel filtration,[65-67] dye solubilisation,[59,68] potentiometric titrations,[69] luminescence quenching[70] and hydrodynamics;[56] these references are illustrative rather than exhaustive. Aggregation numbers are

Surfactant	N	Temp./°C	Ref.
$\underline{n}$-$C_{12}H_{25}\overset{+}{N}C_5H_5I^-$	87	25	5
$\underline{n}$-$C_{12}H_{25}\overset{+}{N}H_3Cl^-$	387	35	73
$\underline{n}$-$C_{16}H_{33}\overset{+}{N}Me_3Br^-$	61	30	5
$\underline{n}$-$C_{12}H_{25}SO_3^-Na^+$	68	45	
$\underline{n}$-$C_{12}H_{25}SO_4^-Na^+$	57	30	74
$\underline{n}$-$C_{12}H_{25}(OCH_2CH_2)_9OH$	400	30	
$\underline{n}$-$C_{16}H_{33}(OCH_2CH_2)_9OH$	150	25	

Table 4. Examples of aggregation numbers (N) for selected surfactants

dependent on the concentration of surfactant, the presence of inorganic and organic additives and the temperature. Increasing the concentration of the surfactant well above the cmc usually results in a change of aggregation number by virtue of a change in micellar size and shape.

Aggregation numbers for non-ionic surfactants are often very high[6] (>250), since head group interactions are minimal compared to ionic surfactants. Furthermore packing of the monomer in non-ionic micelles is more efficient, due to the lack of charge-charge repulsions. The aggregation number was larger when bromide rather than chloride was the counter-ion. The largest micelles occurred with the smaller head groups ($R\overset{+}{N}H_3$ versus $R\overset{+}{N}Me_3$).[71,72] Such results can be interpreted by assuming that the more tightly bound the counter-ion, the larger the aggregation number; unfortunately there is no simple relationship between head group structure and aggregation number.[13] Representative examples of aggregation numbers are given in Table 4.

1.3.2.4 Micelle shape

Recent calculations, based on linking geometric, thermodynamic and interaction free energies, by Tanford,[75] Israelachvili,[76] Jacobus[77] and Dennis[78] show that a range of micellar shapes are possible i.e. spherical ($N \simeq 50$) through ellipsoidsto hemispherical capped cylinders ($N \simeq 200$). These calculations also show that micelles

can change shape in order to incorporate further surfactant monomer as the total surfactant concentration increases. Close to the cmc, however, where the aggregation number is low, the model of a spherical micelle is still useful.

For example, aqueous cetyltrimethylammonium bromide (CTAB) solutions have been examined in the 0.036-26% concentration range by Ekwall *et al.* using viscosity and light scattering techniques.[79] The constancy of the intensity of scattered light for 2-9% CTAB solutions suggest that the structure of the micelle changes little in this region. This is best described as a strongly hydrated spherical micelle. Above 9% the rapid increase in viscosity has been ascribed to the formation of rod-shaped micelles, whose length increases with surfactant concentration. At 26% CTAB, a mesomorphous soap forms in which the rod-shaped micelles are packed in hexagonal arrays.

1.3.3 The thermodynamics of micelle formation

A number of approaches have been used to relate the cmc with the free energy change on micellisation.[32] Phase separation and mass-action approaches appear to provide the most realistic description of micelle formation.

In its simplest form the aggregation process for an ionic micelle, may be given by the equilibrium shown in equation (2) i.e.

$$mS^- + pX^+ \rightleftharpoons S_mX_p^{(m-p)-} \qquad \text{equation (2).}$$

Neglecting activity coefficients the micelle equilibrium

constant, K_m, is given by equation (3)

$$K_m = \frac{\left[S_m X_p^{(m-p)-}\right]}{\left[S^-\right]^m \left[X^+\right]^p} \qquad \text{equation (3)}$$

From equation (3) some fundamental thermodynamic functions can be obtained. The standard free energy of micelle formation, ΔG_m, for one mole of monomer is given by equation (4)

$$\Delta G_m = YRT\ln(cmc) \qquad \text{equation (4)}$$

where Y is a constant dependent on the concentration of bound counter-ions, R is the gas constant and T is the absolute temperature.

From equation (4) the standard free enthalpy, ΔH_m, and entropy, ΔS_m, are given by

$$\Delta H_m = -YRT^2 \frac{d}{dT}[\ln(cmc)] \qquad \text{equation (5)}$$

$$T\Delta S_m = -YRT^2 \frac{d}{dT}[\ln(cmc)] - YRT\ln(cmc) \qquad \text{equation (6)}$$

The derivation of these equations using a combination of the phase-separation and mass-action calculations makes a number of assumptions:-

(a) micelles are of a uniform size i.e. monodisperse

(b) interaction between micelles at the cmc is negligible

(c) for ionic micelles counter-ions can be regarded either as "bound" or "unbound", with no intermediate states

(d) the micelle does not contain solvent or ions other than counter-ions and surfactant ions

(e) the cmc is a sharp phenomenon

(f) constant monomer activity above the cmc.

As has been stated in previous sections not all of these assumptions are experimentally justifiable and whilst a very simple picture of micelle formation is presented, a framework is obtained which is useful for the interpretation of experimental data.

The simple nature of equations (4), (5) and (6) has encouraged many studies on the thermodynamics of micellisation by following the changes in the cmc.[80] For example in a study of sodium dodecyl sulphate[81] at 20°C ΔG_m was found to be $-38.6 kJmol^{-1}$, $\Delta H_m = 1.7 kJmol^{-1}$ and $T\Delta S_m$ was $40.3 kJmol^{-1}$, demonstrating that micellisation is due to favourable entropy changes. Neither the mass-action nor phase-separation approach (or combination of both) is rigorously correct e.g. for low aggregation numbers the mass-action model predicts less sharp and higher cmc values than the phase-separation model. Some of the inherent disadvantages in these methods have been overcome by application of small system thermodynamics.[82] The

distinguishing feature of this method is that normally intensive variables e.g. mean energy, depend on the size of the system, making possible the calculation of thermodynamic quantities for a single micelle rather than an ensemble of micelles. Using small systems thermodynamics for micelles, assuming ideality, Hall[83] has achieved some success in derivations of various thermodynamic quantities for both ionic and non-ionic micelles. Unfortunately data are not available to test all predictions as yet; such comparisons should provide a good test for this method.

A complete understanding of the energy changes leading to micellisation requires a quantitative description of "hydrophobic association". Such a treatment is obviously not available, due to its inherent complexity, and so a semi-empirical model has been developed by Tartar,[84] Tanford[7,75] and Stigter.[85] In this treatment the energy changes resulting from the interaction of the alkyl chains and electrostatic repulsion of the polar head groups are balanced to determine the most favourable micelle size when the surface area per surfactant molecule is at a maximum. These models have achieved some success in being able to predict micellar shapes, aggregation numbers and cmc's.[75-77]

1.3.4 Kinetics of micelle formation

Micelles are not static species but exist in a dynamic equilibrium whereby micelles form and dissociate very rapidly. Indeed the kinetics have been measured for surfactants by a number of techniques e.g. stopped flow,[86,87] temperature jump,[73,88-90] pressure jump,[90-93] ultrasonic relaxation,[94-96] n.m.r.[97,98] and e.s.r.[99,100] It is well known that in a surfactant there exist two relaxation processes associated with the micelle-monomer equilibrium. The fast process, $t_{\frac{1}{2}} \ll 10^{-5}$S, designated by relaxation time T_1, has been observed by ultrasonic absorption, whilst the slower process, $t_{\frac{1}{2}} = 10^{-2} - 10^{-5}$S, designated T_2 has been observed by pressure or temperature jump techniques. There has been considerable controversy as to the interpretation of these results and the origin of these two relaxation times. The following interpretation is now generally accepted:[101-103] the fast process is attributed to the perturbation of the exchange equilibrium of monomer between the bulk and micellar phases and the slow one to the net disintegration of the micelle to monomers and vice-versa.

So far several models have been proposed to relate the data obtained on these two processes to the rate constants for micelle association. The merits of these models has been summarised by Nakagawa.[84] In particular, the model originally proposed by Aniansson[105]

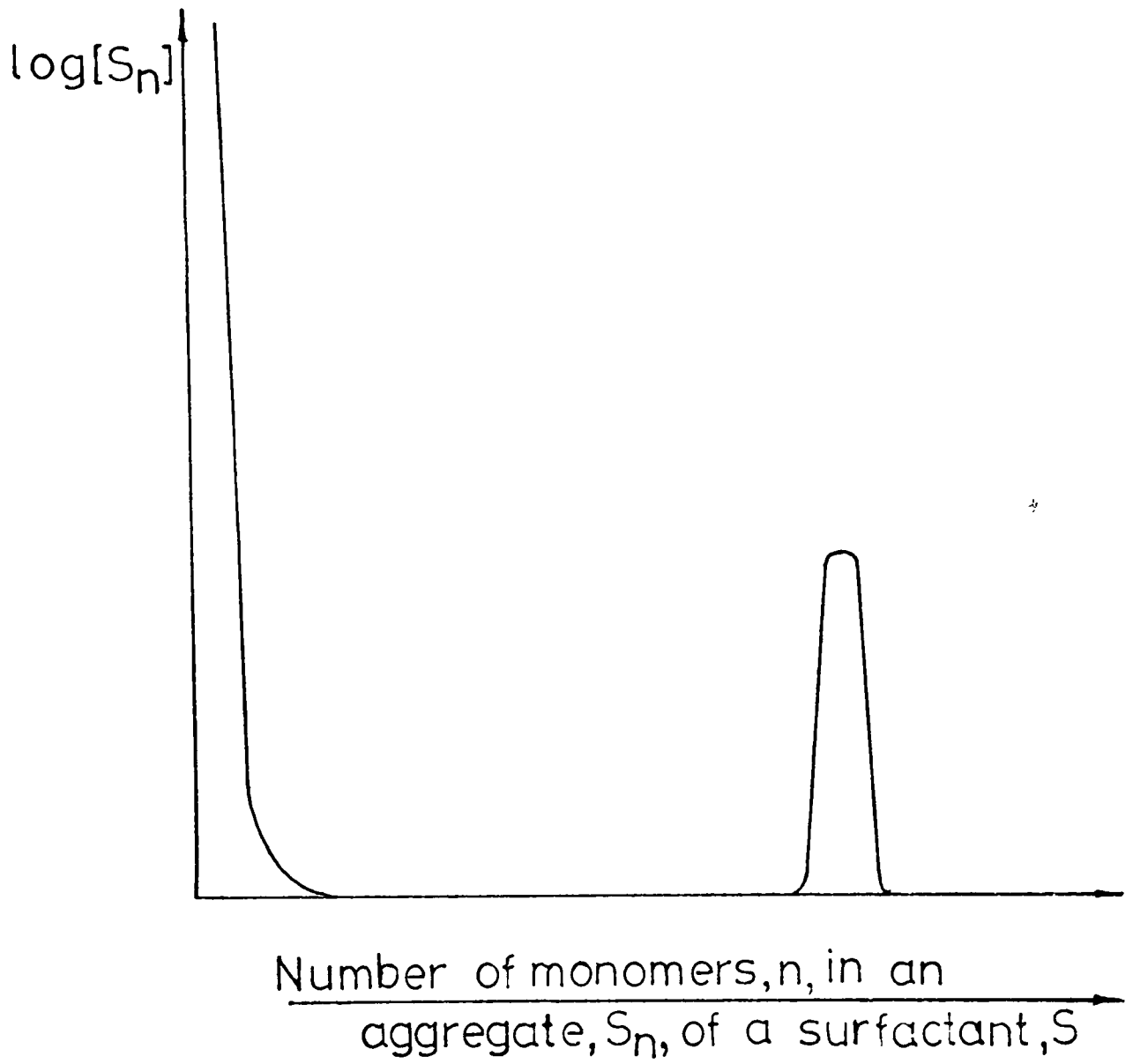


Figure 10. Distribution of aggregates to form a micelle by the method of Aniansson[105,106]

has been successfully used to correlate experimental data with theoretical calculations.[106]

In this approach micelle formation is viewed as a series of equilibria for a surfactant S,

$$S_1 + S_1 \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} S_2 \qquad \text{equation (7)}$$

$$S_1 + S_2 \underset{k_3^-}{\overset{k_3^+}{\rightleftharpoons}} S_3 \qquad \text{equation (8)}$$

$$S_1 + S_3 \underset{k_4^-}{\overset{k_4^+}{\rightleftharpoons}} S_4 \qquad \text{equation (9)}$$

$$S_1 + S_{(n-1)} \underset{k_n^-}{\overset{k_n^+}{\rightleftharpoons}} S_n \qquad \text{equation (10)}$$

where S_n is an aggregate of n monomers. A complete solution to the rate equations given above is very difficult, but a close approximation has been achieved by Aniansson using mathematics previously employed in heat diffusion. The micellisation process is viewed as a system of two large metal blocks connected by a thin wire, one block corresponding to surfactant monomers and oligomers up to S_4, the other to micelles of the most probable size. The thin wire connecting the two blocks represents the progression of n monomers from S_4 to $S_{(n-4)}$ aggregates where the concentration of such aggregates is low.

Above the cmc the distribution of aggregates is thought to be as shown in Figure 10.

For n monomers to form a micelle the aggregate, S_n, must grow stepwise by monomer addition, passing through aggregates present in extremely low concentrations. Since collisions between premicellar aggregates are very rare due to their almost negligible concentration, steps such as in equation (11)

$$S_1 + S_7 \underset{k_8^-}{\overset{k_8^+}{\rightleftharpoons}} S_8 \qquad \text{equation (11)}$$

occur at a slow rate ($t_{\frac{1}{2}} \simeq 10^{-2}$s). The low concentration of S_7 aggregates, rather than any prohibitive activation energies associated with such processes, thus determines the rate of micelle formation. A similar argument applies in the breakdown of micelles into n monomers, for processes such as

$$2S_1 + S_{(n-1)} \underset{k_n^-}{\overset{k_n^+}{\rightleftharpoons}} S_n + S_1 \underset{k_{n+1}^-}{\overset{k_{n+1}^+}{\rightleftharpoons}} S_{(n+1)} \qquad \text{equation (12)}$$

occur very rapidly, giving rise to the very fast exchange times observed, T_1, observed by transient techniques e.g. e.s.r., ultrasonic absorption.

Whilst the development of this model requires the use of semi-empirical relationships for hydrophobic bonding, the agreement between experimental and theoretical data is very good. This approach gives the rate constants for monomer association with a micelle i.e. k_n^+ and k_n^- in equation (12) e.g. for sodium hexadecyl sulphate at 30°C, $k_n^+ = 1.3 \times 10^8 M^{-1}S^{-1}$ and $k_n^- = 6 \times 10^4 S^{-1}$, showing that k_n^+ is close to the diffusion limit. Also from this approach it has also been possible to predict

cmc's, aggregation numbers and degrees of polydispersity in micelles.[106]

It can be seen that micelles break up and reform steadily with monomers and/or solubilised substrates readily entering or leaving the micelle rather than being a static species.

1.3.5 Solubilisation sites in micelles

The most useful property of micelles is their ability to "solubilise" organic substrates i.e. to dissolve hydrophobic material, leading to the formation of a thermodynamically stable, isotropic solution. Obviously the solubilisation site plays an important role in any solubilisation process particularly in catalysis or inhibition of chemical reaction, since the location of an absorbed substrate in, or on, the micelle determines its reactivity. There are a number of ways in which an organic substrate might associate with a micelle:-

(a) entirely in the micelle interior

(b) occupying the interior whilst a polar moiety is exposed on the micelle surface

(c) in the Stern layer

(d) on the micelle surface.

The modes of such substrate-micelle association have been investigated by a number of techniques e.g. u.v. spectroscopy, X-ray diffraction, e.s.r., n.m.r., and have been reviewed by Fendler and Fendler.[107] Unfortunately different

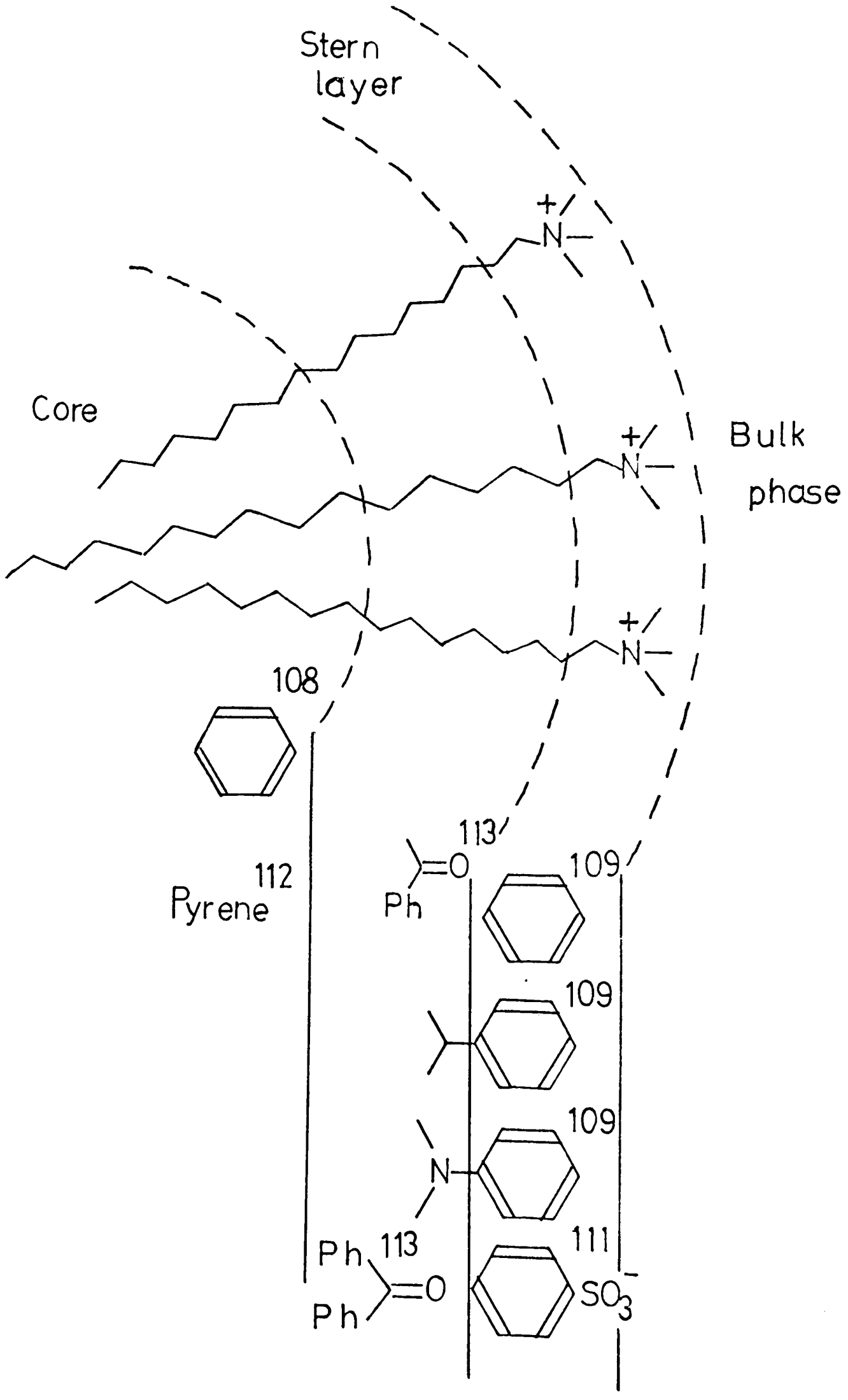
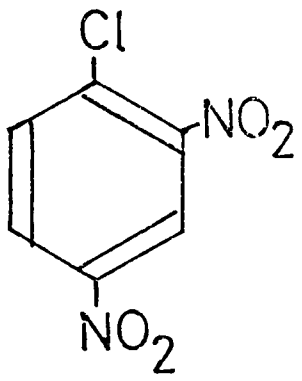
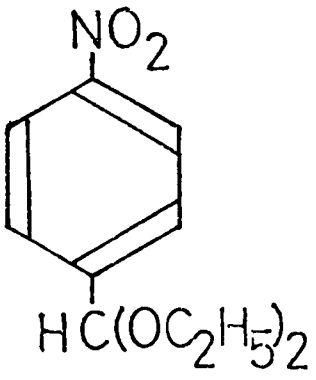
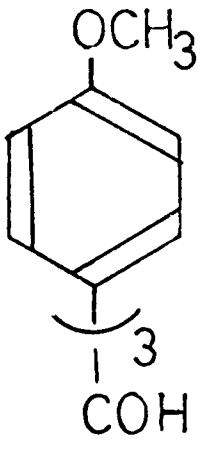


Figure 11. Solubilisation sites of various solutes in cetyltrimethylammonium bromide (CTAB) micelles[108-113]

experimental methods do not always lead to the same conclusions e.g. u.v. spectroscopy suggests that benzene in CTAB is present in the hydrophobic interior [108] whereas n.m.r. suggests that it is close to the tertiary ammonium head groups.[109]

Results obtained to date on solubilisation sites in micelles agree with intuitive predictions, although it must be emphasised that a number of parameters e.g. surfactant chain length, polarity and nature of head groups, presence of additives and temperature influence such solubilisation. Hydrophobic solutes e.g. ethylbenzene, naphthalene, pyrene, are held in the micellar core whereas hydrophilic solutes e.g. benzoic acid, benzophenone, bind in the boundary between the micellar interior and Stern layer. Amphipathic molecules e.g. unsaturated long chain fatty acids, are oriented with polar head groups close to the micelle surface and their hydrophobic tails towards the micellar interior. There is evidence that a number of aromatic compounds interact strongly with tetra-alkylammonium head groups e.g. the enthalpy of transfer for aromatic acids in CTAB are anomalously high compared to nonaromatic acids[110]. The increase in the dissociation constants for aromatic acids in CTAB are larger than those found for analogous aliphatic acids.[111] A general pattern for solubilisation of various molecules in CTAB is given in Figure 11 with data from a number of sources.[108-113]

Substrate	Reagent	Surfactant			Ref.
		Cationic	Anionic	Nonionic	
CH_3CO_2PNP	OH^-	Very slight catalysis	Very slight inhibition	No effect	114,115
$C_8H_{17}CO_2PNP$	OH^-	Catalysis	Inhibition	No effect	115
	OH^-	Catalysis	Inhibition	No effect	116
	H^+	Inhibition	Catalysis	-	117,118
	H^+	Inhibition	Catalysis	Inhibition	119

PNP = p-NO_2-C_6H_4-

Table 5. Micellar catalysis and inhibition of in some bimolecular reactions

1.4 Micellar catalysis in aqueous solutions

1.4.1 General features of micellar catalysis

Rate acceleration (or inhibition) of organic or inorganic reactions in aqueous micellar solution arises from the different rates of reaction for the substrate concerned in the micellar phase and in bulk solution, and the distribution of the substrate between these two phases. Basically the rate effects observed can be attributed to inherent changes in the hydrophobic and electrostatic environments on the substrate and in some cases to alterations in the structure of the surrounding water. Using simple electrostatic considerations, such as those set forth by Hartley[1] many years ago, it can be predicted that cationic micelles enhance reaction rates for nucleophilic anions with uncharged substrates while anionic micelles retard such reactions, but catalyse reactions involving cations. Experimental results qualitatively bear out such expectations and some typical examples are given in Table 5. Uncharged or zwitterionic micelles have little or no effect on reaction rates other than by altering the reaction medium.

Micellar catalysis tends to be more pronounced for surfactants having longer alkyl chains i.e. those which are more hydrophobic. A typical example is catalysis of the hydrolysis of methyl orthobenzoate by sodium alkyl sulphates.[120] The catalytic efficiency of different

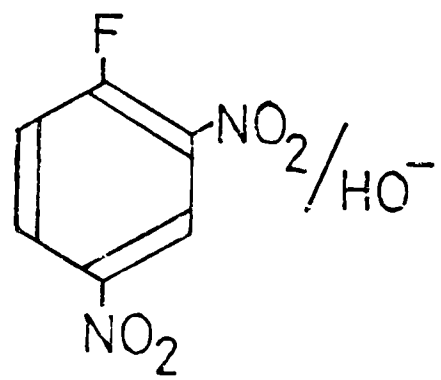
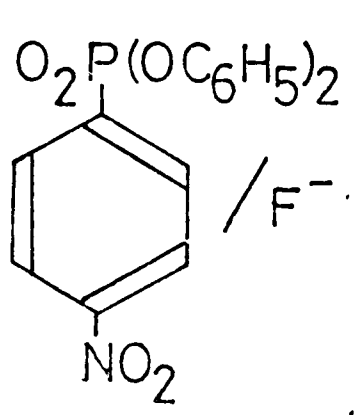
Reaction	Surfactant	Inhibiting ion	Salt order for inhibition	Ref.
RCO_2Ar / HO^-	Cationic	Anion	$NO_3^- > Br^- > Cl^- > F^- >$ no salt	114, 121 122
	Cationic	Anion	$1\text{-}C_{10}H_7SO_3^- > OTs^- > PhCO_2^- > MeSO_3^- >$ no salt	123
	Cationic	Anion	$1\text{-}C_{10}H_7SO_3^- > OTs^- > NO_3^- > Br^- > Cl^- \simeq MeSO_3^-$	124
$C_6H_5C(OCH_3)_3 / H^+$	Anionic	Cation	$R_4N^+ > Cs^+ > Rb^+ > K^+ > Na^+ >$ no salt	114, 121 122
$C_6H_5COPO(OC_2H_5)_2 \,\|\, CH_2 / H^+$	Anionic	Cation	$Me_4N^+ > Na^+ > Li^+ >$ no salt	125

Table 6. Salt effects on some bimolecular micellar catalysed reactions

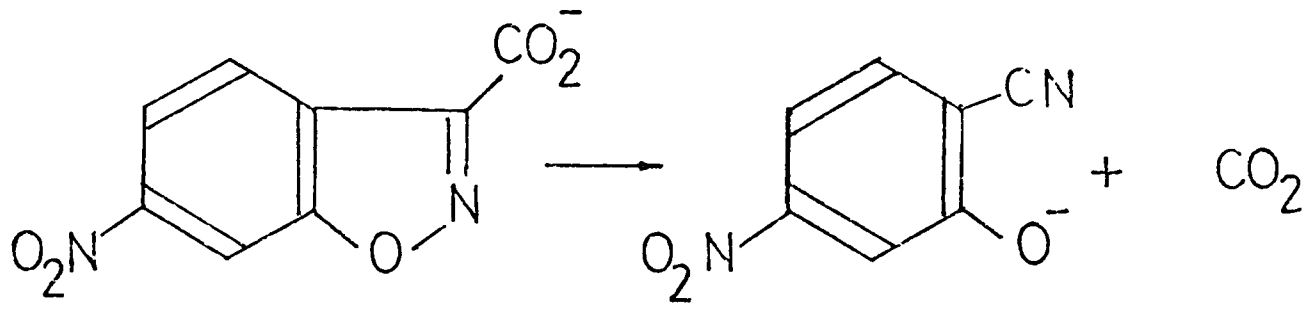
alkyl groups is in the order:-

$$C_{16}H_{33} > C_{14}H_{29} > C_{12}H_{25} > C_8H_{17}.$$

Such effects can be rationalised by postulating increased charge density of the ions on the surface of the micelle with increasing carbon chain length, which in turn increases the electric field of the reaction site.

Variations in the substrate often have profound effects on the magnitude of the catalysis observed. Thus the hydrolysis of methyl orthobenzoate in acidic solution is catalysed by micellar sodium dodecyl sulphate whilst that of methyl orthoformate is unaffected.[121] This example is representative of the general rule that the more hydrophobic a substrate, the more pronounced the micellar catalysis. The dependence of the catalytic efficiency of micelles on the hydrophobicity of surfactants and of the substrate can be advantageously explored by the investigation of substrate partitioning and orientation in the microenvironment of different micellar systems.

The influence of electrolytes on reaction rates is somewhat less predictable. For most reactions micellar catalysis is inhibited by counter-ions and the larger the ion, the greater the effect.[122-124] Some examples are shown in Table 6. A recent exception to the above generalisation is the micellar catalysis of the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion, shown in equation (13).



equation (13)

This reaction is enhanced by electrolytes[126,127] in the order:-

$$SO_4^{2-} \rangle Br^- \rangle Cl^- \rangle F^- \simeq CH_3CO_2^- \rangle \text{no salt}$$

with the order relatively unaffected by the cation size. This enhancement is believed to be due to changes in micellar structure by the salts.[128] Thus the effect of electrolytes on micellar rates can be discussed in terms of their competition with the reagents for available sites, as well as their ability to alter micellar structure.

1.4.2 Kinetics of micellar catalysis

The simplest model for the kinetics of a micellar catalysed (or inhibited) reaction is analogous to that used for enzymatic catalysis[107,128] i.e.

$$M + R \underset{k_o}{\overset{K_{app}}{\rightleftharpoons}} MR \xrightarrow{k_m} \text{products} \qquad \text{equation (14)}$$

where M is the micelle, R is reacting substrate, MR is the micelle-substrate complex, Kapp is the micelle-substrate

binding constant with k_o and k_m being the rate constants for product formation in the bulk solvent and micellar phase respectively. Assuming that,

(a) one substrate molecule is incorporated into each micelle

(b) the reactants do not perturb the micellar properties or complex with surfactant monomer

(c) k_o is unaffected by added surfactant

(d) the concentration of monomers remain constant above the cmc

the observed rate constant for product formation, k_ψ, for a first order reaction is given by[115]

$$k_\psi = \frac{k_o + k_m K_{app}[M]}{1 + K_{app}[M]} \qquad \text{equation (15)}$$

where $[M]$ is the concentration of micelles given by $(C_s - cmc)/N$, C_s is the concentration of surfactant and N is the aggregation number. The derivation of equation (15) assumes that the micelles are in large excess over the substrate and most experiments are conducted under such conditions.[107,128]

Equation (15) predicts that added surfactant will not affect the reaction rate until micelles form at the cmc. In a catalytic reaction, as a substrate is increasingly incorporated into the micelle, the reaction shows a

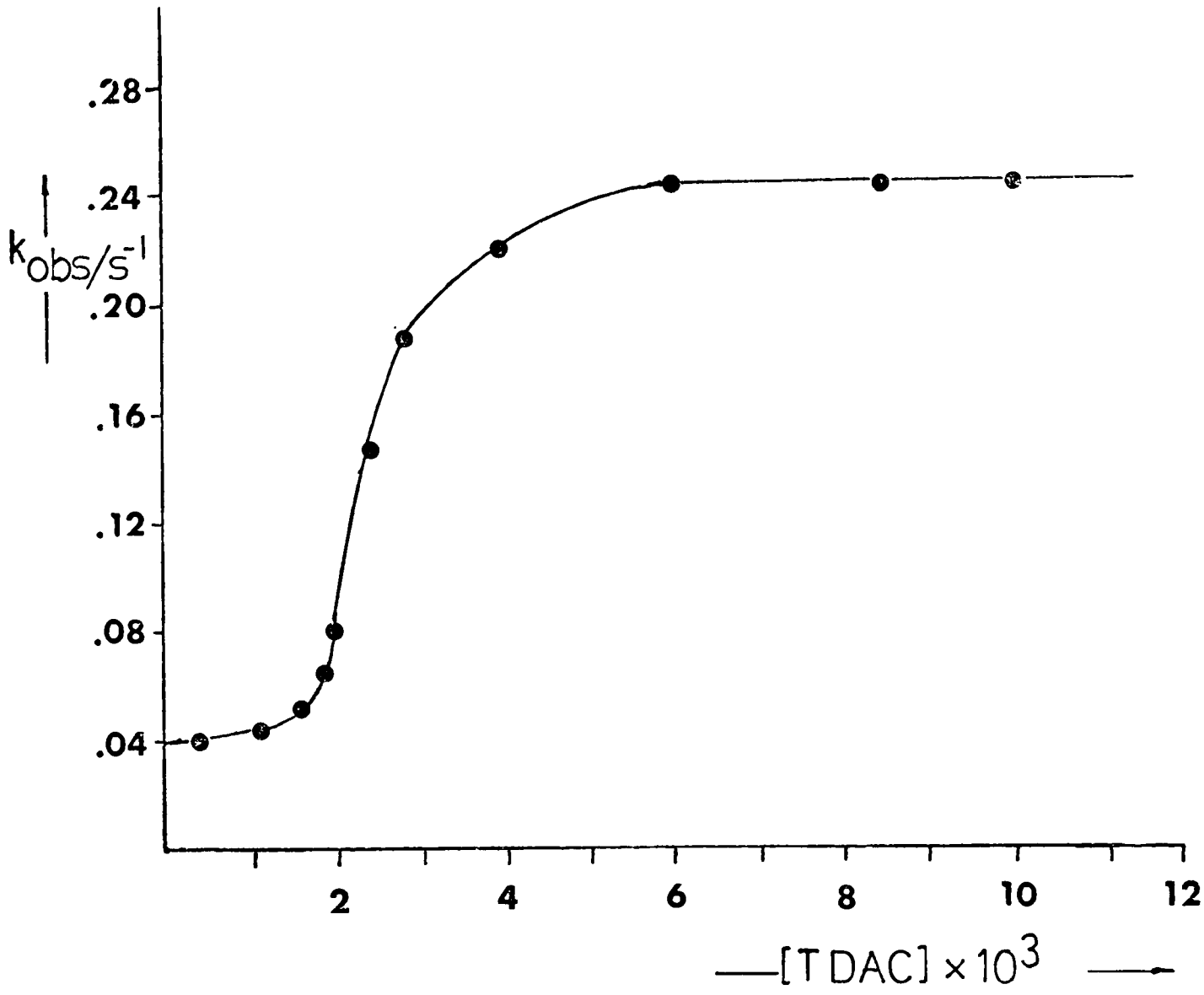


Figure 12. First order rate constants for the hydrolysis of p-nitrophenyl hexanoate at pH 10.15 as a function of [TDTAC] at a constant total chloride ion concentration of 0.02M[114]

sigmoidal increase with increasing surfactant concentration until a constant value is obtained. In practice a plateau is only seen when a constant counter-ion strength is maintained. A classic example is the hydrolysis of p-nitrophenyl hexanoate in tetradecyl-trimethylammonium chloride (TDTAC) at constant total chloride ion concentration,[114] as shown in Figure 12. This bears analogy to the simplest type of enzyme kinetics, analysed by the Michaelis-Menten equation.[107,128,129] Rearrangement of equation (15) gives equations (16) and (17)

$$\frac{1}{(k_o - k_\psi)} = \frac{1}{(k_o - k_m)} + \frac{1}{(k_o - k_m)} \cdot \frac{N}{Kapp(C_s - cmc)} \qquad \text{equation (16)}$$

$$\frac{k_\psi - k_o}{k_m - k_o} = \frac{Kapp}{N}(C_s - cmc) \qquad \text{equation (17)}$$

These have been successfully used when catalysis is observed at surfactant concentrations just above the cmc. Equation (17) is preferred since in equation (16) the value of $(C_s - cmc)^{-1}$ is sensitive to the value of the cmc used.[107,128] Equations (15), (16), and (17) whilst successful in treating micellar catalysis (or inhibition) of unimolecular reactions, are not sufficiently rigorous for many bimolecular reactions. Such reactions usually exhibit an optimal rate at some surfactant concentration[130,131] i.e. a maximum rate is obtained,

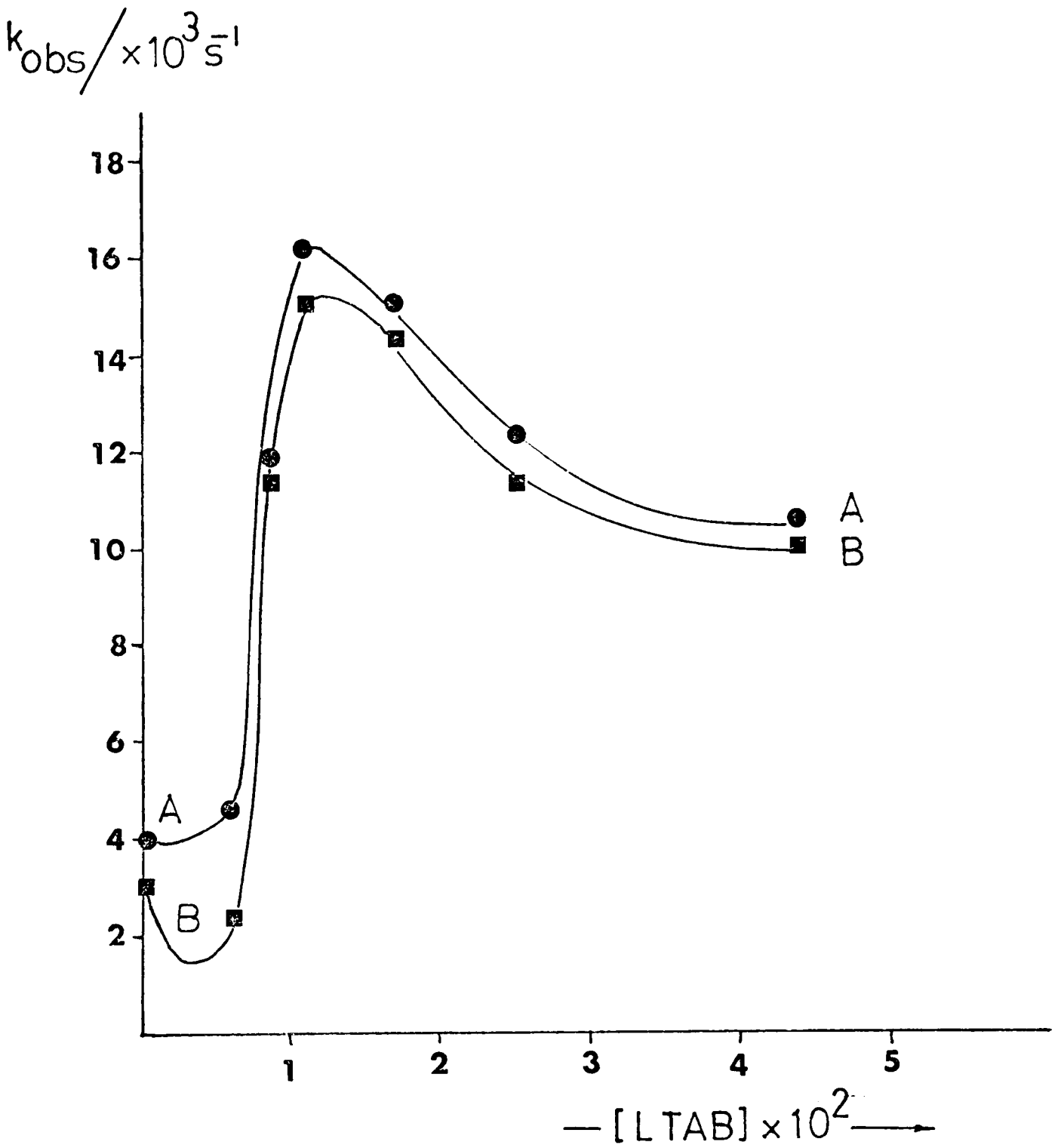


Figure 13. Plots of rate constants for the hydrolysis of mono-p-nitrophenyl dodecanedioate(A), and p-nitrophenyl octanoate(B) as a function of lauryltrimethylammonium bromide (LTAB) concentration at pH 10.49, 50°C and μ=0.2

above which the rates decrease with increasing concentration, an example of which is shown in Figure 13, from the work of Menger.[115] This phenomenon stimulated a search for a more satisfactory kinetic treatment for these more complex cases.

An important contribution by Berezin et al.[132] considered the case of reaction between two uncharged molecules treating micellisation as a phase-equilibrium. The equation, (18), derived was

$$k_\psi = \frac{k_m P^n C_s V + k_o (1-C_s V)}{1 + C_s V (P-1)^n} \qquad \text{equation (18)}$$

where P is the partition coefficient of the substrate between the two phases, V is the molar volume of the surfactant and n is the order of the reaction. This treatment was successful only for uncharged molecules and is not applicable to reactions between ions and organic molecules.

The most generally satisfactory theory is that developed by Cordes[131] and Romstead[133] which takes into account the degree of counter-ion binding to the Stern layer. This treatment quantitatively accounts successfully for the basic features of kinetics in bimolecular micellar systems,[133,134] by use of equation (19),

$$k_\psi = \frac{k_m \beta S K_{app}(C_s - cmc)}{[K_{app}(C_s - cmc)+1][I_t + X_t K]} + \frac{k_o}{[K_{app}(C_s - cmc)+1]}$$

equation (19)

where β is the degree of counter-ion binding, S is the molar density of the micellar phase, I_t and X_t are the total reactive and unreactive counter-ion concentrations, and K is an equilibrium constant of the counter-ion exchange on the micellar surface. Equation (19) predicts a rate maximum, a rate enhancement with increased substrate and surfactant hydrophobicity, effects due to added electrolytes and in the case of first order reactions simply reduces to equation (15). While such treatments are not the final solution to kinetic problems, they are very useful in relating experimental data to a theoretical model.

1.4.3 Applications of micellar catalysis

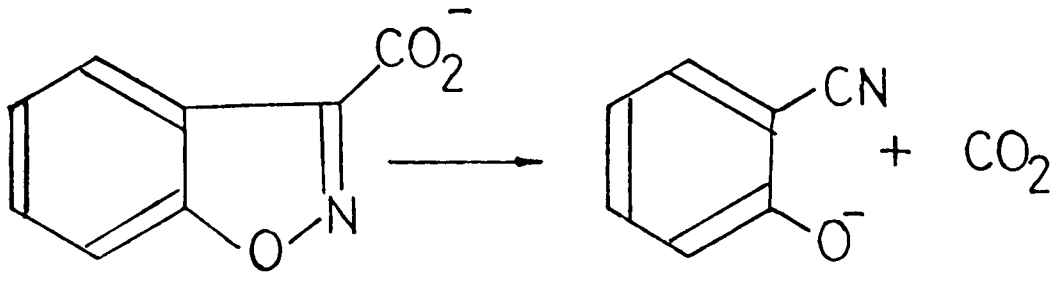
A great many reactions are catalysed in micellar media e.g. indicator equilibria, nitrous acid deamination, ligand exchange and/or aquation of transition-metal complexes. These have been extensively reviewed.[12,107,128-135] A great many of the organic reactions studies have been ester hydrolyses, particularly p-nitrophenyl esters and to a lesser extent acetals, sulphates, phosphonates and Schiff bases.[107] Due to the relative simplicity

of the mechanism of ester hydrolysis and in particular, base-catalysed hydrolysis, these reactions have served as model systems in the investigation of micellar effects on reaction rates and activation parameters.[107] Additionally it is a useful model for ester hydrolysis *in vivo*.

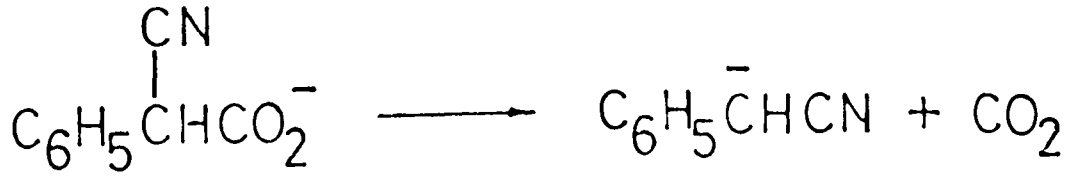
Some typical examples of micelle catalysed reactions are given in the following sections.

1.4.3.1 Unimolecular reactions

Only a few examples of unimolecular reactions have been studied, although they are attractively simple. In a unimolecular reaction also one is only concerned with the distribution of a single reactant between micelle and bulk solvent. Two examples are the decarboxylation of carboxylate anions e.g. a benzisoxazole carboxylate to an α-arylcyanide,[136] as shown in equation (20), and the rate limiting formation of a carbanion from a carboxylate[127] as in equation (21).



equation (20)



equation (21)

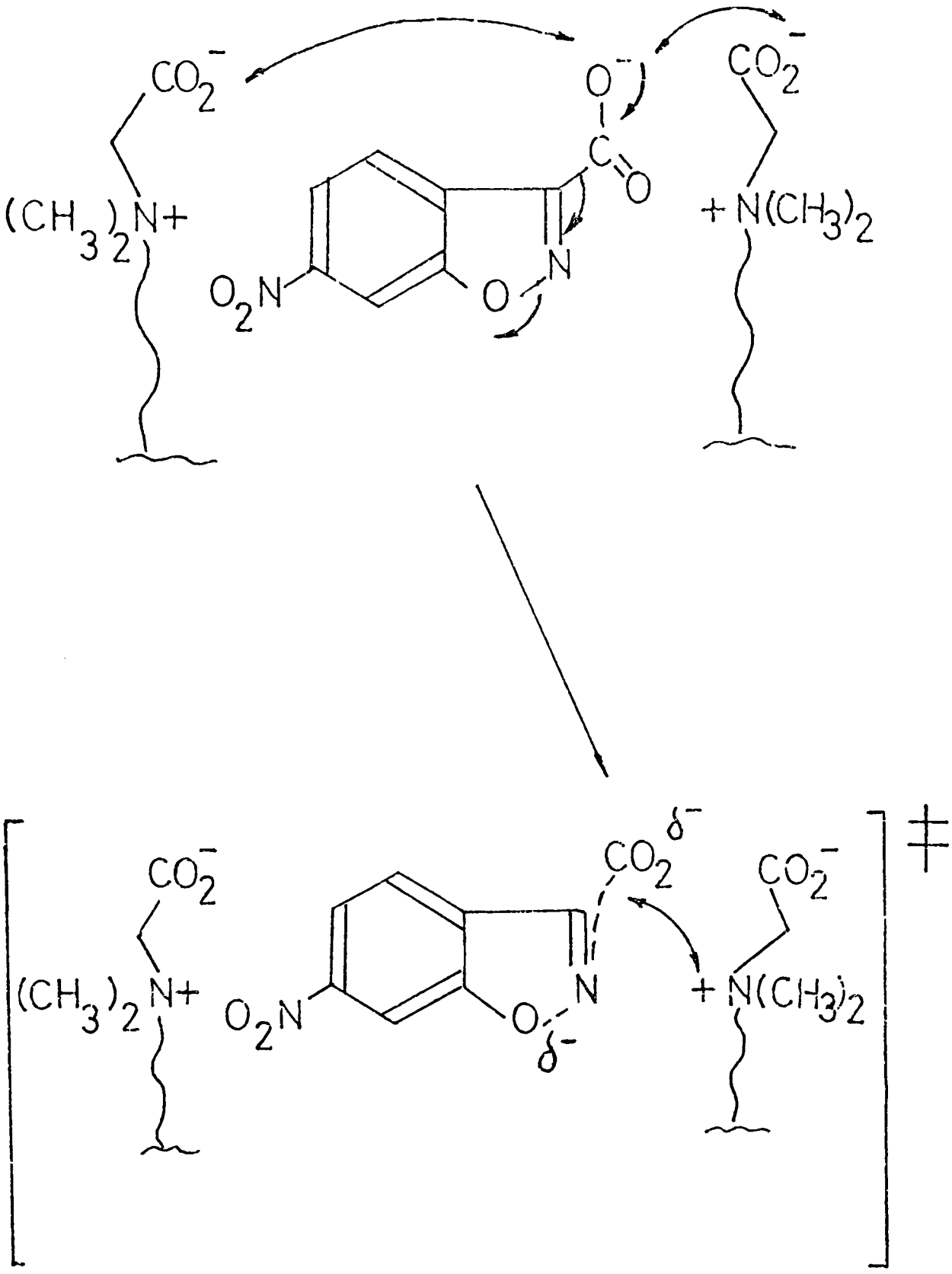


Figure 14. Possible electrostatic interactions between a zwitterionic surfactant and 6-nitrobenzisoxazole-3-carboxylate ion in the ground and transition state[137]

Both of these reactions are strongly catalysed by cationic and zwitterionic micelles[127,136,137] and the analogy between rate enhancements by micelles and aprotic solvents has been made, since both reactions are much faster in organic solvents than in water.[135] In both reactions the catalysis observed can be explained in terms of decreased hydration of the carboxylate ion and favourable electrostatic interaction between the cationic head group of the micelle and the carbanion-like transition state.

Zwitterionic micelles are normally ineffective as catalysts, but not so for these decarboxylations and micelles of zwitterionics surfactants derived from amino acids are particularly effective catalysts for decarboxylation e.g.

$$\overset{+}{R}NMe_2CH_2CO_2^- \quad (R = \underline{n}\text{-}C_{10}H_{21}, \underline{n}\text{-}C_{12}H_{25})$$

The possible explanation for this efficiency is that when the carboxylate ion is incorporated into the micelle the initial ground state repulsions between carboxylate ions are replaced by favourable interactions in the transition state between the quaternary ammonium group and the forming carbanion centre. Figure 14 shows such a scheme for a benzisoxazole,[137] but a similar scheme can be written for $\underline{\alpha}$-cyanophenylacetate.

1.4.3.2 Bimolecular reactions

Many bimolecular reactions have been studied.[107,135] In the case of a bimolecular reaction consideration must

$$Ar = \underline{p}\text{-}(CH_3)_2N\text{-}C_6H_4-$$

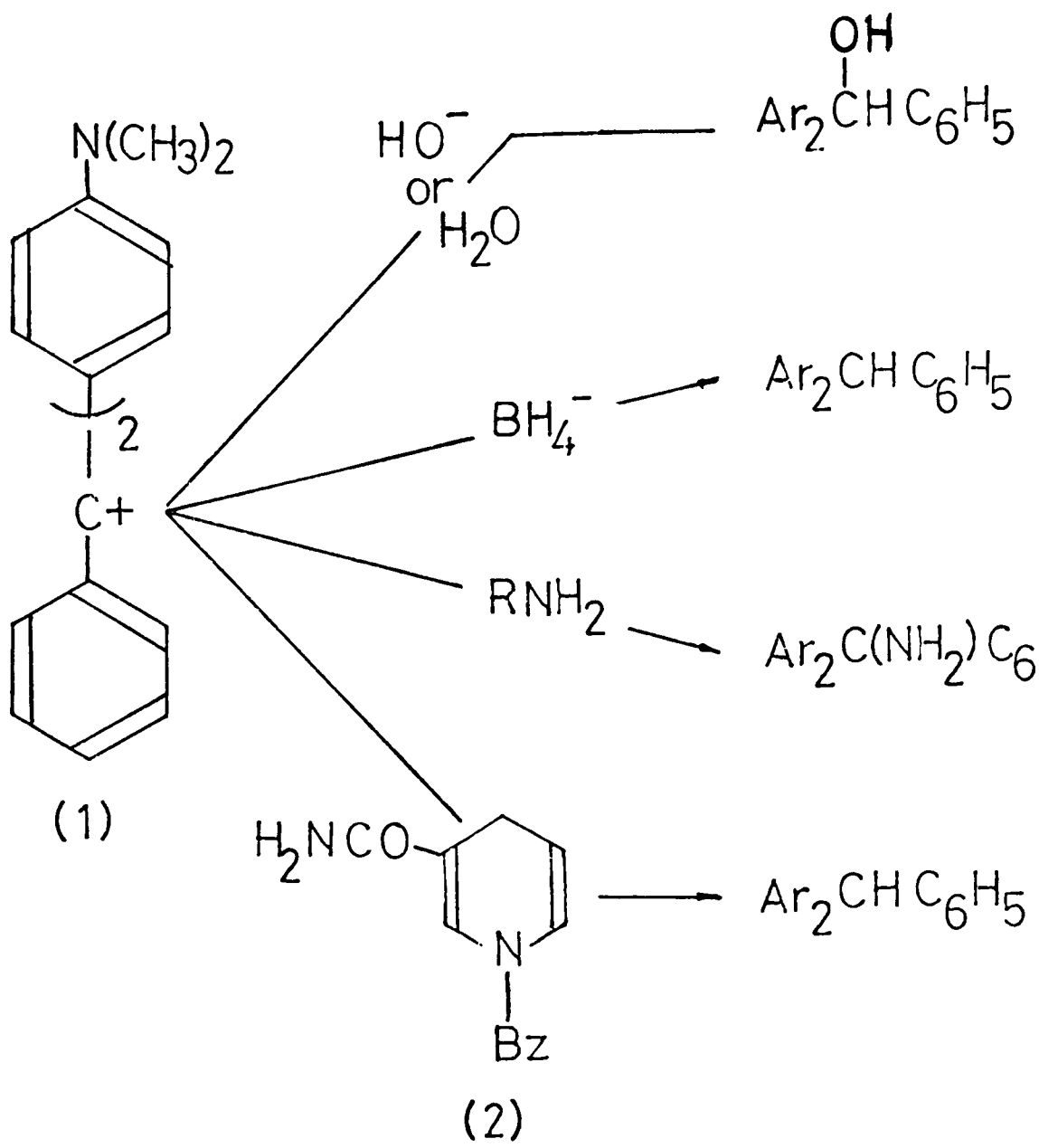


Figure 15. Reactions of Malachite Green with various substrates under micellar conditions[140-142]

be given to the distribution of both reagents in the micellar phase e.g. for some reactions there is a variation of overall reaction rate with substrate which seems to depend on both the second order rate constants and the reactant concentration in the micellar pseudophase.[130]

Micellar effects upon reactions of carbocations with nucleophiles have been extensively studied[135,138-142] and provide an example in which micellar catalysis depends not merely upon the bringing together of the reagents but upon the interactions between the head groups and the reactive centres. Reactions of triarylmethyl cations e.g. Malachite Green (1), have the following characteristics (shown schematically in Figure 15),

(a) the attack of water is essentially unaffected by micelles irrespective of charge

(b) anionic micelles e.g. SDS, suppress the attack of anionic nucleophiles e.g. borohydride and hydroxide, but cationic micelles have no effect[140]

(c) anionic micelles however catalyse the attack of uncharged nucleophiles and N-benzyl-dihydronicotinamide (2), whilst cationic micelles have a small rate effect.[141,142]

In recent years considerable interest has been shown in the mechanisms of hydrolysis of sulphate and phosphate esters as a consequence of their importance in

biochemical systems. Micellar effects on the attack of nucleophiles at the phosphoryl group of di- and trisubstituted phosphate esters is catalysed by cationic micelles, with the rate enhancement being greatest for hydroxide ion rather than fluoride ion. This selective enhancement is due to the stronger binding of hydroxide to the micelle. A typical study is shown in Figure 16.[124,143]

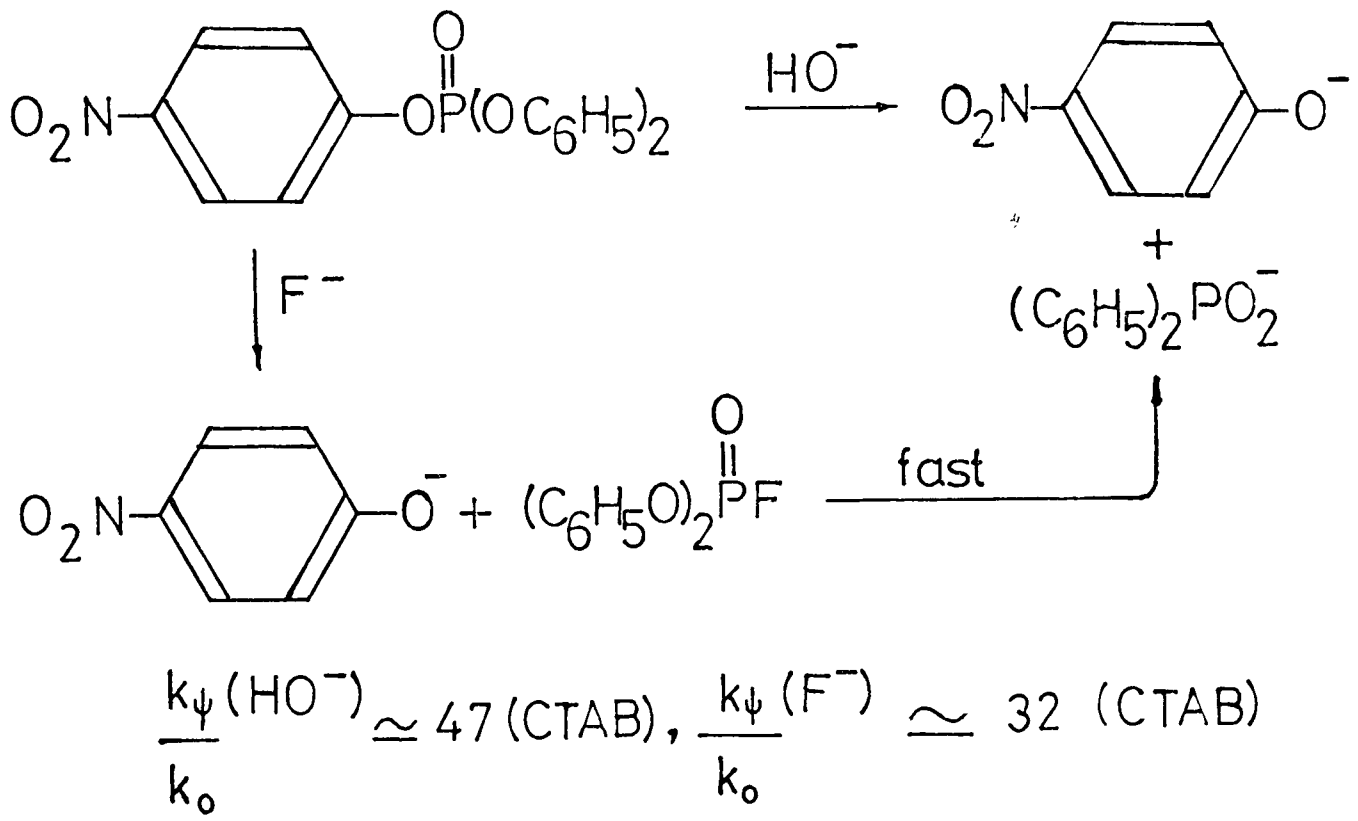


Figure 16. Reaction of p-nitrophenyl diphenyl phosphate with nucleophiles[124,143]

1.4.3.3 Electron transfer and photochemical processes

Micelles may be used either to separate hydrophobic and hydrophilic reactants, such as donor and acceptor molecules in photochemical charge and electron transfer

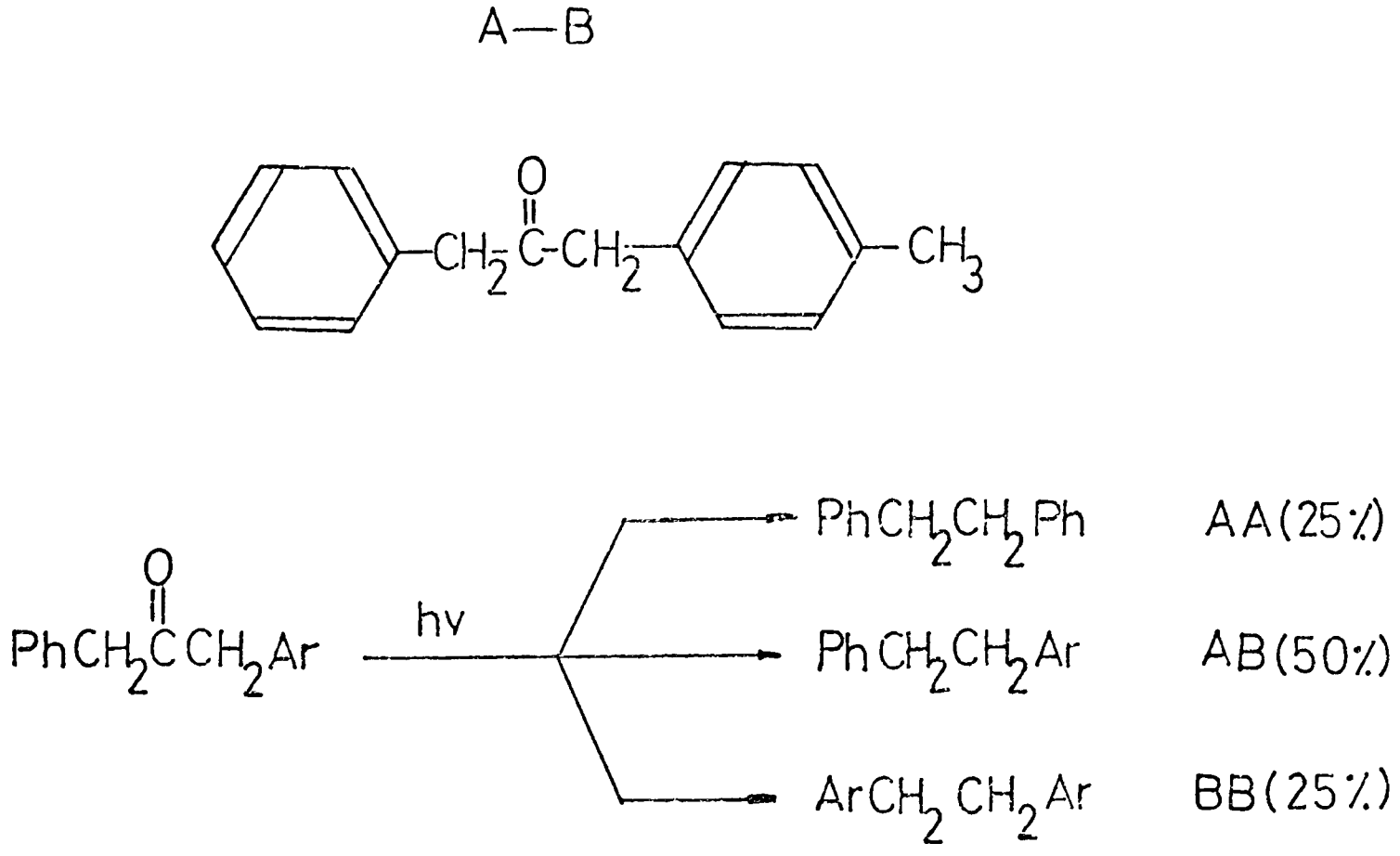


Figure 17. Distribution of coupling products for (p-tolyl)benzyl ketone photolysis in benzene

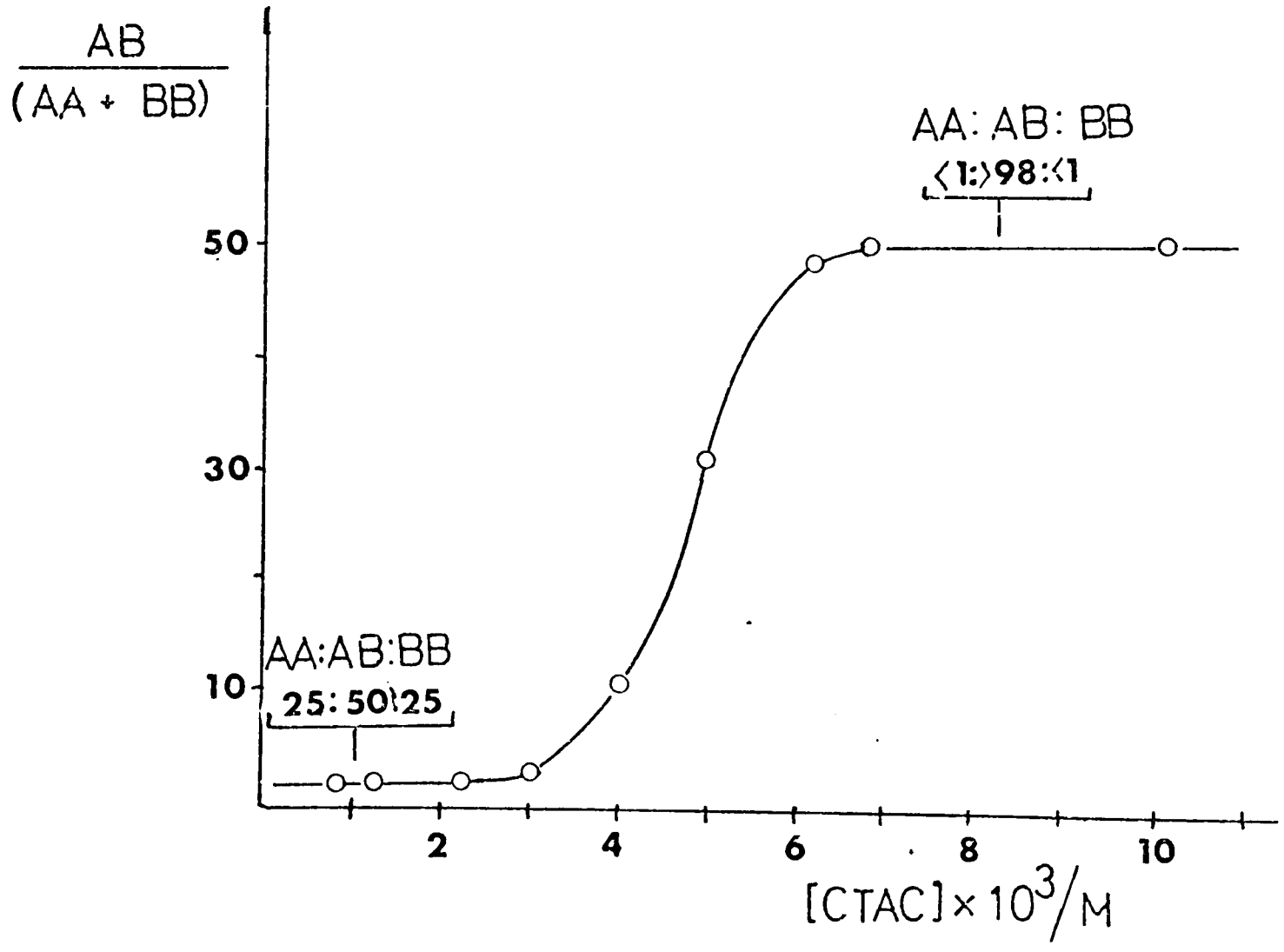


Figure 18. Ratio of coupled photolysis products AB/[AA+BB] as a function of surfactant concentration

reactions, or increase the half life of unstable species.[144-147] In such systems the catalysis or stabilisation observed in the micellar environment mimics important features seen at biological interfaces.[147]

Enhancement of selectivity in a photoreaction has been recently demonstrated by Turro.[148] In homogeneous, fluid solution photodecarbonylation of dibenzyl ketones occurs, via a free-radical mechanism, to produce 1,2-diarylethanes in quantitative yield. In the case of an asymmetric dibenzyl ketone e.g. (p-tolyl)benzyl ketone,(3), a statistical mixture of coupling products AA(25%), AB(50%) and BB(25%) are obtained, as shown in Figure 17. In aqueous cetyltrimethylammonium chloride (CTAC) solution this distribution is drastically changed above the cmc of CTAC. The variation of the product distribution is shown in Figure 18, illustrating an almost exclusive production of AB coupled material above the CTAC cmc of 10^{-3}M. This selectivity has been explained in terms of "reduced dimensionality" for the radicals, A$^{\bullet}$ and B$^{\bullet}$, formed in the photolysis. When produced the radicals are caged by the micelle which prevents diffusion to free radicals. As a consequence of effective confinement a predominant AB coupling occurs rather than a statistical non-selective coupling of free radicals A$^{\bullet}$ and B$^{\bullet}$.

A study of electron transfer by Engberts[149] highlights the use of such reactions in understanding

biochemical functions of metalloproteins. The reduction of $[Mn(cydta)]^-$ by $[Co(edta)]^{2-}$ and $[Co(cydta)]^{2-}$ is catalysed by aqueous CTAB micelles ($cydta^{4-}$ = trans-1,2-diaminocyclohexane-N,N,N,N-tetraacetate ion and $edta^{4-}$ = 1,2-diaminoethane-N,N,N,N-tetraacetate ion The rate enhancements observed have been attributed to the increase in the concentration of reactants in the micellar phase, rather than absorption on the micelle surface. Gratzel et al.,[150-154] having utilised micellar systems in electron transfer reactions of aquated electrons from aqueous solution to a donor molecule in the micellar interior, have more recently studied the photoinduced reduction of cupric ions by organic donors in micelles where the cupric ions constitute the micelle counter-ion.[155] The reduction rate was found to be enhanced in such micelles. The cuprous ion produced in this photochemical redox process is prevented from back reaction with the reduced acceptor ion by the micellar surface potential permitting energy storage.

1.4.4 Aqueous micelles as models for enzymes

An extensive amount of research has been carried out in recent years on chemical model systems for specific enzymes.[156-158] Whilst these have provided useful insight, by and large they have not succeeded in creating micro-environments analogous to that of the active and binding sites of the enzymes. Investigations of aqueous micellar

systems and the kinetics of organic reactions therein have been prompted by the suggestion that micelles mimic this microenvironment.[7,12,107,128-131,135] Reasons for such a comparison are:-

(a) various physical studies indicated similarities between the structures of micelles and globular proteins[159]

(b) protein denaturing agents e.g. urea and guanidinium salts, disrupt micelles

(c) both micelles and enzymes bind substrates, the order of magnitude of the binding constants being similar

(d) the kinetics of micellar catalyses resemble, in many respects, that exhibited by enzymes. Usually the Michaelis-Menton equation is obeyed and inhibitor effects observed in micelle catalysed reactions are similar to inhibitions observed in enzymatic catalyses.

Thus, at first sight, similarities between micelles and globular proteins are apparent, but aqueous micelles are relatively poor models for complex bio-organic enzymes. In particular the catalysis observed for micelles is rarely greater than a factor of 100 and only a modest degree of substrate specificity is observed in the majority of reactions.[12] The main reason for this poor catalytic effect and specificity of aqueous micelles is related to

the dynamic equilibrium which exists between the monomeric and micellar surfactant. Unlike enzymes, which generally maintain their configuration prior and subsequent to binding substrates at the active sites, micelles as shown in previous sections are being continuously formed and reformed on a millisecond time-scale. Secondly, the hydrophobic hydrocarbon chains in micelles are fairly mobile, whilst in enzymatic binding sites the hydrophobic interactions are more fixed.

In all, a number of features of catalysis in micelles resemble those in enzymes, but like most models aqueous micelles have definite weaknesses, as shown above.

1.5 Functional micellar reagents

Whilst the comparison of micelles and enzymes is now commonplace, the rational design of functionalised surfactants, to refine this analogy, is a more recent venture.[107,128,135] Synthetic surfactants have been used since it is relatively easy to obtain a homogeneous sample, whereas some biological surfactants e.g. phospholipids, require tedious and laborious purification. Studies of the catalytic properties of functional micelles, as enzymatic models, have centred on the synthesis of surfactants containing functionalities found in the active sites of enzymes[156-158] e.g. imidazole,[160,161] amino,[162] hydroxyl,[163] mercapto.[164]

This class of surfactant is a special case in

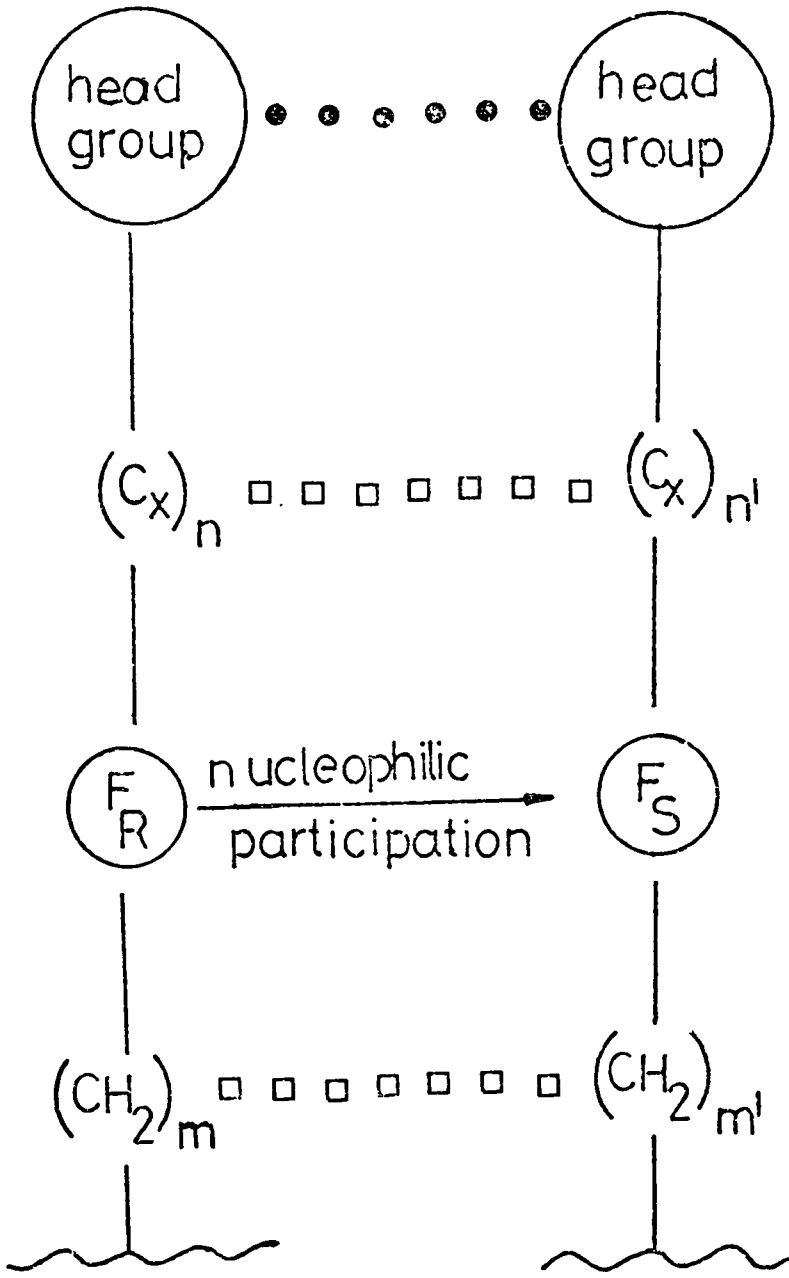


Figure 19. Schematic representation of the possible modes of interaction in functional micelles

(□ □ □ □ □ hydrophobic interactions, ... electrostatic interactions)

which a group, chemically bound to a surfactant, interacts directly with the substrate in a micellar environment. The micelle may consist of such chemically reactive surfactants, or a comicelle of them with a chemically inert surfactant e.g. sodium dodecyl sulphate. Figure 19 illustrates the relationship between a micelle and the substrate for such specifically designed surfactants. In the micellar environment the reactive functionality, F_R, generally a nucleophile or base, reacts with the substrate functionality, F_S, whilst experiencing the hydrophobic, and perhaps any electrostatic, interactions between F_R and F_S. Consequently by varying:-

(a) the nature and charge of the head group e.g. positive or negative, change of heteroatom

(b) the hydrocarbon chain length e.g. n, n', m, m', C_x from alkyl to aryl

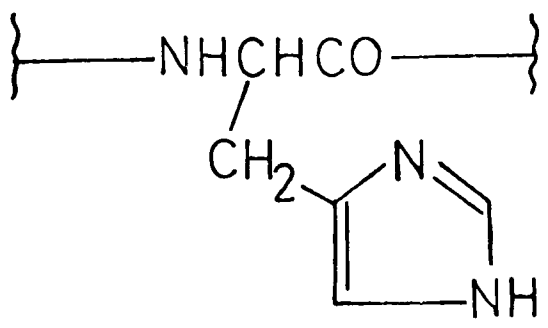
and (c) the functional group of the reactive functionality, F_R, or the substrate, F_S,

the effects of electrostatic and hydrophobic interactions can be investigated in detail with respect to the reaction mechanism.

Many of these functionalised surfactants have been used as models to mimic the hydrolytic action of the esterase enzyme, $\underline{\alpha}$-chymotrypsin.[165] $\underline{\alpha}$-Chymotrypsin, perhaps the most thoroughly studied enzyme because of

its stability and availability, primarily catalyses the hydrolysis of amide bonds of proteins and peptides adjacent to the carbonyl group of the aromatic L-amino acid residues of trytophan, tyrosine and phenylalanine. The enzyme is monomeric consisting of 245 amino acid residues (MW $\simeq$ 25,000) and X-ray data showed that the molecule was ellipsoidal, 51x40x40Å, with a hydrophobic cavity as an active site of size 10-12x5.5-6.5x3.5-4.5Å. By chemical modification it was found that histidyl, imidazole and the seryl hydroxyl groups were involved in the catalytic process which features an acyl enzyme intermediate formed at the seryl residue.

Although various catalytic mechanisms had been proposed the mode of action was derived mainly from X-ray diffraction. In 1969 Blow et al.[166] proposed that a series of hydrogen bonds between the histidyl imidazole, (4), the seryl hydroxyl, (5), and aspartyl carboxyl, (6), existed at the active site of α-chymotrypsin. This association of functional groups, shown in Figure 20 which effected the hydrolysis, was termed a "charge relay" mechanism by Blow.[166]



Histidyl residue

(4)

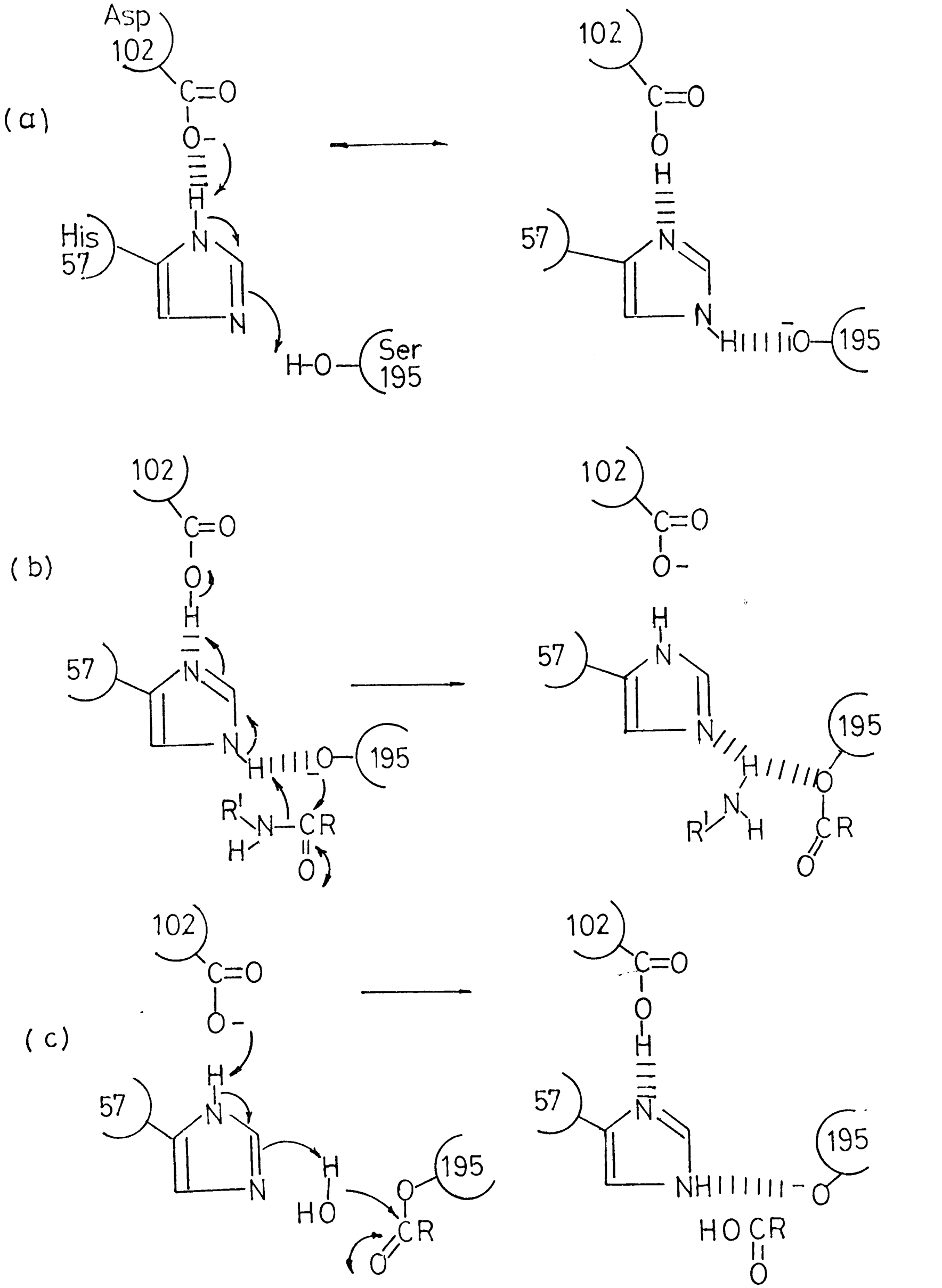
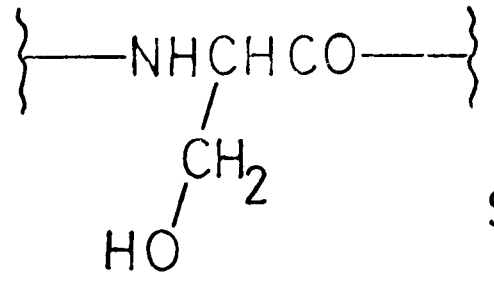
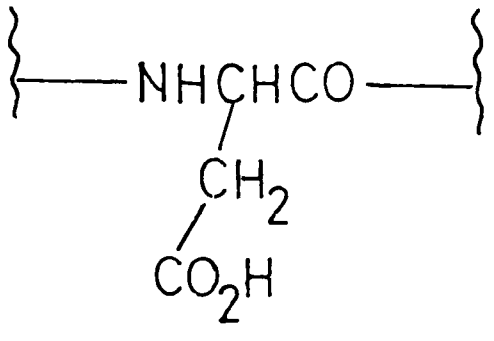


Figure 21. Postulated mode of action of α-chymotrypsin (a) "charge relay system" at pH 8, (b) first step of hydrolysis; acylation of the enzyme, (c) second step of hydrolysis; deacylation of the enzyme



Seryl residue

(5)



Aspartyl residue

(6)

Figure 20. Amino acid residue present in the active site of α-chymotrypsin

The proposed course of this charge relay, according to Blow, is shown in Figure 21. Recent work by Roberts[167] has supported the geometry postulated for such a mechanism, but not the idea of an unusual weakly basic histidine or an unusual strongly basic aspartate carboxyl anion e.g. as in Figure 21(a). Such a result offers no support for the charge relay proposed by Blow.

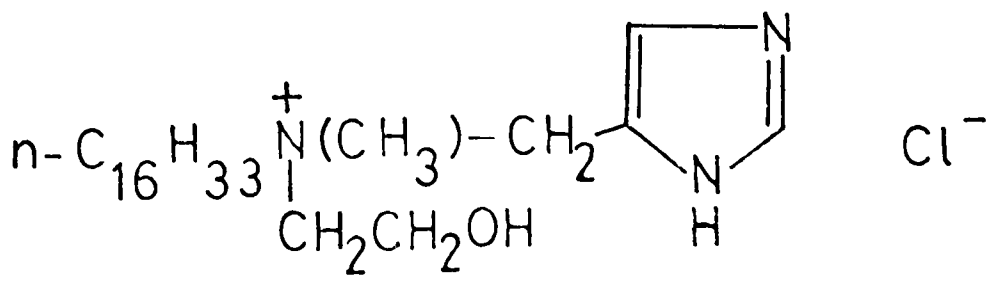
While the actual mechanistic pathway is again unclear, the histidine residue in particular plays an important role in the catalytic action of the enzyme.

Consequently a large number of functionalised surfactants containing the imidazole function have been synthesised in an attempt to mimic the action of α-chymotrypsin and other enzymes which incorporate the imidazole group[158] in the active binding site's action. The imidazole moiety has been utilised in such micellar reagents as:-

(a) a hydrophobic acylhistidine or benzimidazole solubilised in a comicelle[160]

or (b) an integral part of the surfactant.[161]

Whilst these micellar reagents are reactive in enhancing the rates of bimolecular hydrolyses for various p-nitrophenyl esters,[168] the catalytic efficiencies were found to be much lower than that of α-chymotrypsin. A similar situation was also experienced with other surfactants containing amino,[162] hydroxyl[163] and mercapto[164] functionalities. In order to refine the analogy to α-chymotrypsin a number of bifunctional micellar catalysts have been prepared e.g. incorporating the imidazole and hydroxyl groups.[169,170] The bifunctional reagent, (7), synthesised and studied independently by Tonellato[169] and Moss[170] illustrates an early venture in this field.



(7)

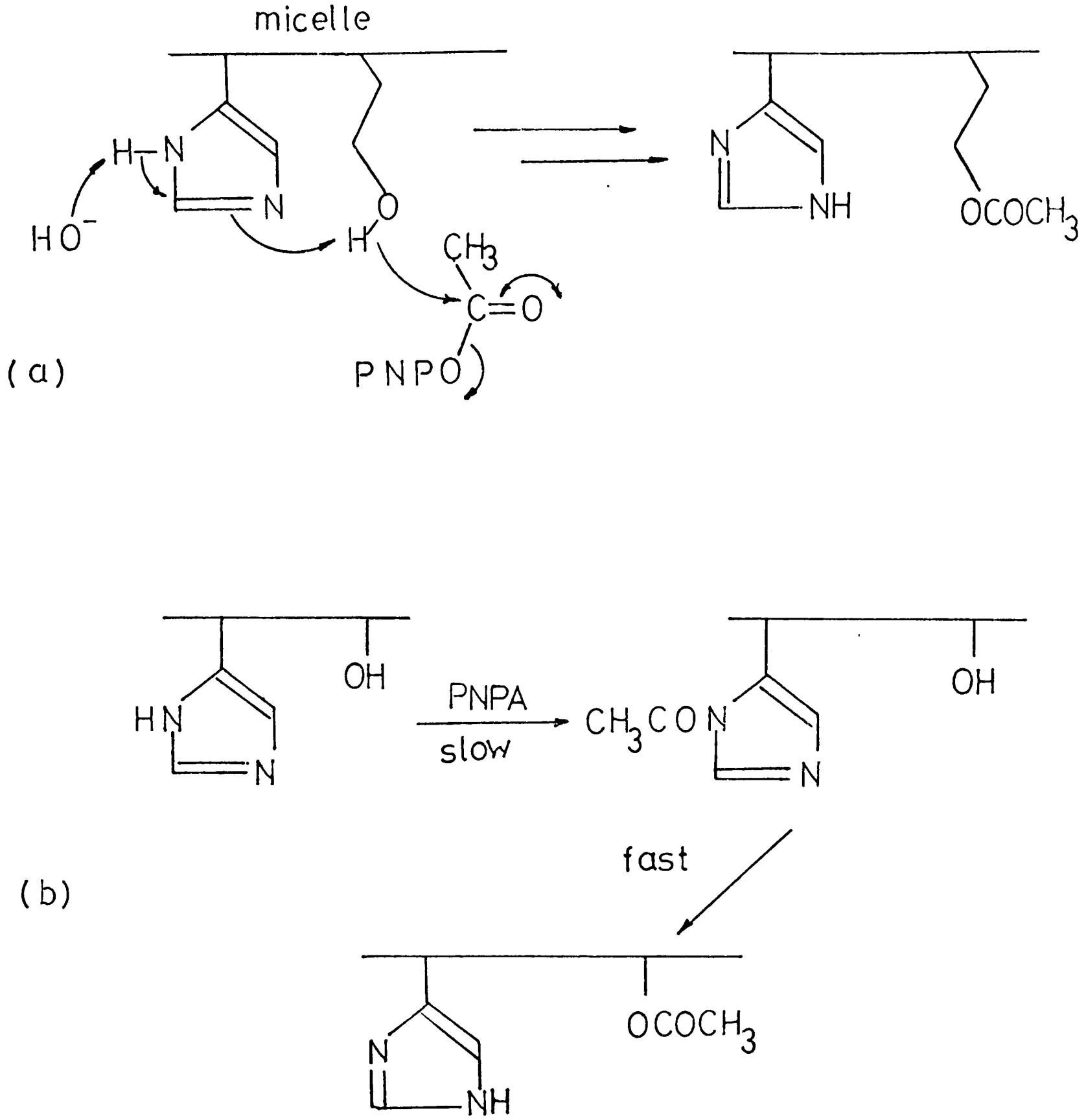


Figure 22. Possible mechanisms for the hydrolysis of p-nitrophenyl acetate by the bifunctional surfactant (7). (a) Co-operative process. (b) Stepwise process

The hydrolysis of p-nitrophenyl esters, under pseudo-first order conditions, with (7) can proceed by a co-operative process, as shown in Figure 22a, or by a stepwise process as in Figure 22b. In either mechanistic case, the key imidazole and hydroxyl moieties which effect the hydrolysis could be in a micellar environment, on the same surfactant molecule (i.e. an intramolecular mechanism), or adjacent surfactant molecules (i.e. an intermolecular mechanism). (7) was found to hydrolyse activated esters by a sequential mechanism in which a slow N-acetylation of the imidazole moiety was followed by a rapid, hydroxyl mediated deacetylation. The major deacylation process was found to occur by an inter-molecular rather than intramolecular pathway. The later requires an eight-membered transition state,[170] as shown in Figure 23.

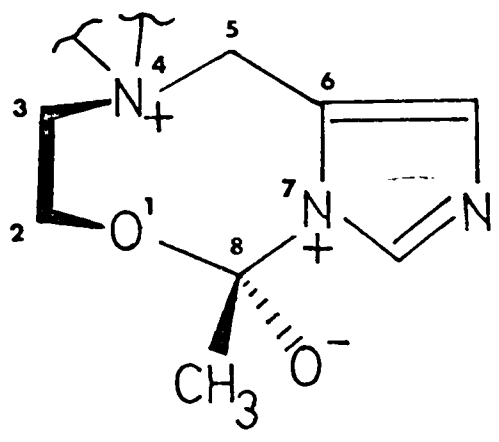
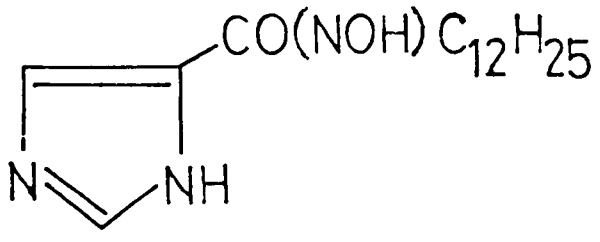


Figure 23. Transition state for intramolecular, hydroxyl mediated, N-acetylation of (7)

The efficiency of functionalised micellar reagents has rarely approached that of α-chymotrypsin. More recent

developments in synthetic micellar reagents have concentrated on enhanced nucleophilic character in monofunctional systems, or establishing combinations of complementary groups in bifunctional systems. In earlier work with polymeric catalysts, Kunitake et al. found that certain complementary groups e.g. hydroxamate and imidazole, gave enhanced catalytic efficiency.[171] Kunitake then synthesised the bifunctional micellar reagent (8).[172]

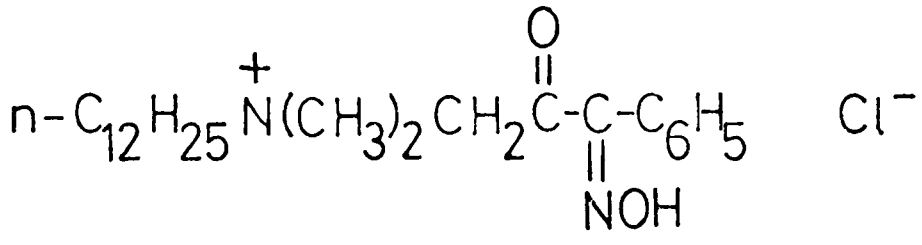


(8)

This reagent as a comicelle in aqueous CTAB displayed a catalytic efficiency exceeding that for α-chymotrypsin at pH 8 for the hydrolysis of p-nitrophenyl acetate. The catalysis observed, although not concerted as displayed in the charge-relay system, was found to operate predominantly by acyl transfer to the hydroxamate anion and subsequent deacylation of the acyl intermediate by intramolecular imidazole catalysis. Both of these processes were greatly accelerated, with the catalysis observed being attributed to the activation of anionic nucleophiles in cationic micelles by formation of hydrophobic ion pairs.[173]

More recently monofunctionalised micellar reagents

containing hydroxamate,[174] oxime[175] and thiocholine[176] moieties have been shown to be the most effective nucleophilic catalysts in activated ester hydrolyses. Tonellato et al. synthesised (9) and investigated its hydrolytic action.[177]



(9)

In aqueous CTAB micelles at pH 8,(9) was found to have substantially greater reactivity towards activated esters than α-chymotrypsin, or any other functional micellar reagent. This enhanced reactivity is believed to be due to the pronounced α-effect exhibited by (9), by virtue of the carbonyl function adjacent to the oxime group.[178]

1.5.1 Micellar control of stereochemistry

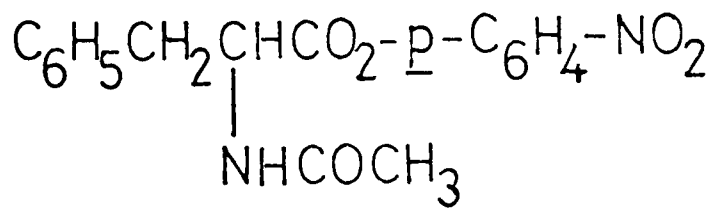
There have been a number of investigations of stereoselectivity in micellar reactions particularly directed to chiral recognition.[107,130] For example, nitrous acid deamination has proved to be a fertile field for investigation of stereochemical control by substrate micellisation.[107] The deamination of chiral primary amines generally involves extensive racemisation with partial inversion of the product alcohol. If the alkyl group is sufficiently hydrophobic for substrate micellisation

2-Aminoalkane	Stereochemistry
Butane	22.9 $\pm$ 0.43, inversion
Pentane	22.9 $\pm$ 2.33, inversion
Hexane	19.0 $\pm$ 0.62, inversion
Heptane	3.5 $\pm$ 0.44, inversion
Octane	6.0 , retention
Decane	11.8 $\pm$ 0.52, retention

Table 7. Stereochemistry of 2-alkanol formation in the deamination of 2-aminoalkanes[179]

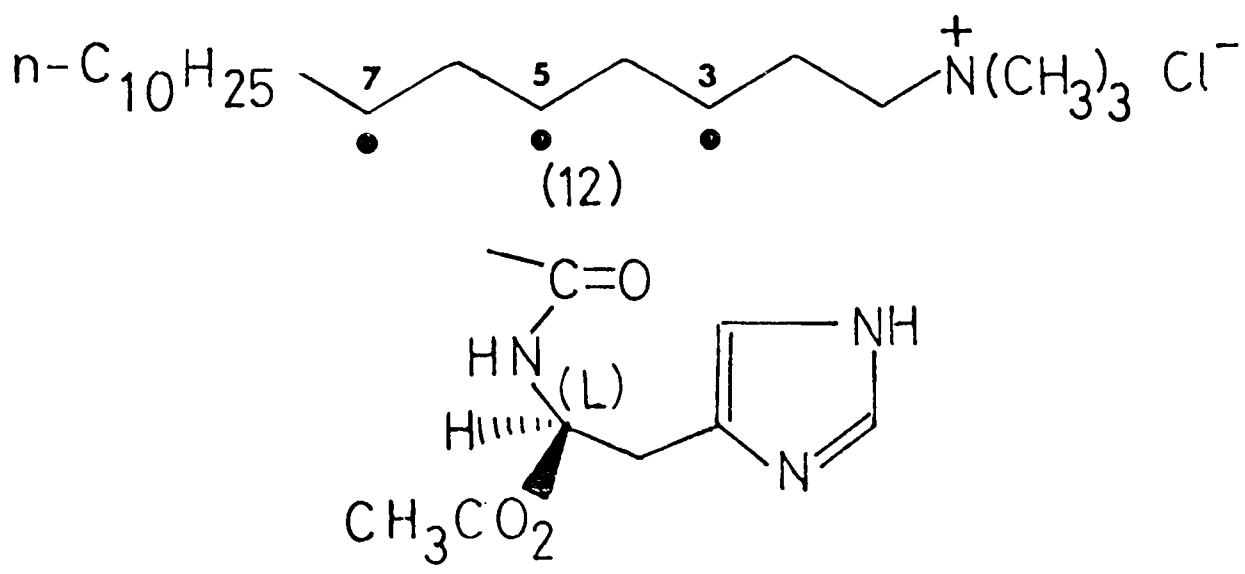
the product has a partially retained configuration since micellisation causes the intermediate carbonium, or ion-pair, to be predominantly attacked by water molecules, from the "front" side.[179] Some examples from the work of Moss et al. are shown in Table 7.

Micelles of optically active surfactants have been used as catalysts in a number of reactions of chiral substrates but the effects observed are small,[179,180] probably due to the fact that micelles are continually interchanging with monomer. A large degree of stereochemical control, approximately three-fold, has been exhibited in the hydrolysis of the phenylalanine derivative (11)[161(b)] i.e. $^{k}S/k_{R}$ = 3.10,



(11)

by the optically active functional micelle derived from the 5-substituted-(12).



(12)

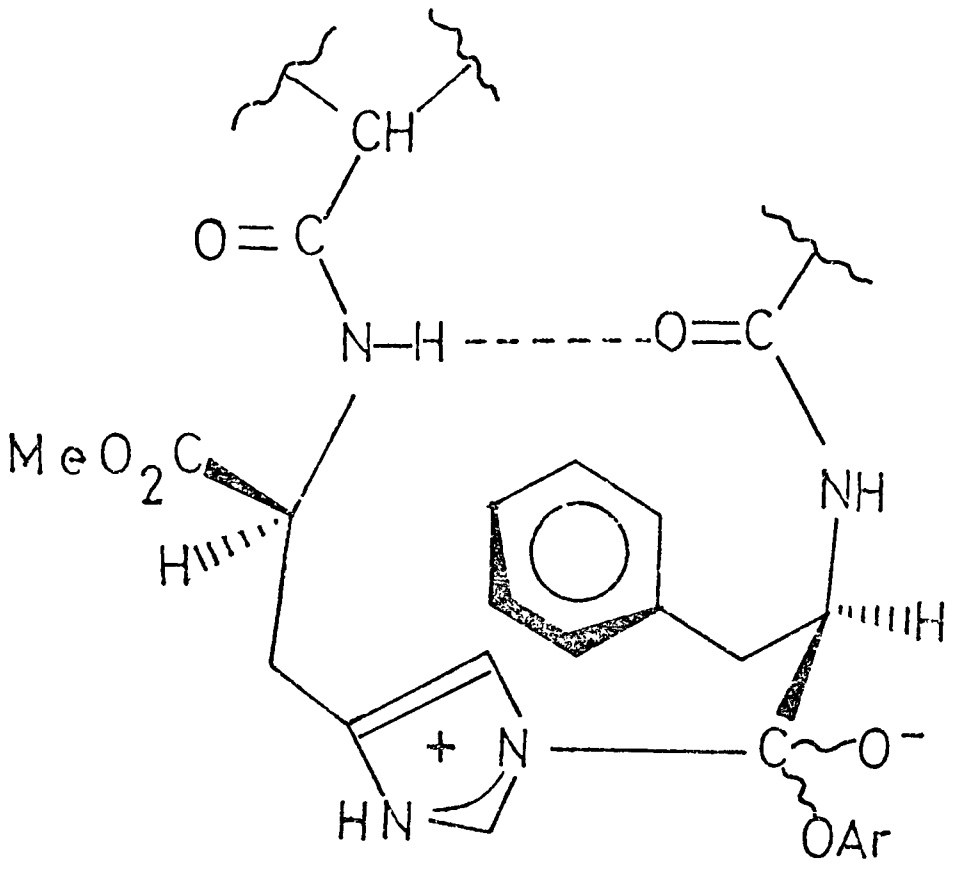


Figure 24. Proposed tetrahedral intermediate in the reaction of 5-substituted-(12) with amino acid (11)

	S, k_{rel}	k_s/k_R
3-Histidine-(13) (mixed diastereoisomers)	0.92	1.50
5-Histidine-(13) isomer A	1.00	3.10
isomer B	0.21	1.04
7-Histidine-(13) (mixed diastereoisomers)	0.51	1.67

Table 8. Stereoselectivity in hydrolysis of (11) by chain-histidine substituted(12)

However only a small chiral recognition was found in the hydrolysis of substrate (13)

$$C_6H_5CH(CH_3)CO_2\text{-}\underline{p}\text{-}C_6H_4\text{-}NO_2$$

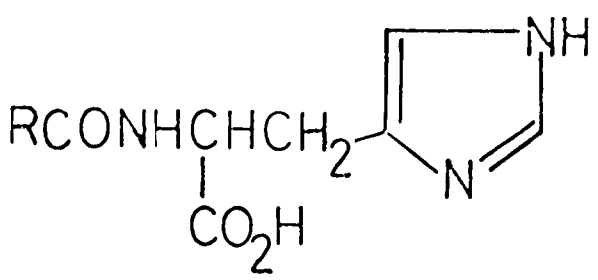
(13)

and this suggested that chiral recognition depended on hydrogen bonding in the transition state, as shown in Figure 24 for the (R)-(-)-ester. For the (R)-ester an unfavourable phenyl-imidazole interaction occurs in the tetrahedral intermediate, but not in the case of the (S)-ester. The hydrolysis was also found to be critically dependent on the configuration of the carboxyl side chain in (12), as shown in Table 8 and the more reactive the diastereoisomer the more selective was its action.[181] Thus the stereoselectivity observed is dependent on transition state rather than initial-state interactions, and this observation suggests that micellar stereospecificity is probably dependent on the presence of a functional group in the optically active surfactant.

A similar system of comicelles of CTAB and various N-acyl-L-histidines (14) have also exhibited stereoselectivity in the hydrolysis of p-nitrophenyl-N-acylphenylalanines (15).[182]

	k_c ($1 mol^{-1} s^{-1}$)					
	L-15a	D-15a	$k_c(L)/k_c(D)$	L-15b	D-15b	$k_c(L)/k_c(D)$
14a	2.75	1.96	1.4	-	-	-
14b	174	101	1.7	-	-	-
14c	1739	690	2.5	877	403	2.2
14d	2740	985	2.8	-	-	-

Table 9. Apparent catalytic rate constants, k_c, in the presence of mixed micelles of (15) and CTAB at pH 7.3



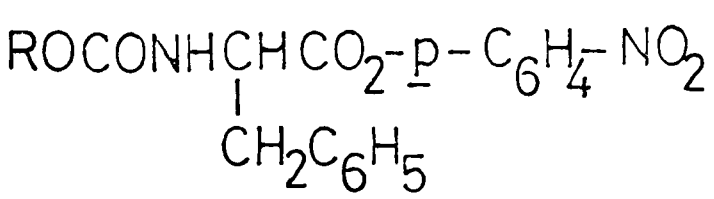
(14)

(a) $R = CH_3$

(b) $R = C_6H_5$

(c) $R = C_9H_{19}$

(d) $R = C_{16}H_{33}$



(15)

(a) $R = CH_2C_6H_5$

(b) $R = CH_3$

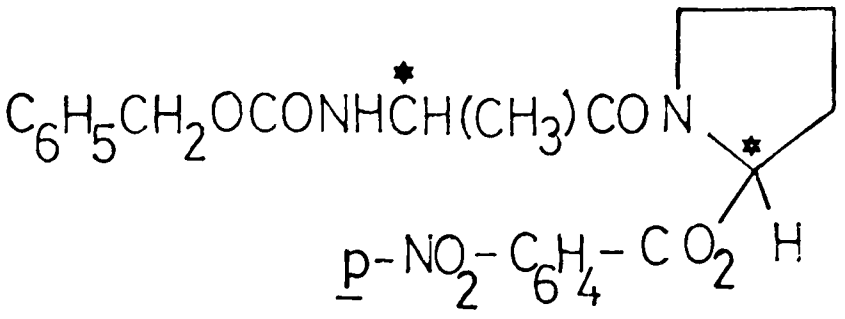
From the rate constants shown in Table 9, it can be seen that the hydrophobicity of the substrate and the functional surfactant play important roles in the rate and the stereochemical control of the enantiomeric substrates (15). The enantiomer rate ratio was also found to be relatively unchanged on dilution of (14c) with inert surfactant. This stereoselectivity can again be explained in terms of interactions in a tetrahedral transition state as shown in Figure 24.

Recent work by Moss et al.[183] has achieved the highest chiral recognition to date, in the hydrolysis of the LL- and DL-forms of the dipeptide (16), using the

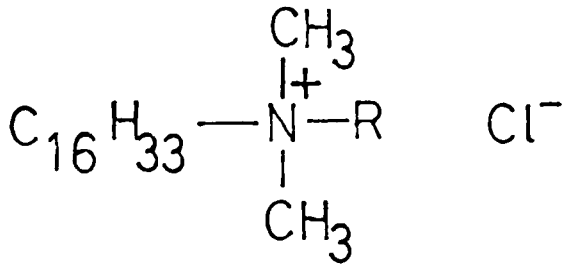
	k_{ψ}^{LL}/s^{-1}	k_{ψ}^{DL}/s^{-1}	$k_{\psi}^{LL}/k_{\psi}^{DL}$	$k_{\psi}^{LL}/k_{\psi 17a}^{LL}$
(17a)	0.00134	0.00134	1.00	1.00
(17b)	3.42	0.79	4.33	2554
(17c)	0.0150	0.00559	2.68	11.2
(17d)	0.0146	0.0054	2.70	10.9
(17e)	0.649	0.168	3.86	484

Table 10. Rates of reaction of surfactants (17a) - (17e) with (LL)- and (DL)-16 at pH 7.0 at 25°C and μ = 0.05 (KCl)[183]

surfactants (17a)-(17e).

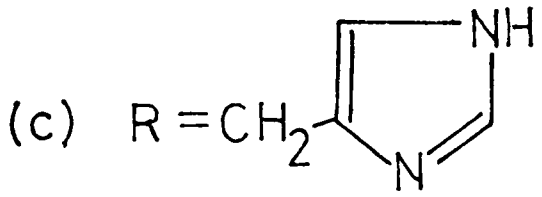


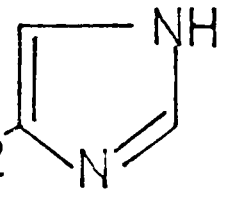
(16)



(17)

(a) R = CH_3 (b) R = CH_2CH_2SH

(c) R = 

(d) R = $CH_2CH_2NHCOCH(NH\text{-}\underline{t}\text{-}BOC)CH_2$ 

(e) R = $CH_2CH_2NHCH(NH_2)CH_2SH$

The data obtained by Moss <u>et al</u>. is shown in Table 10 and the following observations can be derived from it:-

(a) the reactivity of <u>LL</u>-(16) to the micellar catalysts is in the order

(17b) > (17e) > (17d) ≃ (17c) > (17a)

- similar to that observed for the hydrolysis of p-nitrophenyl acetate[184]

(b) the extent of stereoselectivity increases with the kinetic reactivity of the surfactant used, leading to $k_{\psi}^{LL}/k_{\psi}^{DL}$ of 3.9 and 4.3 with thiol surfactants (17e) and (17b) respectively

(c) both binding and functionalisation are necessary for substantial stereoselectivity in cleavage of (16) c.f. (17a) and (17b); only in functional surfactants is stereo-selectivity observed

(d) a chiral surfactant is not required for stereoselectivity; indeed the most stereoselective surfactant is the achiral thiocholine (17b).

A rationale for this stereoselectivity has been put forward in terms of the binding of (16) to a micelle; such a polar molecule should be solubilised within the Stern layer of cationic micelles. Examination of models suggested that (LL)-(16) can assume an extended conformation more readily than (DL)-16, which optimises binding to the micelle. By virtue of this binding in an extended conformation, the carbonyl group is exposed, whilst the hydrophobic moieties are projected into the hydrophobic micelle interior. Such a pronounced binding of the

(LL)-isomer would lead to a more rapid micelle-mediated hydrolysis.

These three examples are however exceptions in studies of asymmetric induction in micelles, although a great deal of effort has been expended in this field.[107,128-131,135,183]

RESULTS AND DISCUSSION

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2.1 Aims of the work

At the outset of this investigation many examples of micellar effects on reaction rates had been reported.[107] A closer examination of the literature showed that:-

(a) the majority of such reactions were simple and/or degradative in nature e.g. hydrolyses, complex formation, association-dissociation, or ligand exchange

(b) the number of reactions of any preparative value was negligible

and (c) oxidation had been neglected.

It has been known for some time that oxygen is much more soluble in hydrocarbons than water.[185] Since surfactants bear a hydrophobic, hydrocarbon chain the concentration of oxygen should be higher in the micellar interior than in bulk water. Metal-ion catalysed aut-oxidation of hydrocarbons e.g. with Co^{2+} or Mn^{2+} ions, involves the formation and breakdown of secondary hydro-peroxides. These reactions are normally non-regiospecific, consequently n-decane would give a mixture of all the possible secondary alcohols on autoxidation-reduction.[186] Thus an attractive objective is the synthesis of a functional surfactant which might effect a catalytic, site-selective, metal-ion autoxidation. Recent interest in molecular oxygen activation by transition-metal complexes,[187] clarifies

Initiation

$$Co^{II} + O_2 \rightleftharpoons Co^{III}O_2^{\cdot-}$$

Propagation

$$Co^{III}O_2^{\cdot-} + AH \longrightarrow Co^{II}O_2H + A\cdot$$

$$A\cdot + Co^{II}O_2H \longrightarrow AO_2H + Co^{II}$$

$$AO_2H + Co^{II} \longrightarrow AO\cdot + Co^{III} + HO^-$$

$$AO_2H + Co^{III} \longrightarrow AO_2\cdot + Co^{II} + H^+$$

$$AO_2\cdot + AH \longrightarrow AO_2H + A\cdot$$

Termination

$$AO\cdot + AO_2H \longrightarrow AOH + A\cdot$$

$$AO\cdot + Co^{II} \longrightarrow AO^- + Co^{III}$$

$$A\cdot + AO_2H \longrightarrow AOH \quad AO\cdot$$

Scheme 1. Typical reactions which can occur in a transition metal catalysed autoxidative system[186] (Co^{2+} can be equally substituted with Fe^{2+}, Mn^{2+}, Cu^{+})

the basic physiochemical properties of such species.

For a potential metal-chelating surfactant, a number of criteria need to be considered:-

(a) whilst molecular oxygen can be activated by number of transition metals e.g. Co, Rh, Fe, Ir, the oxygen can either be bound irreversibly or reversibly;[187b] for aut-oxidative purposes reversibility in oxygen binding is desirable

(b) the metal-ion must be bound within the micellar interior yet accessible for molecular oxygen co-ordination and subsequent activation

(c) the oxidation step must regenerate the reduced state of the metal ion; consequently the use of a transition metal having a number of stable oxidation states e.g. $Fe^{2+} \underset{+e}{\overset{-e}{\rightleftharpoons}} Fe^{3+}$, $Cu^{+} \underset{+e}{\overset{-e}{\rightleftharpoons}} Cu^{2+}$, $Mn^{2+} \underset{+e}{\overset{-e}{\rightleftharpoons}} Mn^{3+}$, $Co^{2+} \underset{+e}{\overset{-e}{\rightleftharpoons}} Co^{3+}$, will facilitate a catalytic redox system as shown in Scheme 1

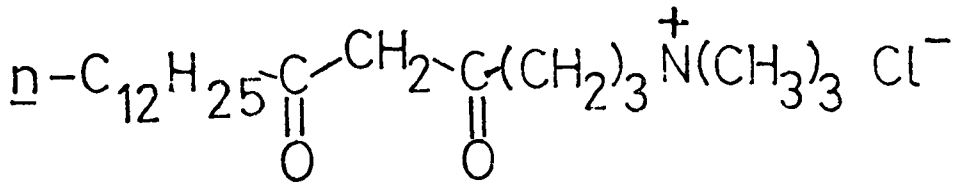
(d) 1:1 complexation between the metal ion and dioxygen must occur, rather than 2:1 complexation which has been previously observed in some species e.g. Co,[188] and which would be expected to cause deactivation in oxidation reactions

(e) the metal-ion binding site must be planar

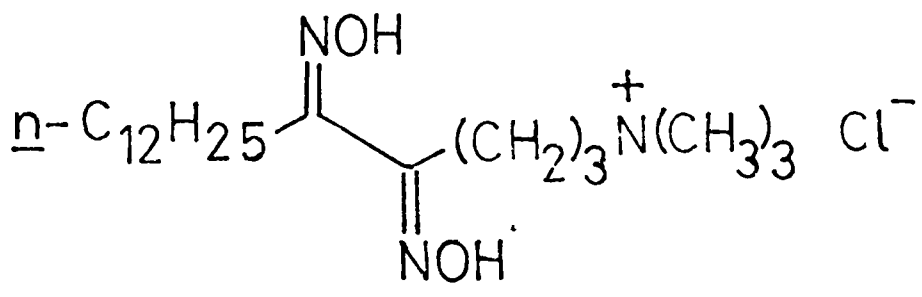
in order that any oxygen adduct may attain a square pyramidal, or octahedral stereochemistry depending on whether a co-ordinated solvent molecule is involved

(f) the synthetic route to any such functionalised surfactant should be flexible in order to enable variation of the metal-ion binding site within the micelle.

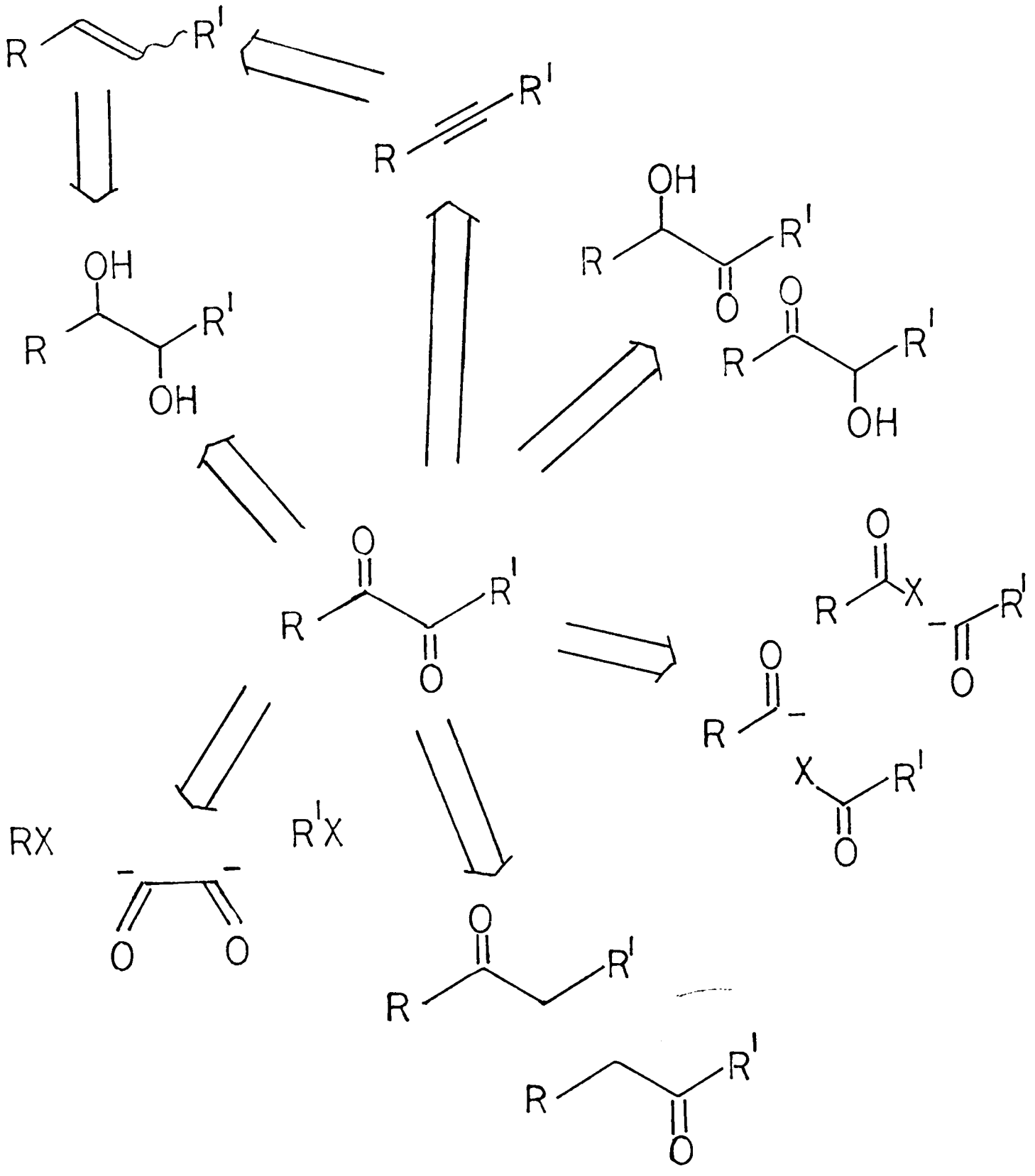
These criteria suggest that (18) and (19) are possible objectives. The choice of (19) was attractive since substantial literature is available on the binding of various transition metal-ions to α-dioximes.[189-191] Additionally a number of reversible dioxygen adducts[192] and vitamin B_{12} models[193] have employed the α-dioxime chelate system.



(18)



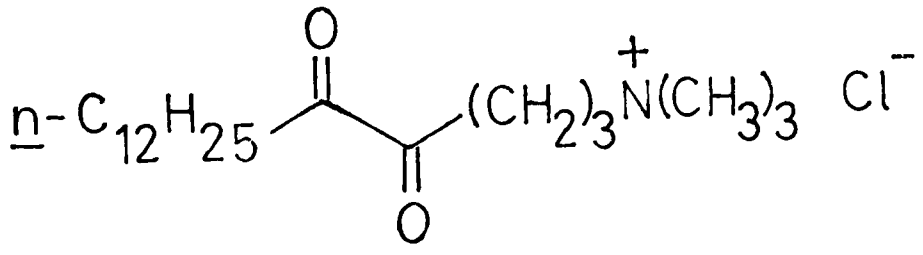
(19)



Scheme 2. Retrosynthetic procedure for an unsymmetric diketone ($R \neq R'$) as a model for (20)

2.2 Synthetic routes

The most obvious synthetic precursor is the diketone (20).



(20)

Surfactant (20) can be derived in a number of ways by retrosynthetic analysis, as shown in Scheme 2. Whilst a number of routes are possible, several of those shown require new synthetic methods or extensions of existing methods. Any proposed synthesis needed to be

(a) as short as possible

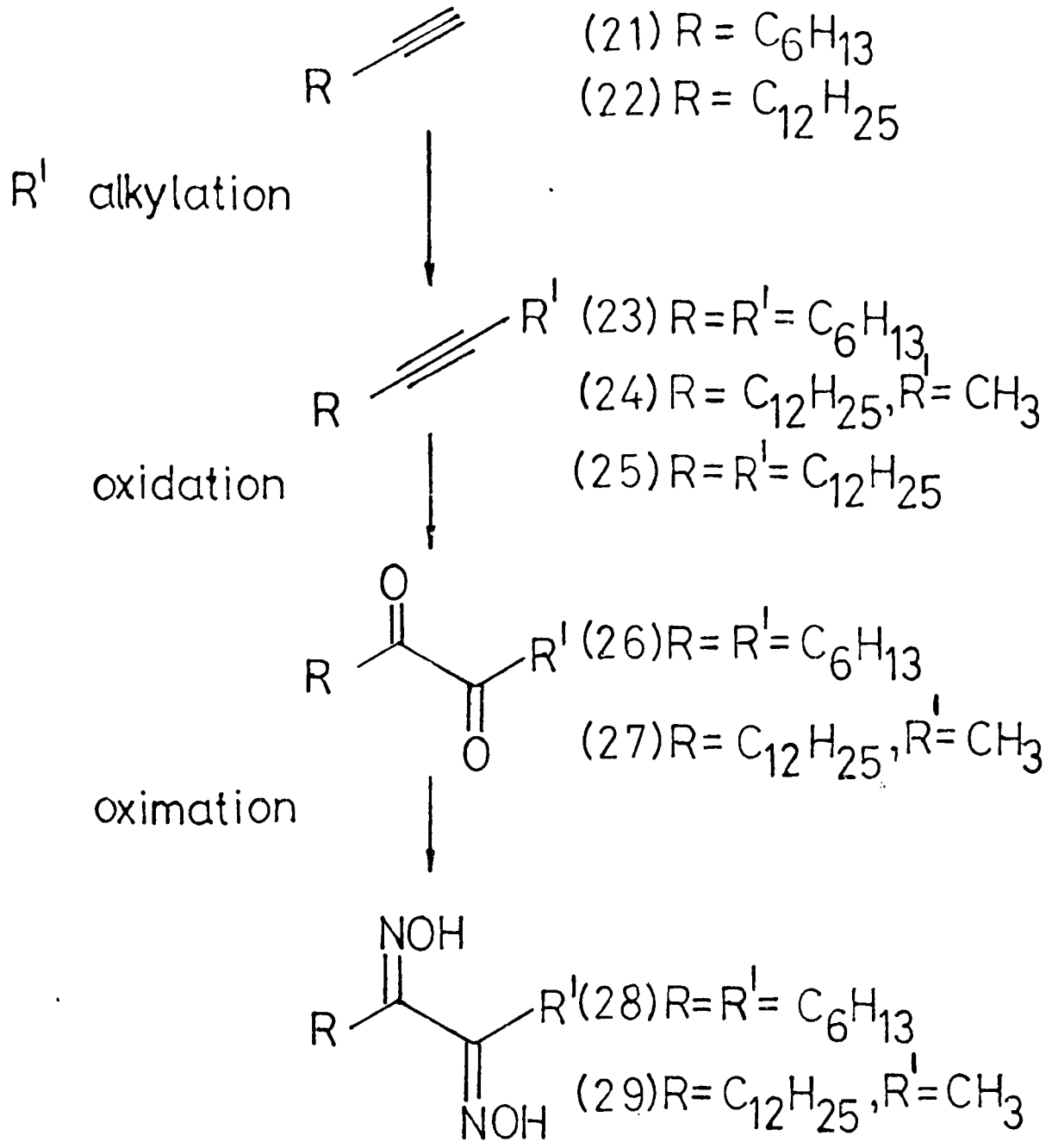
(b) amenable to the introduction of a long alkyl chain, whilst taking into account the reactivity of the prospective binding site and the quaternary centre

and (c) sufficiently versatile that the position of the binding site within the surfactant could be varied.

2.3 Synthetic work

2.3.1 Simple α-diketones

By considering the retrosynthetic plan shown in Scheme 2 the preparation of a α-diketone from a disubstituted



Scheme 3. Synthetic strategy for the preparation of α-dioximes (11) and (12) from alkyne precursors

alkyne was felt to be the most promising route since

(a) methods for the preparation of disubstituted alkynes are well documented[194]

(b) a number of reagents are available for the transformation of alkynes to diketones e.g. N-bromosuccinimide,[195] potassium permanganate,[196] thallium nitrate,[197] ozone[198]

and (c) if the initial attempts to oxidise an alkyne were unsuccessful, reduction to an alkene could be effected and other synthetic methods then employed.

The two α-diketones selected were (26) and (27), as shown in Scheme 3.

The synthesis of 7-tetradecyne (23) was particularly attractive since this could be used as a synthon for 1-tetradecyne (24) by using the isomerisation method of Brown.[199] The preparation of 1-octyne by alkylation of sodium acetylide in liquid ammonia with n-hexyl bromide,[200] gave a colourless liquid, which was found to be 80% 1-octyne (21) and 20% hexyl bromide by n.m.r. analysis. The desired alkyne (21) was obtained pure, in 37% yield, by refluxing the crude product with thiourea in dimethyl-formamide. This procedure removes the alkyl bromide as as the thiouronium salt, which was insoluble in diethyl ether, the extraction solvent. Further alkylation of (21)

under the same conditions with n-hexyl bromide, gave 7-tetradecyne (23), in modest yield (25%). Whilst the yield of (23) was only 9% over two steps employed, sufficient quantities were obtained.

Having successfully prepared 7-tetradecyne (23) the preparation of 1-tetradecyne by isomerisation with potassium 3-aminopropylamide was then attempted. Brown has shown that an easy internal-to-terminal migration of the alkyne could be obtained using potassium 3-aminopropylamide in 3-aminopropylamine at 0°C in 2-10 minutes[199a] i.e.

$$H(CH_2)_mC{\equiv}C(CH_2)_nH \xrightarrow{\text{isomerise}} H(CH_2)_{m+n}C{\equiv}CH$$

A preparation of 1-tetradecyne by this method was not realised however. It was found the yield of 1-tetradecyne was 10% at best (as analysed by n.m.r.), although a number of attempts were made, including the conditions used by Brown which previously produced 1-tetradecyne in 89% yield.

Numerous attempts were made to prepare 1-tetradecyne following procedures described in the literature for other alkynes.[194,201-205] Low yields were obtained in all cases. Adaptation of the method of Beckmann *et al.*,[206] however, using a solvent mixture of tetrahydrofuran and hexamethylphosphoramide gave 1-tetradecyne in 60-70% yield on a 25 mmol scale.

Optimisation of the reaction gave 90% yields of 1-tetradecyne routinely on a 250 mmol scale, using 1:1($^{v}/_{v}$)tetrahydrofuran-hexamethylphosphoramide as solvent and 0.5 equivalent excess of lithium acetylide at 0°C. The product obtained, on distillation, gave 1-tetradecyne, 97% pure by g.l.c., containing no isomeric allene or 2-alkyne, by i.r. or n.m.r. analysis. The only other product obtained from the reaction, albeit in 2-3% yield, was the disubstituted alkyne 13-hexacosyne (25), isolated from the distillation residues by extraction with hot ethanol, as a white crystalline solid.

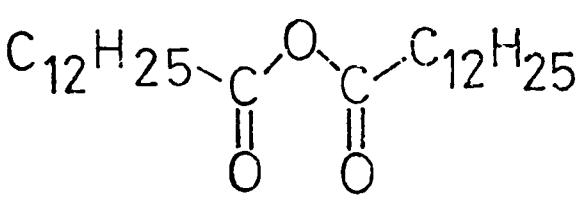
The preparation of 2-pentadecyne (24) was achieved in 95% yield by quenching 1-lithio-1-tetradecynide with excess methyl iodide, at -70°C, using similar conditions established for the preparation of 1-tetradecyne. Quenching 1-lithio-1-tetradecynide at higher temperatures e.g. 0°C, gave 60% of 2-pentadecyne with 40% recovery of 1-tetradecyne. Again no isomeric alkynes or allenes were detected by i.r. or n.m.r. in the distilled 2-pentadecyne. Since this method of alkyne preparation was so successful, the preparation of 7-tetradecyne was reinvestigated and the overall yield improved to 60%.

Attempts to prepare the corresponding diketones, tetradecan-7,8-dione (26) and pentadecan-2,3-dione (27), were then investigated. Oxidation of 7-tetradecyne with ruthenium tetroxide, prepared <u>in situ</u> by reaction of sodium

metaperiodate with ruthenium dioxide,[207] afforded a yellow oil in 70% yield which was a mixture of the desired diketone (26), 10% and starting alkyne (23), 90% by n.m.r. analysis . Given this poor yield, attention was turned to the ozonolysis of alkynes. Criegee[208] had shown that modest yields of carboxylic acid derivatives and α-dicarbonyl compounds could be obtained on ozonolysis of alkynes. Recent studies by Bailey et al.,[209] Ohloff et al.[210] and Yang have shown that α-diketone may be obtained in good to excellent yields, depending on the solvent e.g. ethyl acetate, methanol, dichloromethane, and quenching agent e.g. potassium iodide, triphenyl phosphine, tetracyanoethylene, employed. A method adapted from the work of Bailey and Ohloff[209,210] i.e. ozonolysis in methanol at -30°C with sodium iodide work-up, gave a low yield of a bright yellow product. I.r. analysis indicated thatan α-diketone ($1715cm^{-1}$) and an ester ($1740cm^{-1}$) were present, and n.m.r. analysis indicated a 1:1 mixture of tetradecan-7,8-dione (26) and methyl heptanoate. The method of Yang i.e. ozonolysis in ethyl acetate in the presence of tetracyanoethylene,[211] also gave a low yield of (26) accompanied by alkyne decomposition products. Adaptation of Criegee's conditions[208] i.e. ozonolysis at -25°C using 4:1($^{v}/_{v}$)carbon tetrachloride-glacial acetic acid and quenching at low temperature with sodium iodide in acetic acid, gave a bright yellow product. Recrystallisation from methanol gave tetradecan-

7,8-dione, as lustrous yellow plates, in 48% yield.

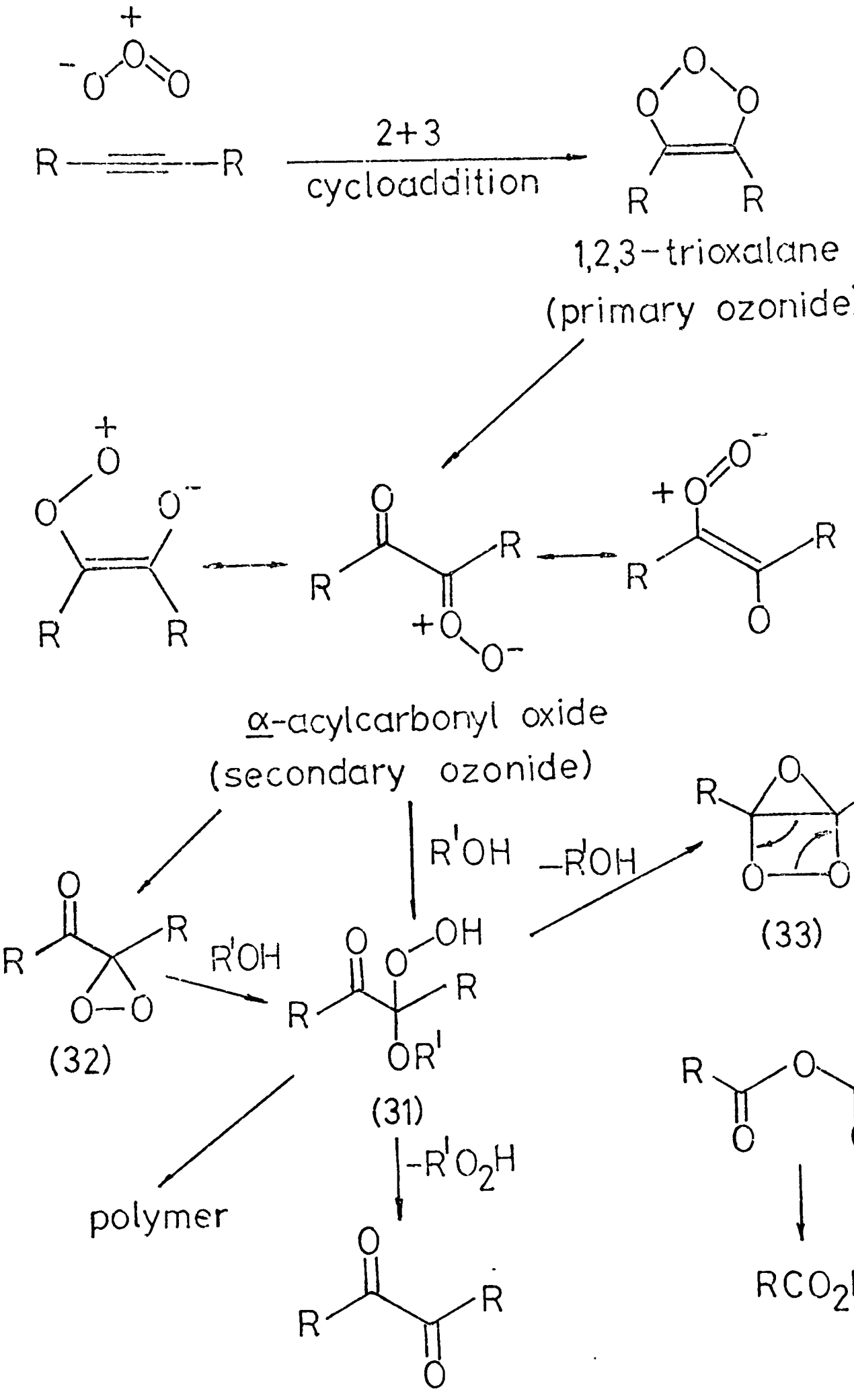
Ozonolysis of 2-pentadecyne, under the same conditions given above, gave a yellow, low-melting solid, for which i.r. analysis indicated the presence of an anhydride (1820 cm^{-1}) and an α-diketone (1715cm^{-1}). Initial attempts to separate the components by chromatography were unsuccessful. Both components were however separated by fractional crystallisation from dichloromethane. The anhydride, obtained as fine white platelets, was identified by mass spectrometry, n.m.r. and melting point as the known tridecanoic anhydride (30).



(30)

The yield and relative ratio of α-diketone (27) and anhydride (30) were found to be dependent on the concentration of starting alkyne. Optimum conditions using 2g of (24) in 25 ml of solvent gave a 70% yield of a ca. 4:1 mixture of (27) and (30). Other conditions which were explored were found not only to decrease the yield of the mixture of (27) and (30) but decrease the ratio of (27):(30).

The formation of a diketone and an anhydride from the ozonolysis reaction can be accounted for by the general mechanism for a symmetrical disubstituted alkyne, as shown in Scheme 4. The most likely precursor for both the



Scheme 4. Possible intermediates in the ozonolysis of alkynes[208,211]

diketone and anhydride is (31), a solvent adduct of an α-acylcarbonyl oxide (which is a secondary ozonide). Into the solvent system studied in this investigation, the intermcdiate (31) is an acetoxy hydroperoxide, formed by addition of acetic acid to the ozonide. Intermediates such as (31) can be isolated from alkyne ozonylses as stable, crystalline products.[209] Another intermediate which could produce (31), by addition of solvent, is the dioxirane (32); however its lifetime is considered to be very short[212] ($\simeq 10^{-12}$s). The formation of anhydride probably occurs by thermal rearrangement and loss of peracetic acid; however the metastable trioxabicyclo[2,1,0]pentane (33) has been put forward as the anhydride precursor[211] and cannot be excluded on the basis of present evidence.

With the diketones (26) and (27) in hand the stereochemical species associated with the α-dioximes (28) and (29) were considered next. Such α-dioximes give rise to a number of geometrical isomers; for a symmetrical α-diketone three isomers are obtained, whilst four are obtained for an unsymmetrical α-diketone. A classic example in which the four isomers of an unsymmetrical diketone have been separated is that of (-)-(D)-camphorquinone. Such geometrical isomers are normally very difficult to separate efficiently, and their structural assignments require careful examination.[213] The structures of the four isomers of camphorquinone dioxime, α-, β-, γ-, δ-,

obtained by Forster, have recently been revised by Daniel and Pavia on the basis of their ^{1}H-n.m.r. spectra. The reassigned structures are shown in Figure 25.[214]

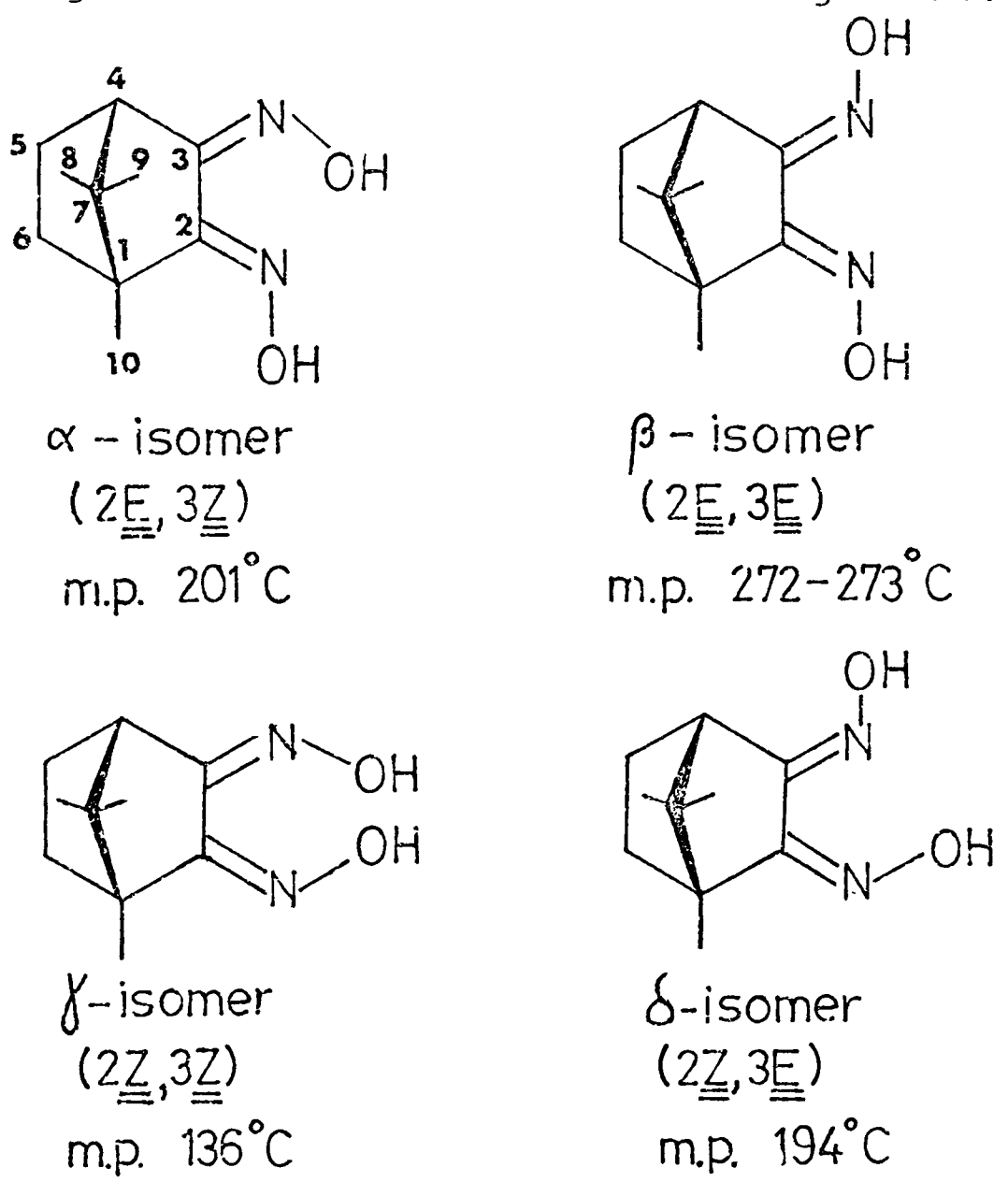
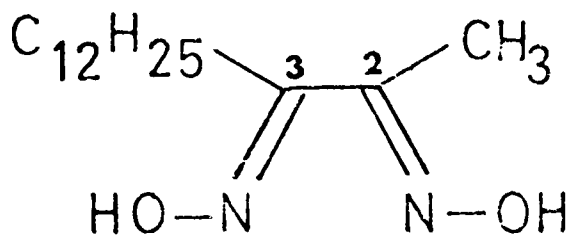


Figure 25. Geometrical isomers of (-)-(D)-camphorquinone dioxime

This method of n.m.r. structural assignment is based on the shielding effect caused by the nitrogen lone pair. The higher chemical shift of the C_4 methine proton signal or the C_{10} methyl protons reflect the proximity of the nitrogen lone pair. For example the α-isomer shows a high methine doublet, 2.38 p.p.m., and a low C-10 methyl signal, 1.31 p.p.m., whereas the δ-isomer shows a methine

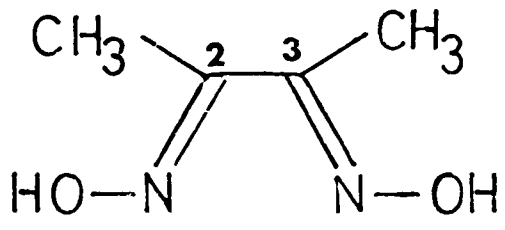
signal at 3.07 p.p.m. with a methyl signal at 0.99 p.p.m. Such assignments have been verified by recent i.r., n.m.r. and X-ray structural studies.[215-217]

Diketone (27) was reacted with a slight excess of hydroxylamine to give a white solid. This product was examined by both ^{1}H- and ^{13}C-n.m.r. before and after recrystallisation, since dioxime isomers have previously been isomerised in refluxing solvents.[213] The ^{1}H-n.m.r. spectrum exhibited only one methyl resonance at 1.92 p.p.m. with two oxime hydroxyl resonances at 10.16 and 10.23 p.p.m., whilst the ^{13}C spectrum also exhibited only one oxime methyl signal at 9.1 p.p.m. and two oxime carbons at 152.2 and 156.5 p.p.m. No trace of any other peaks could be detected in these regions, even on recovery from refluxing methanol which might have produced thermal isomerisation. Thus n.m.r. indicated a single isomer was present rather than a mixture of isomers. The i.r. spectrum indicated that intermolecular hydrogen bonding was present, with a broad band at 3600-3300 cm^{-1}, rather than intramolecular bonding which would give a band between ca. 3200-3050 cm^{-1}.[215,217] This indicated that the α-dioxime (29) was of the (2E, 3E) configuration i.e.



(2E,3E)-(29)

Examination of the ^{13}C-, ^{1}H-n.m.r. and i.r. of (2E, 3E)-dimethylglyoxime (34)

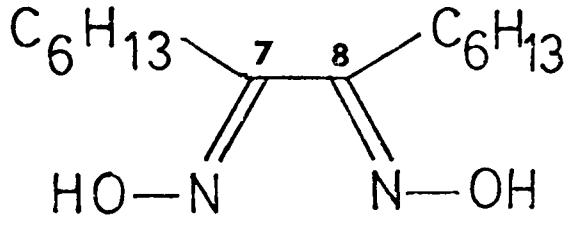


(34)

confirmed this assignment since the ^{1}H-n.m.r. exhibited a methyl resonance at 1.89 p.p.m. and an oxime hydroxyl at 10.85 p.p.m. The ^{13}C-n.m.r. spectrum had only two peaks, at 9.5 and 153.7 p.p.m. due to the methyl and the oxime carbons respectively. By comparison with (34) the two oxime ^{13}C resonances for (29) at 152.2 and 156.5 p.p.m. were assigned to the C_2 and C_3 atoms in the dioxime (29) respectively. The i.r. spectrum of dimethylgloxime (34), which has the well-defined (2E, 3E) configuration, showed only a band due to intermolecular hydrogen bonding from 3600-3290cm^{-1}, similar to that for (29).

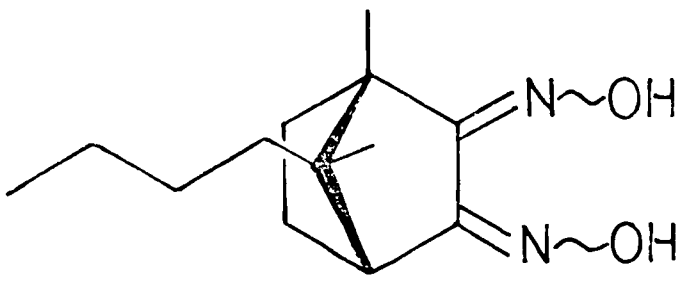
With the dioxime (29) in hand the preparation of dioxime (28) was attempted. Again (26), on reaction with a slight excess of hydroxylamine, gave a white material, exhibiting one oxime hydroxyl resonance in the ^{1}H-n.m.r., at 11.18 p.p.m., both before and after recrystallisation. The product obtained was small white crystals and melted at 178-181^{o}C with decomposition. The i.r.

spectrum again showed only a band at 3610-3300cm^{-1}, indicative of the presence of intermolecular hydrogen bonding. Once again this evidence showed that the α-dioxime (28) had the (7E,8E) configuration as below

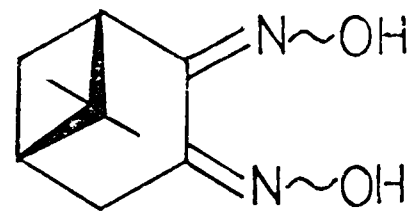


(28)

Thus only the (E,E)- isomers were obtained for oximes (28) and (29). The (E,E)- isomer may be thermodynamically favoured with respect to the other isomers. This assignment is fully supported by recent work of Nakamura et al.[215] with the asymmetric dioximes (35) and (36)



(35)



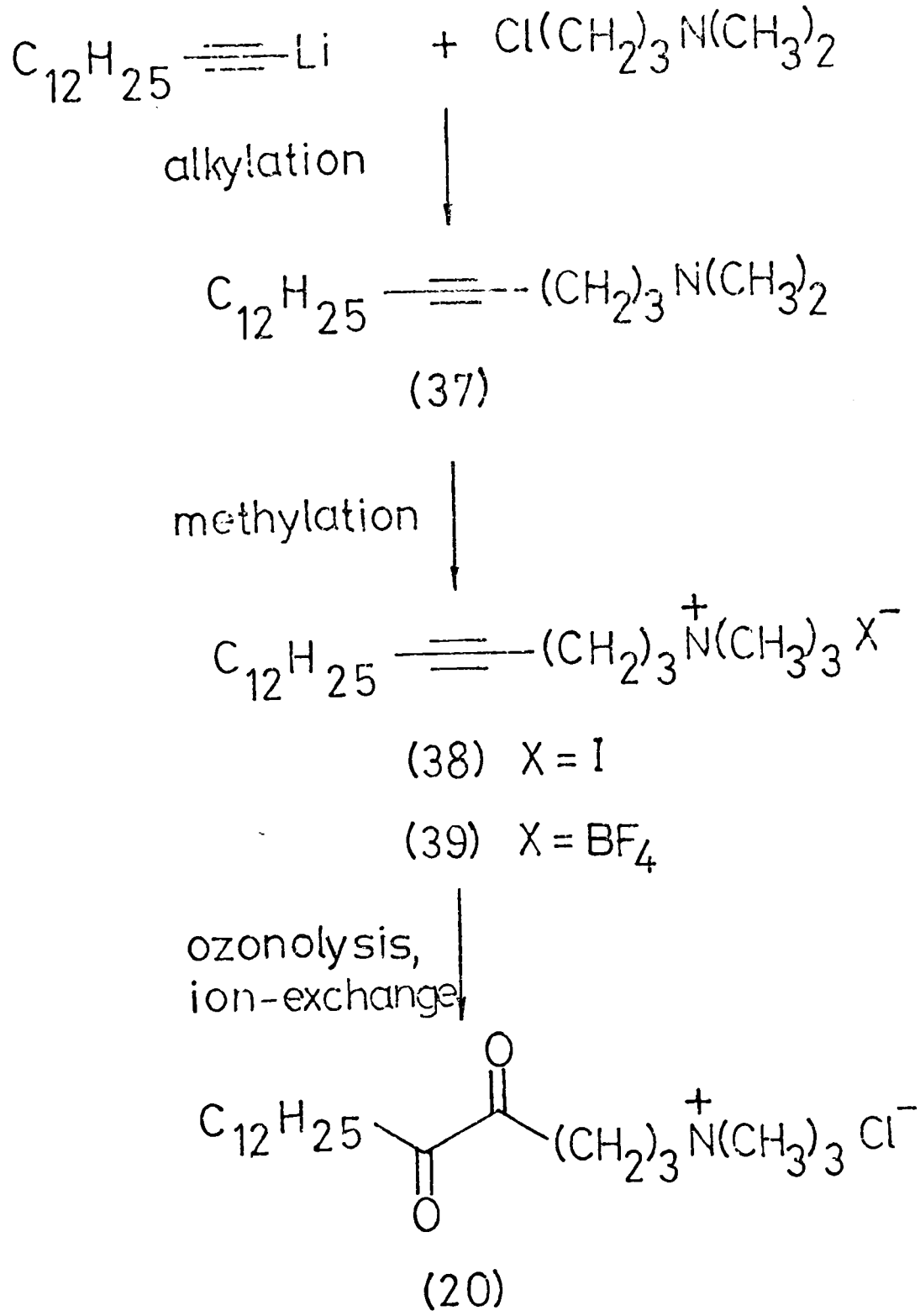
(36)

Attention was now turned to the synthesis of (20).

2.3.2 Functionalised diketones

2.3.2.1 Linear synthetic attempts using alkynes

Using the methods already established the proposed preparation of (20) is shown in Scheme 5. Since N,N-dimethylamino-3-chloropropane decomposes at room temperature,



Scheme 5. Prospective synthesis of (20) via ozonolysis of a quaternary ammonium alkyne (39)

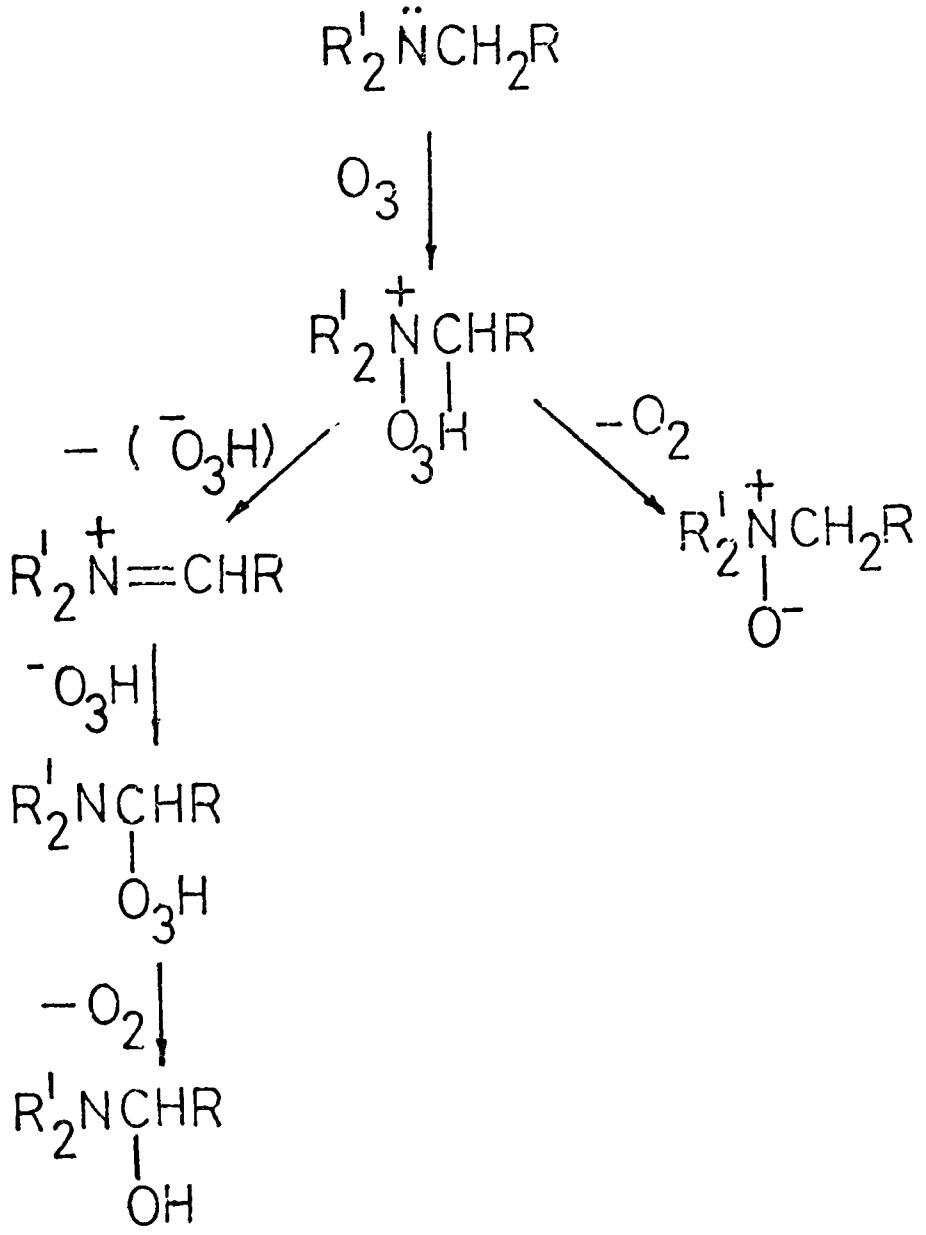
this material was stored at -30°C under nitrogen and checked by n.m.r. before use. The desired (37) was obtained in ca. 40% yield (by n.m.r.), by the reaction of 1-lithio-tetradecynide with (19) at 0°C in tetrahydrofuran - hexamethylphosphoramide. (37) was not isolated pure but immediately methylated after evaporation of the crude reaction mixture, producing (38) as a white crystalline material, in 21% yield after recrystallisation from acetone-hexane.

With (38) thus prepared, its ozonolysis to the desired diketone (20) was attempted. Since ozonolysis of the iodide (38) produces iodine by oxidation, the surfactant was converted into the crystalline tetrafluoroborate (39) by ion-exchange. To assess the sensitivity of a quaternary ammonium function towards ozone the surfactant (40) was prepared by ion-exchange of cetyltrimethylammonium chloride.

$$C_{16}H_{33}\overset{+}{N}(CH_3)_3 \quad BF_4^-$$

(40)

This compound on ozonolysis, using either dichloromethane-tetracyanoethylene or carbon tetrachloride-glacial acid conditions, was recovered in ca. 90% crude yield. Thus it appeared that the quaternary ammonium group in (40) was stable to ozonolysis conditions previously employed in preparing (26) and (27).



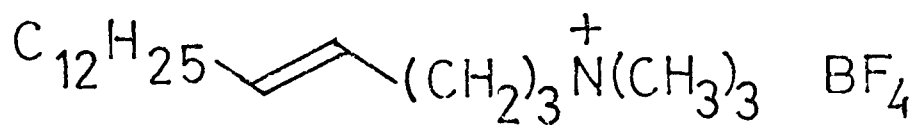
Scheme 6. Reaction of ozone with tertiary amines, according to Bailey et al.[218]

A number of attempts to prepare (20) from (39) by ozonolysis were uniformly unsuccessful. Analysis of the reaction product by t.l.c. indicated a number of products (>5) were present. N.m.r. analysis showed that the quaternary ammonium functionality was absent, and i.r. indicated the possible presence of a carboxyl functionality on account of broad bands occurring at 3600-3200 cm^{-1} and 1730-1710 cm^{-1}. From this it appeared that fragmentation to carboxylic acids, rather than a diketone, had occurred to (39) on ozonolysis. Tridecanoic acid was identified in the product, albeit in modest yield, by comparison of its n.m.r. with an authentic sample. No other products could be identified.

Ozonolysis of amine (37), isolated by column chromatography, again gave a large number of products, even when a stoicheometric amount of ozone was used. The decomposition of (17) on reaction with ozone can be explained by an electrophilic attack of ozone on the amine, followed by decomposition of this amine-ozone adduct. After completion of this work, Bailey et al. published results on the ozonolysis of tertiary amines,[218] in which the product distribution was in fact explained in terms of such an amine-ozone adduct. The major products obtained were due to intramolecular side-chain oxidation as shown in Scheme 6, together with a little amine oxide as a minor product. While such a scheme probably accounts for the

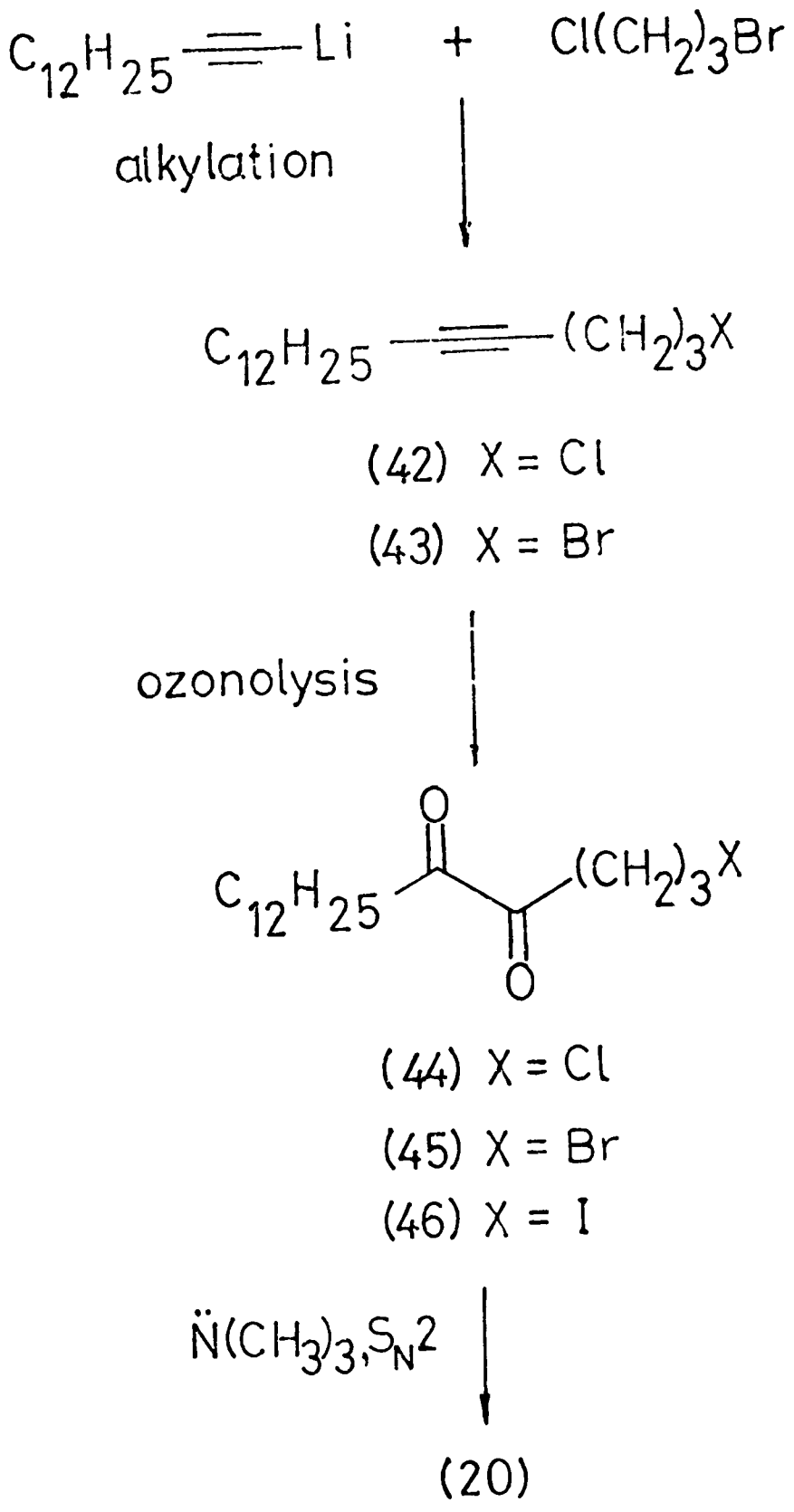
reaction of ozone with (37), such an explanation is not applicable to the reaction of (39) with ozone, when the removal of the quaternary head group was observed. No explanation for the failure of this latter reaction can be presented at present.

Since the alkyne (39) could not be used to prepare (20) attention turned to (41).



(41)

Alkenes have been converted into α-diketones by Sharpless using potassium permanganate in acetic anhydride.[219] The olefin (41) might alternatively be epoxidised and then transformed to (20), by hydrolysis and oxidation. (41) was prepared in 52% yeild from (39) by hydrogenation in absolute methanol using an optimum 10% by weight of Lindlar's catalyst. Use of less catalyst gave a much slower rate of hydrogenation, while greater than 10% catalyst gave over-reduced contaminants. The sensitivity of the quaternary ammonium group to Sharpless' conditions (potassium permanganate-acetic anhydride) was again tested with surfactant (40). Unfortunately (40) was found to be completely decomposed under such conditions. No trace of the quaternary head group was detected after reaction.



Scheme 7. Prospective synthesis of (20), by introduction of the diketone moiety followed by the quaternary head group

As in (40), (41) was also decomposed with permanganate-acetic anhydride. Since these conditions were not conducive to the preparation of (20), epoxidation of (41) was investigated.

Reaction of (41) with m-chloroperbenzoic acid gave 90% recovery after reaction in dichloromethane at 0°C for 2.5 hours and room temperature for 7 hours. The alkenic surfactant (41) was extensively decomposed upon reaction with m-chloroperbenzoic acid at 0° or 25°C for 2 hours. Reverting to conditions of refluxing (41) in dichloromethane caused decomposition to a mixture of products even on short reaction times e.g. 15 minutes. At this point routes involving quaternary ammonium compounds were abandoned.

An alternative synthesis of (20) is shown in Scheme 7, which still used the methods established for the synthesis of (26) and (27). As can be seen this synthetic method involves preparation of the α-diketone moiety, as in (42), followed by introduction of the quaternary ammonium group by nucleophilic displacement.

Initial attempts to prepare (42) by an alkylation procedure, at -70°C, employing 1-bromo-3-chloropropane and 1-lithiotetradecynide in tetrahydrofuran-hexamethylphosphoramide gave a 10% isolated yield of a 3:1 mixture of (42) and (43) but 90% based on the recovered starting alkyne. The yield of (42) and (43) was improved to 25% isolated yield, by numerous experiments under various conditions.

An initial suspicion that hexane, present in the reaction from generation of the lithioacetylide, was a detrimental influence was in fact found to be the case. Removal of all solvent from the lithioacetylide, in vacuo at 0°C, gave a grey material, which was immediately redissolved in 1:1 (v/v) tetrahydrofuran-hexamethylphosphoramide to give a homogeneous solution. Cooling to -70°C and addition of 1.5 equivalents of 1-bromo-3-chloropropane as a neat liquid, gave a ca. 3:1 mixture of (42) and (43) as found by ^{1}H-n.m.r. analysis (Figure 26).

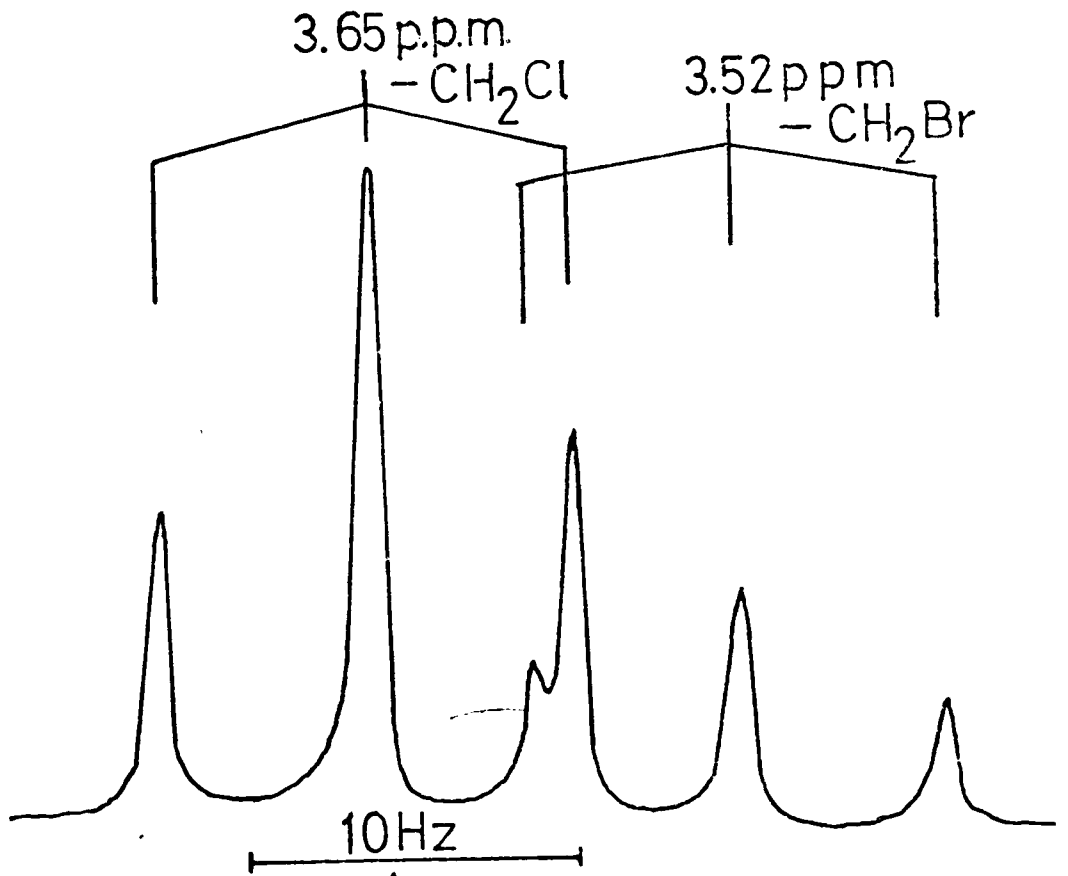


Figure 26. Features of 90MHz ^{1}H-n.m.r. for a ca. 3:1 mixture of (42) and (43), in $CDCl_3$

1-tetradecyne was recovered to the extent of 66%, and whilst the isolated yield of (42) and (43) was only 25%, the yield based on consumed acetylene was ca. 90%. Addition of 1-bromo-3-chloropropane at higher temperatures e.g. -30°C,

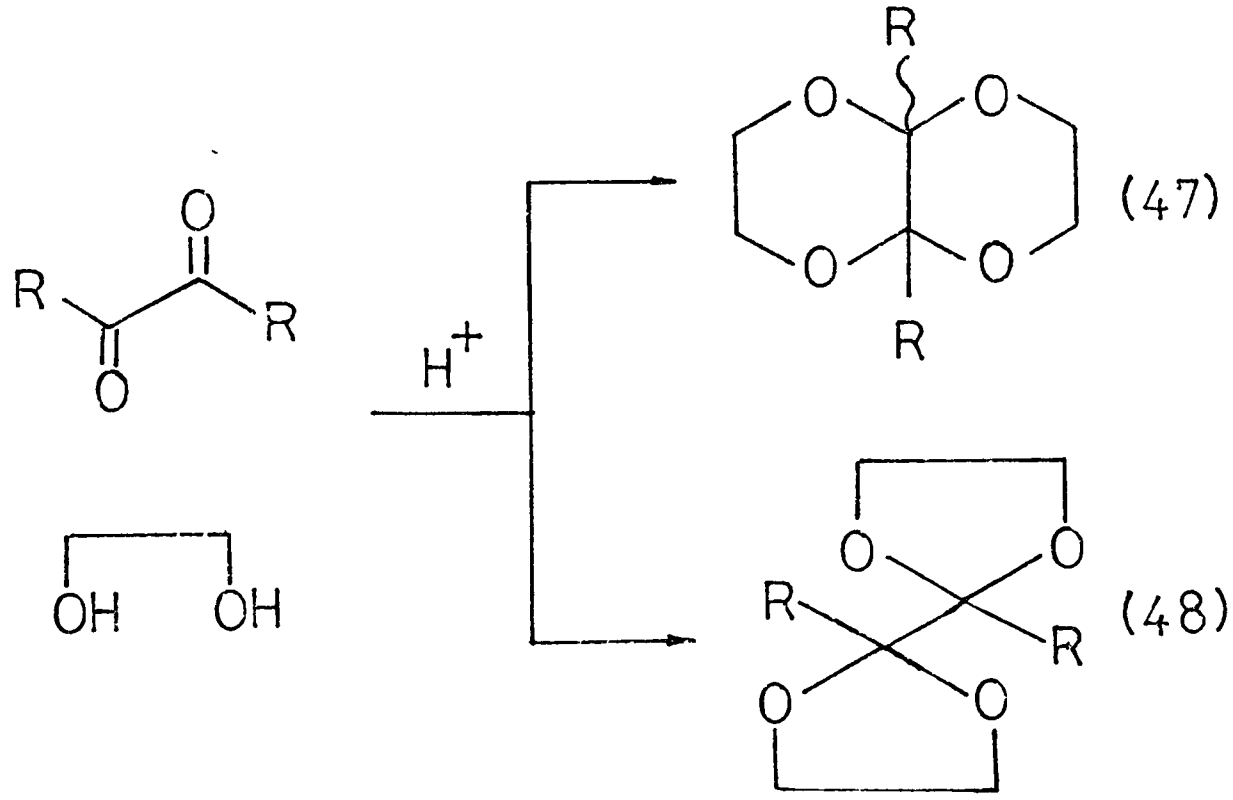
gave a lower isolated yield of a 2:1 mixture of (42) and (43).

On ozonolysis of the mixture of (42) and (43) a low melting, bright yellow solid was obtained. Mass spectrometry revealed that this solid was a mixture of (44), m/e 302 and 304 (M^+), (45) m/e 346 and 348 (M^+) and tridecanoic acid m/e 214 (M^+) and 197($M-OH^+$). In particular the peaks for (45) at m/e 346 and 348 were approximately 1:1 in intensity, in accordance with the natural isotropic ratio of ^{79}Br and ^{81}Br. The tridecanoic acid was easily removed from this crude reaction product by washing with caustic soda solution, to give a mixture of (44) and (45) as a yellow solid, melting at 41-46^{o}C in ca. 55% yield. N.m.r. analysis indicated again a ratio of (44):(45) of ca. 3:1, as observed for (42) and (43). The ratio of (44):(45) was found to be again dependent on the concentration of alkyne in the ozonolysis step. This phenomena was very similar to that previously observed in the preparation of (27); fortunately the effect was not as critical as previously seen for ozonolysis of (24), in terms of the yield of (44) and (45), since yields of ca. 50-60% were routinely obtained.

With the mixture of (44) and (45) available, nucleophilic displacement of the halogen atom in (44) and (45) with trimethylamine was attempted in a number of solvents e.g. ethanol, tetrahydrofuran, acetonitrile, but

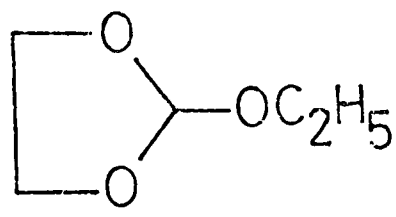
always gave recovery of the starting diketones. Thus attempts to prepare the more reactive iodoketone (46) were carried out. The conditions investigated however e.g. dimethyl sulphoxide, tetrahydrofuran, with 10 equivalents of sodium iodide, gave only displacement of the bromide, produced a mixture of (44) and (46) as a 3:1 ratio by n.m.r. analysis.

Protection of the diketone functionality was next investigated. In the reaction of α-diketones with ethylene glycol two isomeric products have previously been obtained,[220] as shown below

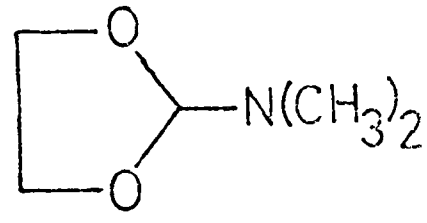


Whilst regeneration of ketones from ketals is easily accomplished, the α-diketone regeneration from either the tetraoxadecalin (47) or bisketals (48) had not been investigated. In an attempt to prepare the protected α-diketone in one isomeric form, preferably (48), it was

resolved to use the mildest conditions possible. Ketalisation agents (49)[221] and (50)[222]

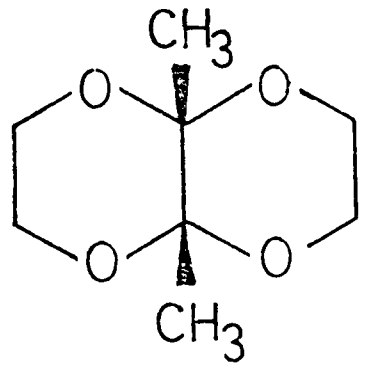


(49)



(50)

appeared to be ideal, since the by-products, ethyl formate and dimethylformamide could be removed by distillation from the reaction mixture. Reaction of the mixture of (44) and (45) with either (49) or (50) however, gave either recovery of starting materials or unidentifiable mixtures of products under varying conditions. To test the initial hypothesis (49) was reacted with butan-2,3-dione and gave only the cis-tetraoxadecalin (51) in 90% yield.



(51)

No trace of the isomeric bisketal could be detected in the n.m.r. spectrum, nor could any other product be seen by t.l.c. analysis. (51) was identified by its melting point and ^{1}H-n.m.r. which exhibited an AA'BB' multiplet.

(3.53 - 4.2 p.p.m.) as shown in Figure 27.

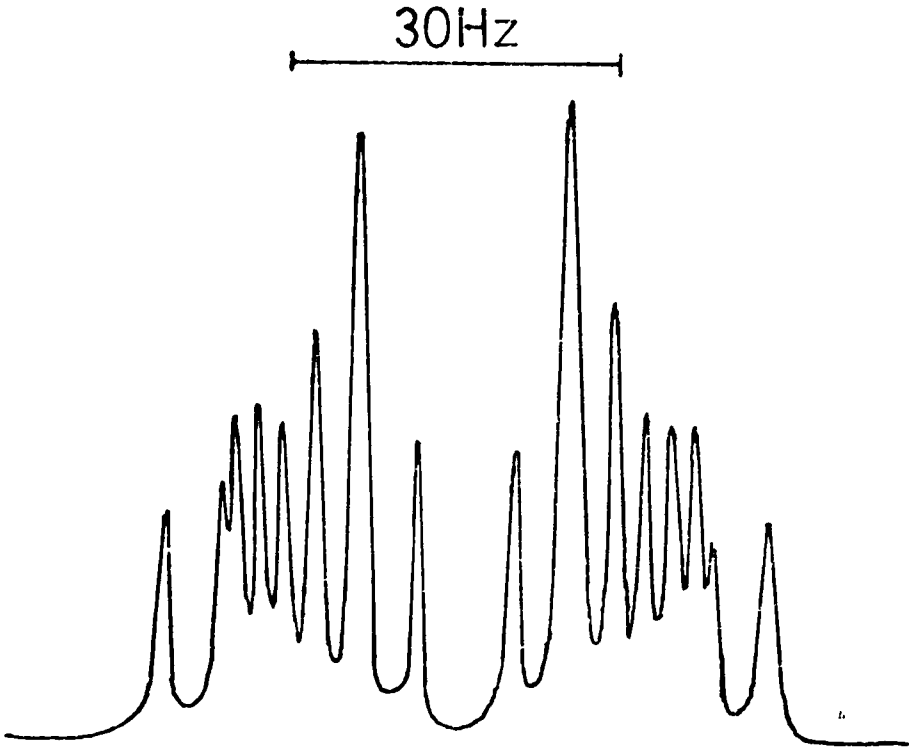
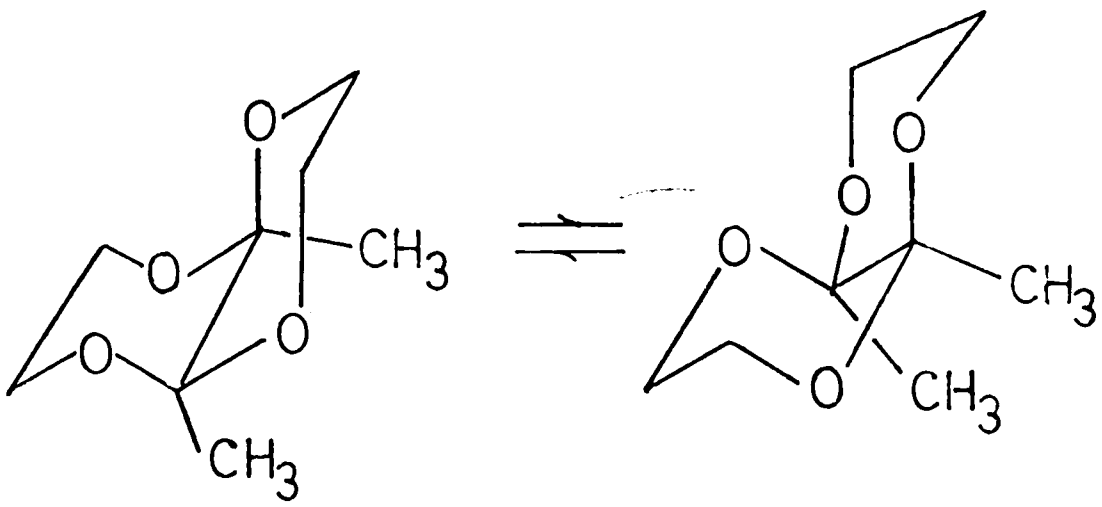
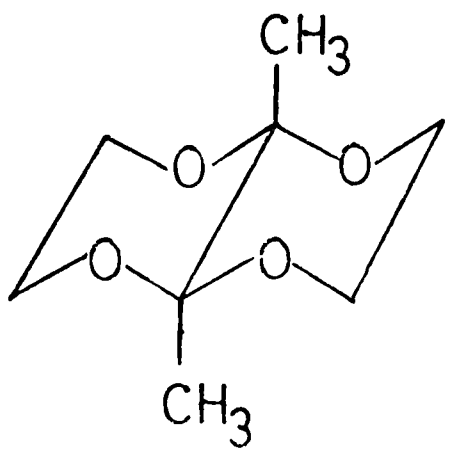


Figure 27. The AA'BB' multiplet (3.53 - 4.2 p.p.m.) exhibited in the 90MHz H-n.m.r. of (51) in $CDCl_3$

The cis-configuration was confirmed by the fact that the AA'BB' multiplet exhibited dynamic properties consistent with a flexible cis-configuration i.e.



rather than a "locked" trans-configuration (52).

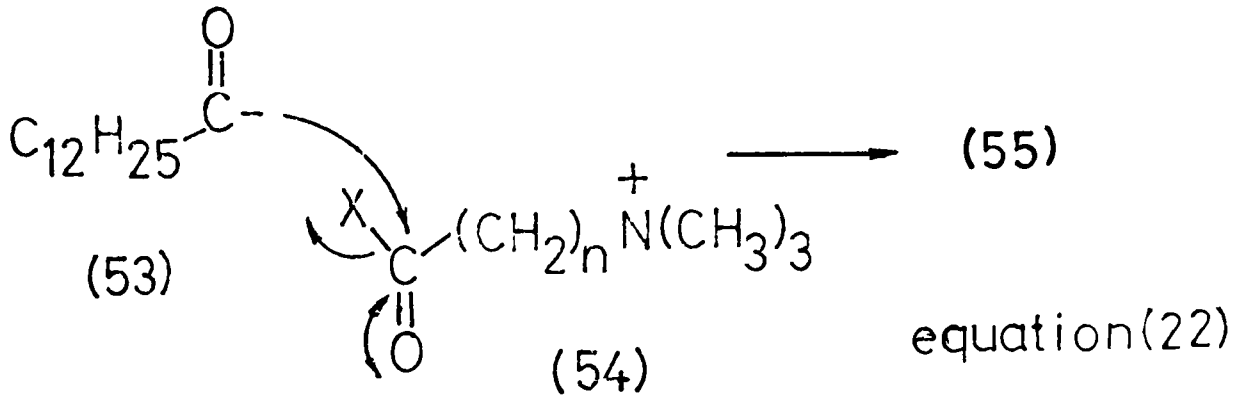


(52)

The analysis of the dynamics of this "flipping" between enantiomeric forms of (51) is discussed in more detail in section 2.6.

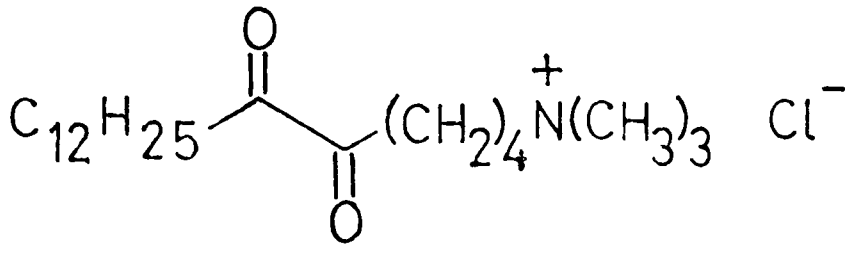
2.3.2.2 Convergent synthetic attempts using umpolung reactivity

A convergent synthesis of (20) was now attempted, as shown in equation (22)



equation(22)

(53) is an "umpolung" synthon in which the aldehyde is transformed, by a masked functionality, into a nucleophilic reagent.[223] Recent years have seen a great deal of research into the design and use of such umpolungs in organic synthesis, and thus a number of masked functionalities, equivalent to (53) could be investigated e.g. metallated derivatives of 1,3-dithianes, enol ethers or aldimines.[224] In the synthesis of (20) a three carbon linkage between the carbonyl and quaternary ammonium groups had been chosen and found to be prone to fragmentation. To circumvent such problems (55) was chosen as an alternative target.



(55)

A four-carbon chain in (55) was employed because of the apparent sensitivity of its lower homologue (20) observed in previous work.

The first step involved methylation of (56) to form (57)

$$HO_2C(CH_2)_4NH_2$$

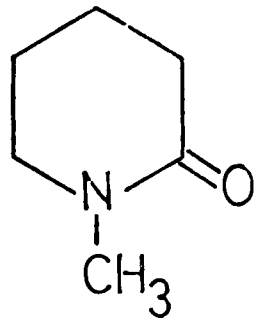
(56)

$$HO_2C(CH_2)_4\overset{+}{N}(CH_3)_3\ Cl^-$$

(57)

Optimum conditions i.e. a three-phase system of refluxing methyl iodide and (56) dissolved in 50% aqueous methanol, in the presence of sodium carbonate, for 10 days gave a 1:1 mixture of (57) and its methyl ester, in quantitative yield. Acid hydrolysis of the ester and removal of water gave a white solid containing 90% (57), contaminated with 10% of inorganic salts. Removal of the inorganic salts from the required (57) were only partially successful in that the purity of (57) was increased to ca. 95%. Purification of (57) was difficult due to its solubility characteristics with respect to the by-products from this synthetic method. (57) whilst being very soluble in water, was only sparingly soluble in ethanol or methanol and insoluble in many other solvents e.g. ether, acetonitrile and tetrahydrofuran. In an attempt to simplify the

preparation of (57), particularly in the work-up procedure, a method based on the hydrolysis of N-methylpiperidone (58) to (59) was attempted.



(58)

$HO_2C(CH_2)_4NHCH_3$

(59)

Previously (58) had been hydrolysed to (59) by refluxing with hydrochloric acid for five days;[225] it was found that on heating (58) in aqueous 6M hydrochloric acid, under nitrogen for 24 hours, complete hydrolysis had occurred. Removal of the water gave an oil which on cooling produced a beautiful crystalline solid. Two recrystallisations from anhydrous ethanol-diethyl ether gave the hydrochloride hydrate of (59) as fine white needles. The methylation of (59) with methyl iodide was then attempted. On refluxing with methyl iodide in a hetergeneous mixture of absolute ethanol and anhydrous sodium carbonate for 15 hours, (59) gave a quantitative conversion to ca. 1:1 mixture of (57) and its respective methyl ester. Hydrolysis of this mixture with 6M acid gave a red-brown solution, which after filtration and evaporation gave an unpleasant smelling red-brown paste, obviously still contaminated with iodine. Dissolution in warm distilled water, two charcoal decolourisations and evaporation gave a yellow-orange

solid which on dissolution in absolute methanol was applied to an ion-exchange column. Careful elution of the column with methanol (monitoring fractions with silver nitrate) and evaporation gave a white solid, which on recrystallisation from anhydrous ethanol-diethyl ether gave (57) as white crystals in 62% yield. Whilst such a preparation was laborious and tedious, the product obtained was homogeneous and free from inorganic contaminants. (57) was converted to the corresponding methyl ester (60) by esterification in methanol containing ether previously saturated with hydrogen chloride gas.

$$CH_3CO_2(CH_2)_4\overset{+}{N}(CH_3)_3 \quad X^-$$

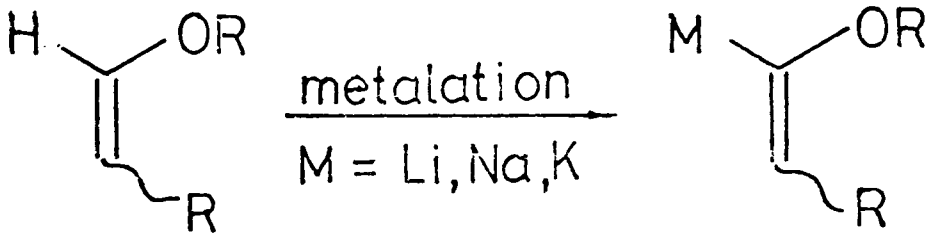
(60) X = Cl

(61) X = I

The counter-ion, chloride in (60), was changed to iodide for (61) since microanalysis and i.r. investigations showed that the chloride tenaciously held water. Again ion-exchange, eluting with methanol, provided a homogeneous, white crystalline material after recrystallisation from anhydrous methanol-diethyl ether.

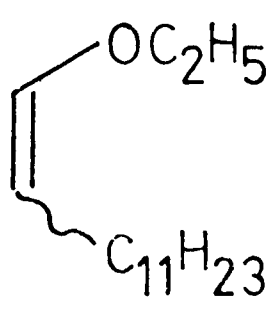
Attention was turned to the synthesis of a suitable "umpolung" reagent, containing a long alkyl chain. For the task in mind an acylation reagent (53) as shown in equation (22), was required. A number of suitable

functional groups which could be used for "umpolung" were available.[224] With the need to generate the α-dicarbonyl functionality, a particularly sensitive moiety, a very mild "unmasking" operation was required after the acylation step. Metalated enol ethers (62) were a particularly attractive proposition since enol ethers may be hydrolysed to carbonyl compounds under extremely mild conditions e.g. hydrogen chloride-saturated methanol.[226]

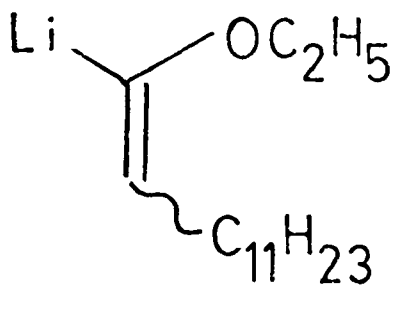


(62)

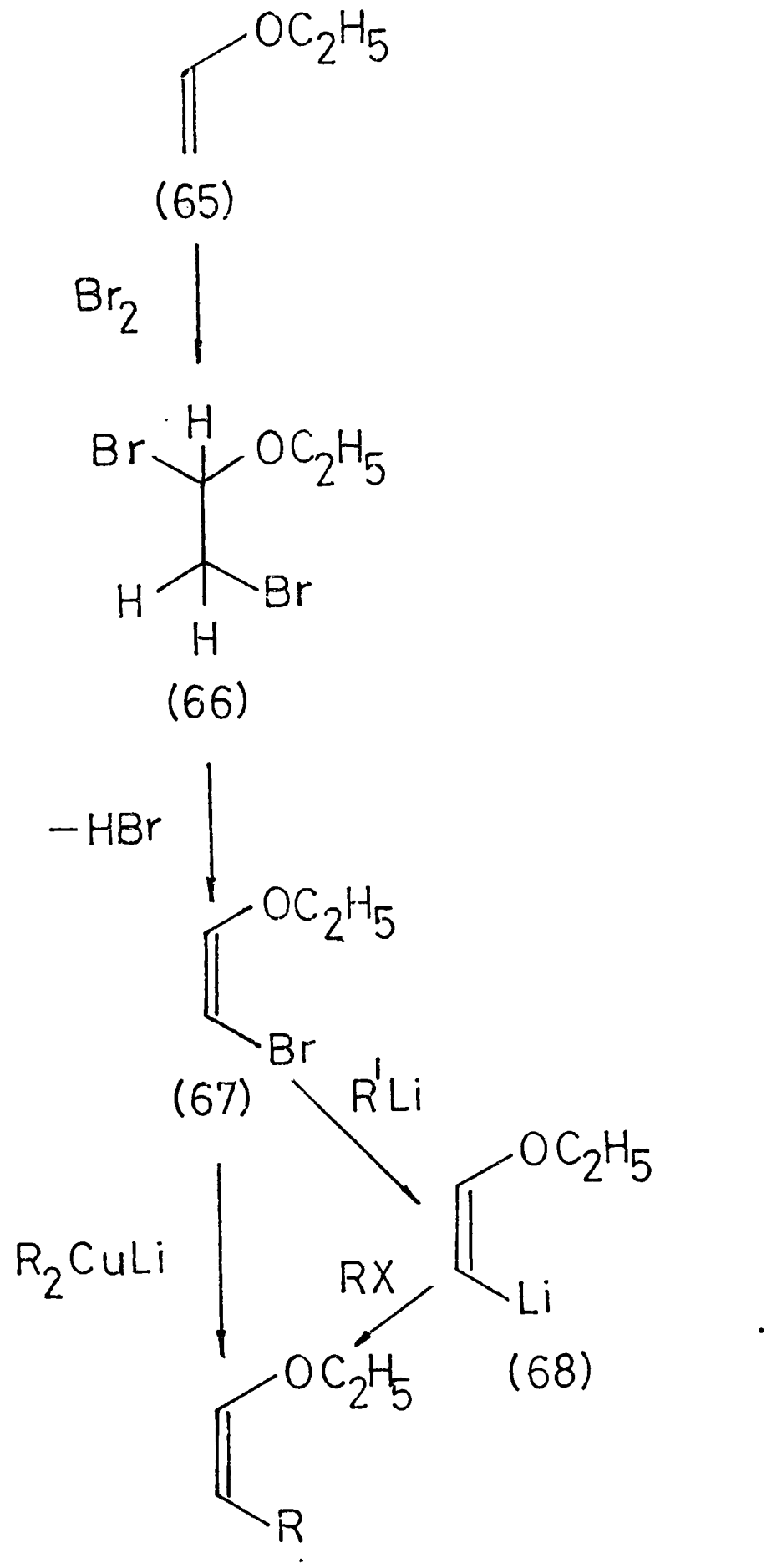
Baldwin et al. have shown that methyl or ethyl vinyl ethers could be quantitatively α-metalated with t-butyl lithium in tetrahydrofuran at 0°C.[226] The products exhibited excellent nucleophilic properties at low temperatures, with a variety of electrophiles e.g. ethyl iodide. For our purpose enol ether (63) was required, which on metalation would produce the required acylating agent (64)



(63)



(64)



Scheme 8. Synthetic scheme for preparation of long chain enol ethers from ethyl vinyl ether

A potential synthon for (63) was in fact ethyl vinyl ether (65) by the sequence of reactions shown in Scheme 8. This scheme through the intermediate (67) was attractive for two reasons. First the high reactivity of alkenyl halides towards organocuprates; several total syntheses of natural products have used this substitution reaction as a key step.[227] Alternatively halogen-metal exchange to the lithio derivative (68) and reaction with the electrophile RX could produce the enol ether.

Bromination of ethyl vinyl ether at -70°C gave an almost quantitative yield of the lachromatory dibromide (66). (66) exhibited a complex n.m.r. spectrum, as shown in Figure 28, due to the presence of two pairs of diastereotopic hydrogens, as shown in Figure 29.

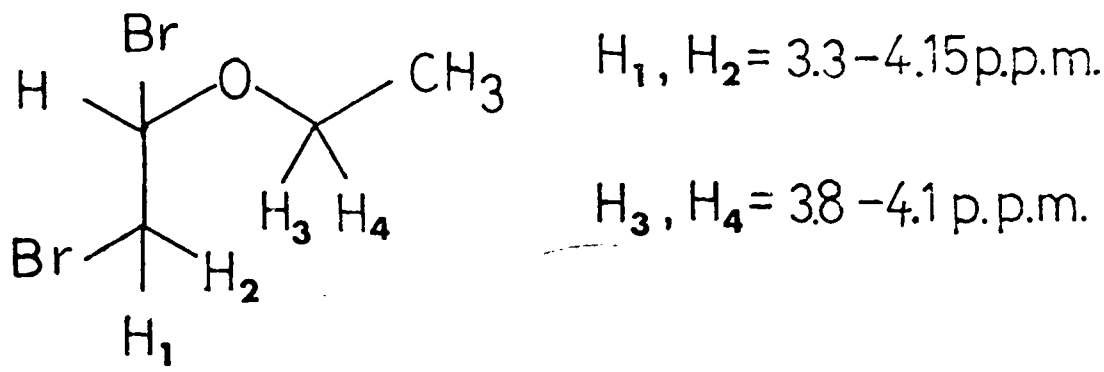


Figure 29. Diastereotopic protons in 1-ethoxy-1,2-dibromoethane (66)

The dibromide (66) which eliminated hydrogen bromide on standing, was used immediately to prepare (67). An initial attempt of dehydrobromination in refluxing N,N-dimethylaniline, according to the literature, gave a low yield of a mixture

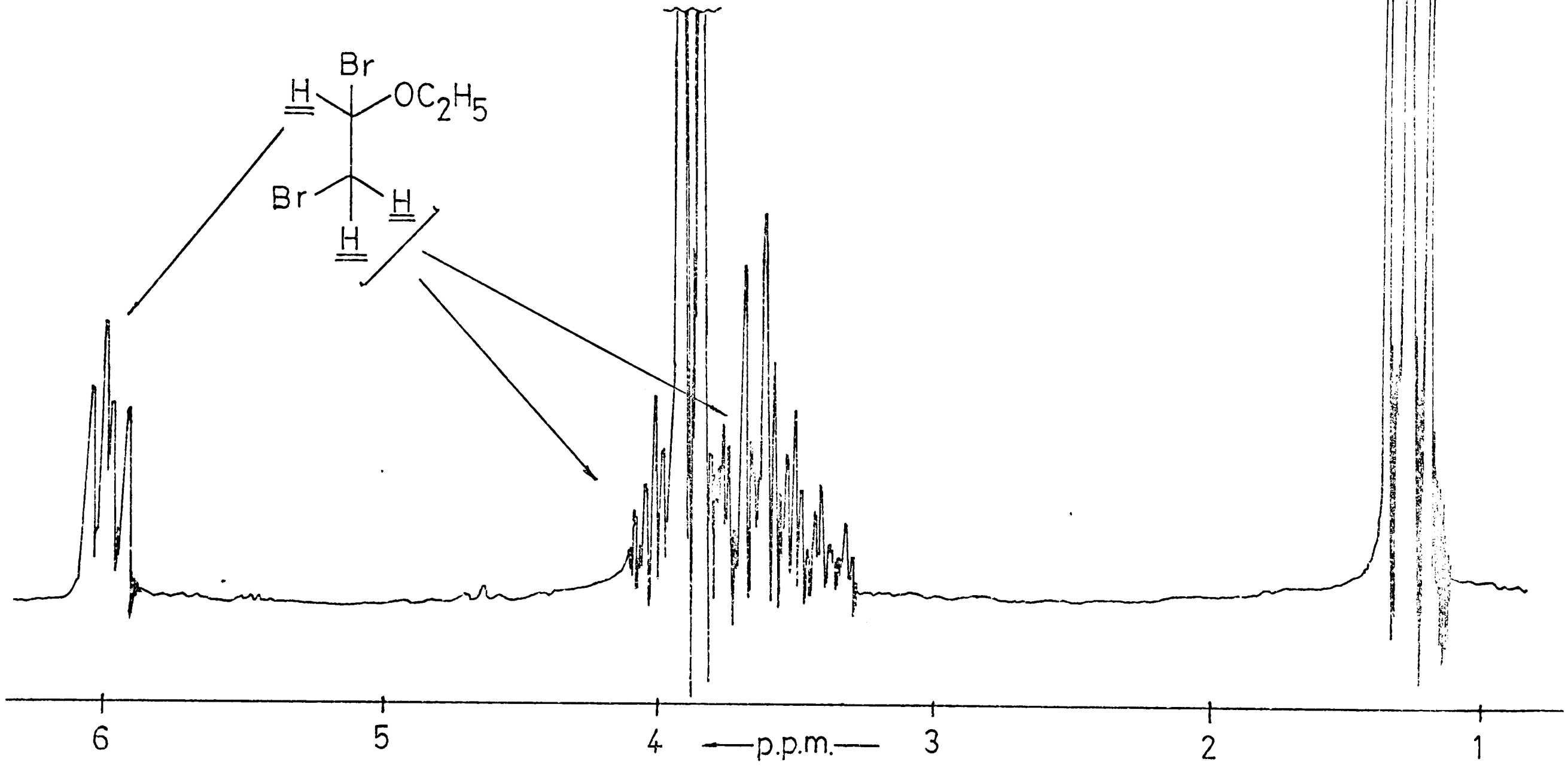


Figure 28. 90MHz H-n.m.r. spectrum of (66), illustrating the presence of diastereotopicity

of the E- and Z-isomers of (67).[194] However reverting to the much milder conditions of refluxing triethylamine gave the desired alkenyl bromide (67) in 90% yield. N.m.r. analysis of the product indicated that the Z-isomer had been formed in 90% yield. A sample, after bulb-to-bulb distillation, when carefully analysed by g.l.c. indicated a 96:4 ratio of the Z:E-isomers. The high degree of stereoselectivity demonstrated was totally unexpected, since previous preparations of (67) had always given a mixture of the E- and Z-isomers. After completion of this work, Schlosser published a similar method of preparing (67), using tributylamine,[228] but obtained a mixture of isomers, which were separated by preparative g.l.c.

With the enol ether (67) now available the alkylation *via* organocuprate coupling was attempted.

Examination of a large number of organocuprate reactions indicated a number of limitations:-[227]

(a) the need to use large excesses of organocuprates, $R_2Cu(I)Li$, to achieve complete conversion to product

(b) the homogeneity of the reaction media

and (c) the stability of such cuprates containing sensitive alkyl functionalities.

Some of the limitations shown above have recently been substantially improved by the use of mixed cuprate (I) reagents, (Het)RCuLi, allowing selective alkyl group

transfer,[227b] where (Het) is a heteroatom group e.g. t-butoxide, thiophenoxide, phenolate, and the use of soluble adducts of cuprous halide e.g. cuprous bromide-dimethyl sulphide complex.[229]

A number of initial attempts to prepare organocuprates using "purified" cuprous salts were unsuccessful due to substantial impurities in such salts. To circumvent this the soluble complex of cuprous bromide with dimethyl sulphide was prepared.[229] This adduct, very soluble in organic solvents, was used to generate lithium di(dodecyl)-cuprate, from dodecyl lithium, and reacted with the enol ether (67) at -70°C. On work-up it was found that no transfer of the dodecyl group to the enol ether had occurred. In fact a very high yield of n-tetracosane $C_{24}H_{50}$, was obtained by coupling of the alkyl function. From this preliminary experiment it appeared that on reaction with the enol ether the preferred pathway was coupling of the alkyl functions rather than substitution of the bromine atom in (67). Efforts were then concentrated on using Posner's mixed heteroatom cuprates[227b] e.g. (69)

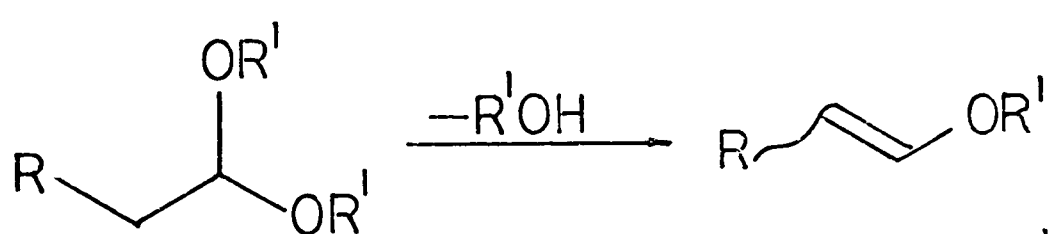
(ϕS)(n-Bu)Cu(I)Li (69)

Whilst (69) was effective in alkylation of model substrates, numerous attempts to alkylate (67) with (69) were uniformly unsuccessful. Very high recoveries of the enol ether (67) (90%) were obtained in all cases.

Another approach to the alkylation of (67) was by metal-halide exchange with e.g. n-butyl lithium, to give

(68), which was then subsequently alkylated to the required enol ether (63). All attempts to prepare (68) by such exchange and subsequent quenching with deuterium oxide were unsuccessful, even on prolonged reaction at -80°C for 4-5 hours with n-butyl lithium.

From these experiments it appeared that the enol ether (67) was unreactive under the conditions studied. Enol ethers have been previously prepared from acetals, by the elimination of an alcohol molecule by azeotropic distillation with acid catalysis,[230] as shown in equation (23)



equation (23)

Reaction of triethylorthoformate with n-dodecyl magnesium bromide, under optimised conditions gave (70) in 58% yield.

$$C_{12}H_{25}CH(OC_2H_5)_2$$

(70)

It was found that a slow addition of orthoformate at 0°C was essential in order to prevent the formation of n-tetracosane, by self-coupling of the Grignard reagent. The diacetal (70) was found to be very sensitive to traces of acid in distillation. Traces of acid when present

produced a mixture of the enol ether (63) and (70).
To prevent such an elimination of ethanol on distillation, the crude (70) was extensively washed with aqueous sodium bicarbonate solution and the distillation apparatus rinsed with 10% aqueous ammonia and tetrahydrofuran and dried for 3 hours. Using such a procedure the diacetal (70) was distilled satisfactorily as a clear colourless liquid, which exhibited an AA'BB' multiplet (3.3 - 3.85 p.p.m.) in its ^{1}H-n.m.r. spectrum, as shown in Figure 29.

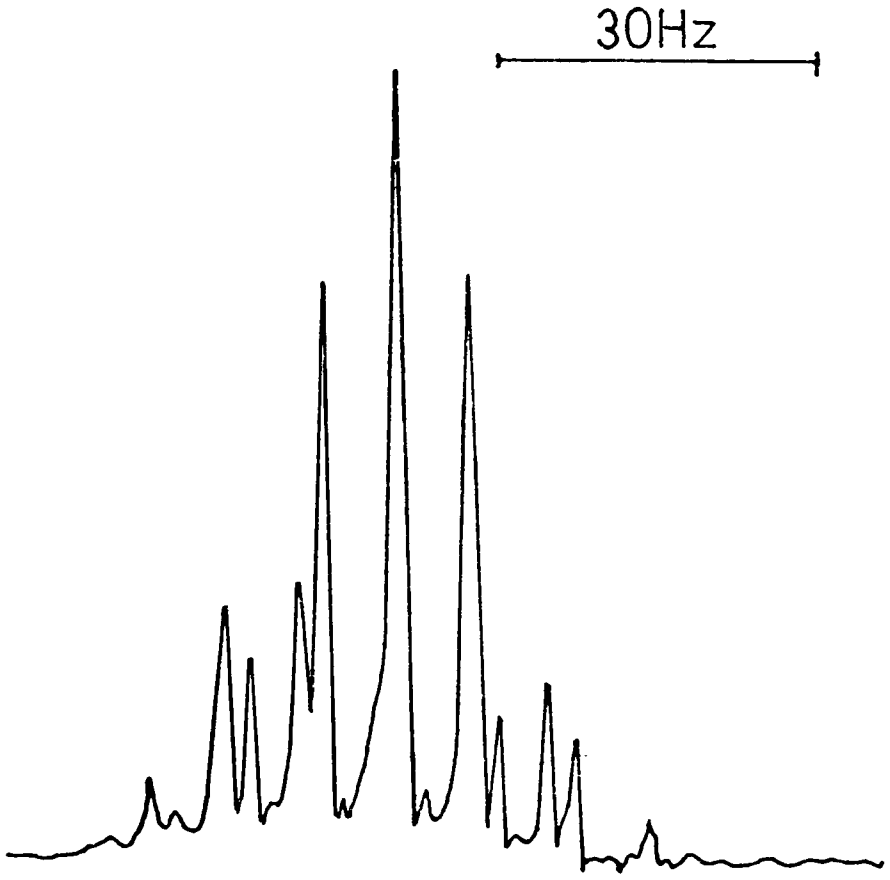


Figure 29. AA'BB' multiplet, 3.3 - 3.85 p.p.m., in the 90MHz ^{1}H-n.m.r. of (70) in $CDCl_3$

This multiplet arose from prochiral methylene protons in the ethoxy groups of (70), as shown in Figure 30.

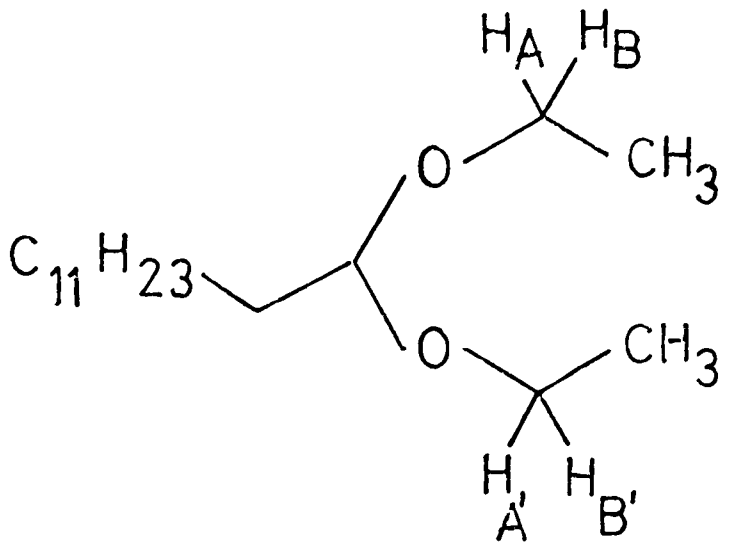


Figure 30. Prochiral methylene protons in (70), causing an AA'BB' multiplet in its ^{1}H-n.m.r. spectrum

Since (63) had been fortuitously prepared from the distillation of (70) in the presence of trace acid, the synthesis of (63) under such conditions as previously proposed[230] was attempted. Initially mixtures of (63) and (70) were produced on heating (70) in the presence of acid whilst azeotropically removing any ethanol formed. After numerous attempts, optimum conditions were found in which the enol ether (63) was obtained in 71% isolated yield. Heating (70) with 3% by weight of p-toluenesulphonic acid under reduced pressure, with azeotropic removal of ethanol under constant reflux conditions, gave a 96% conversion to the enol ether (by the weight of ethanol removed by distillation). The ratio of E- and Z-isomers obtained for (63) was found to be dependent on the rate at which ethanol was removed. The highest ratio observed was 6:4 of E- and Z-isomers respectively, however a 1:1 ratio of the isomers was routinely obtained. The enol ether was

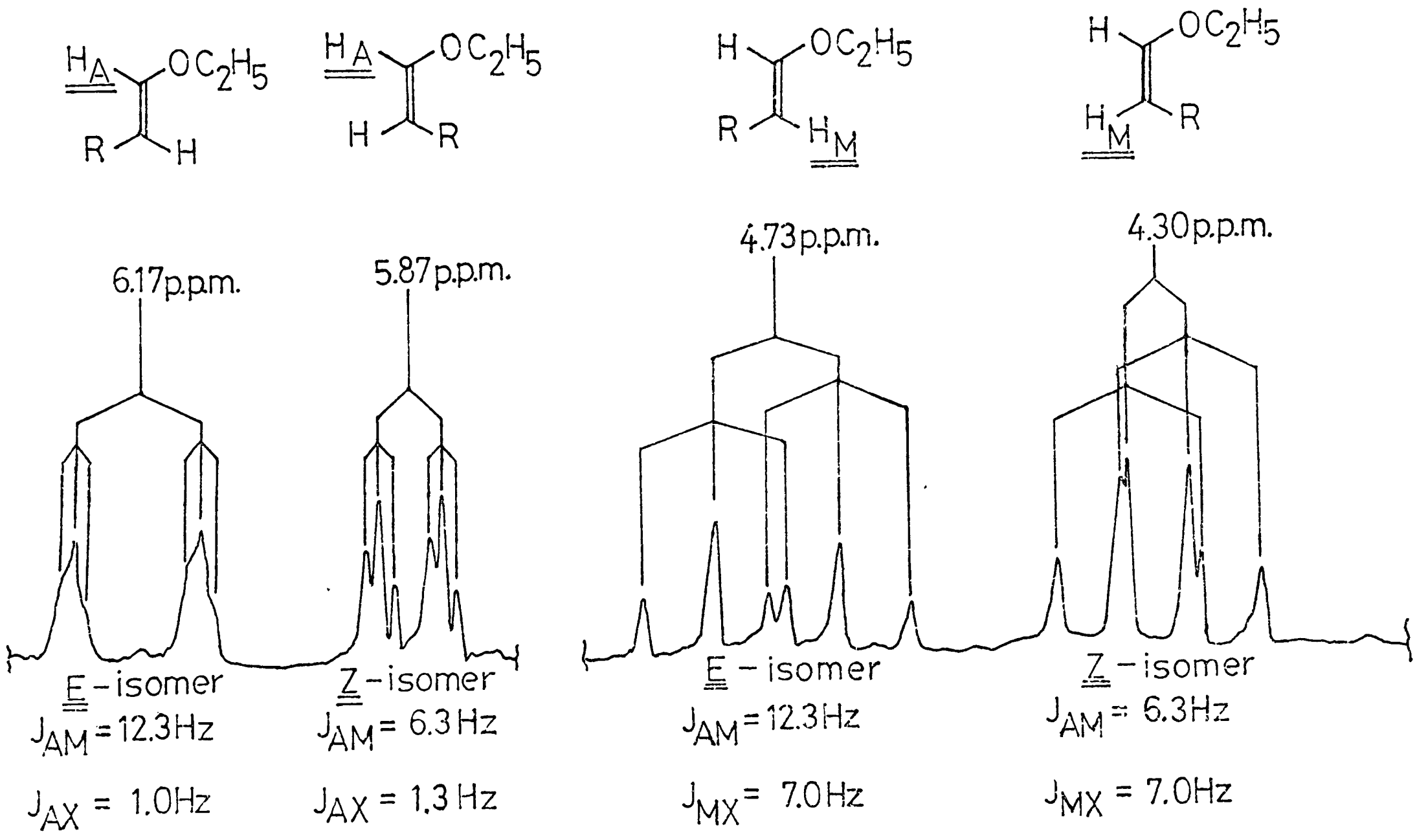
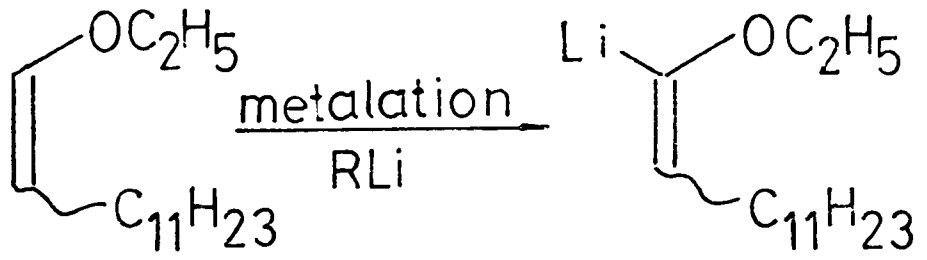


Figure 31. Features of the AMX_2 multiplet observed in the 90MHz n.m.r. for a ca. 1:1 mixture of (E)- and (Z)- (63)

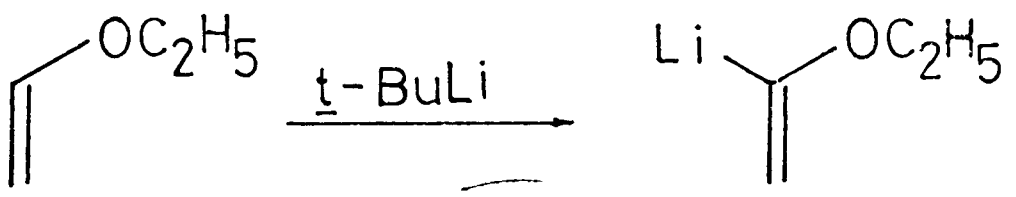
easily identifiable by the AMX_2 multiplet for both the E- and Z-isomers in the region 4-7 p.p.m.,[231] as shown in Figure 31.

With the enol ether (63) in hand the transformation of (63) to (71) by lithiation was investigated i.e.



(63) (71)

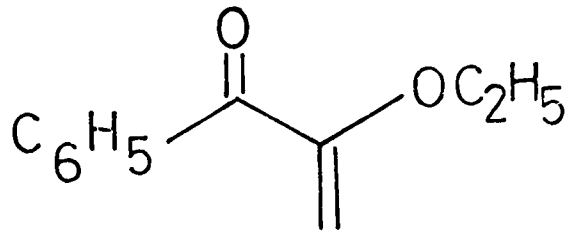
Baldwin et al.,[226] in the preparation of α-ethoxyvinyl lithium (73), had used 1.5 - 1.6 equivalents of ethyl vinyl ether (72) to 1 equivalent of t-butyl lithium.



(72) (73)

Using such conditions it was found that good yields of addition products (70%) could be obtained on reaction of (73) with benzoic acid or ethyl acetate. Attempts to use a 1:1 ratio of ethyl vinyl ether and t-butyl lithium gave much lower yields of the adducts. In these model studies the

intermediate enol ethers were isolated as sensitive oils e.g. α-benzoyl ethyl vinyl ether (74) in the reaction involving benzoic acid, and α-ethoxyvinyl lithium (73)



(74)

Features of the ^{1}H-n.m.r. spectrum of (74) particularly the two methylene resonances are shown in Figure 32.

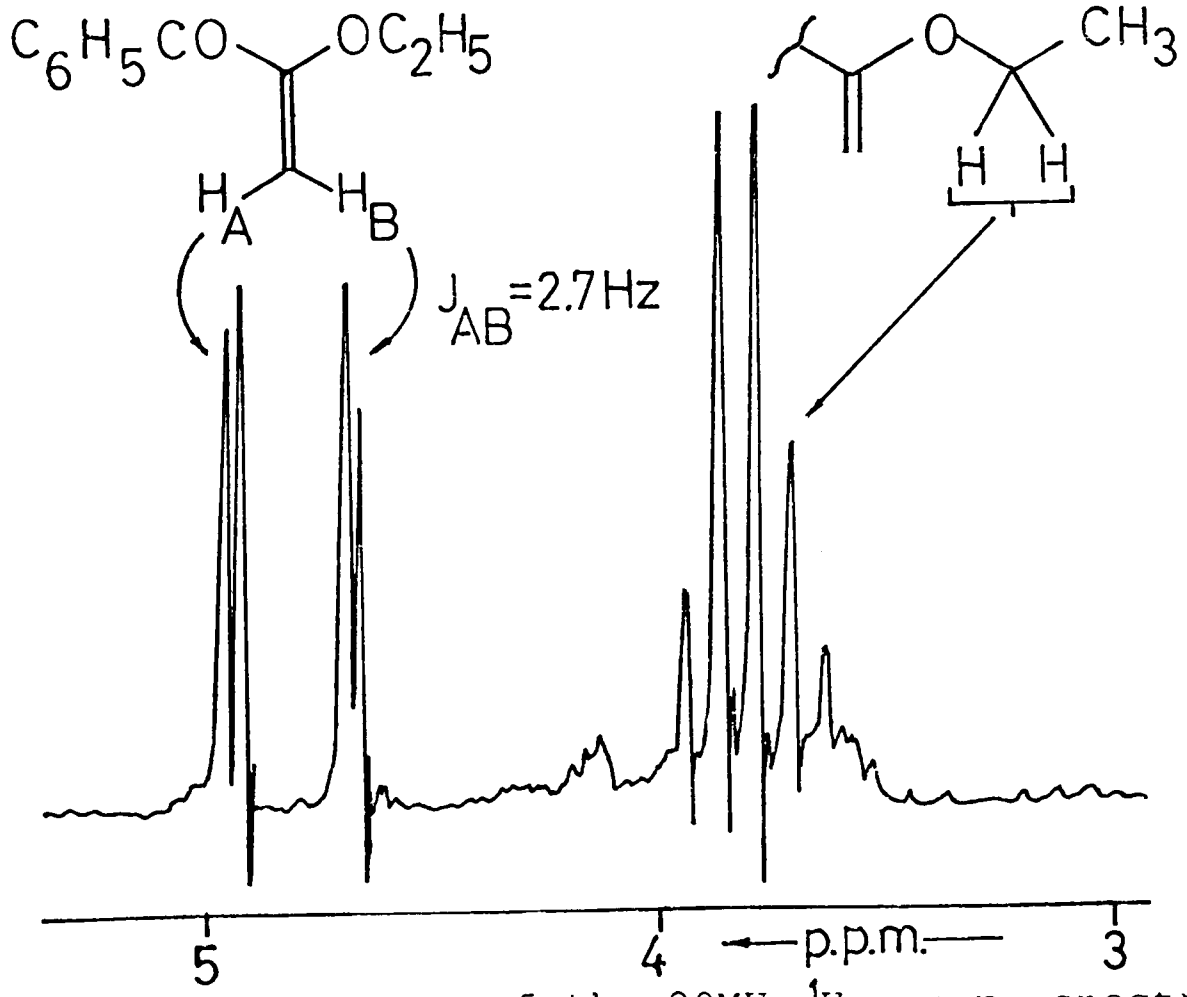
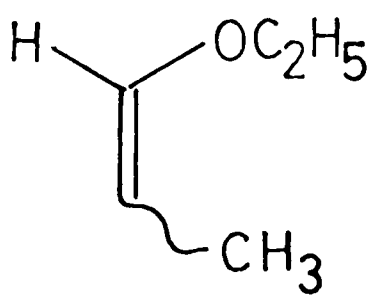
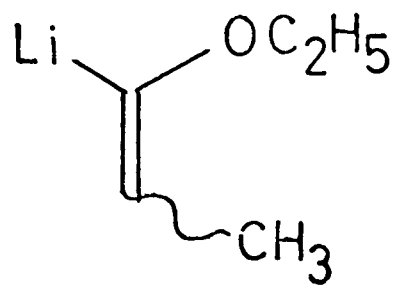


Figure 32. Features of the 90MHz ^{1}H-n.m.r. spectrum of crude (74) in $CDCl_3$

Having reproduced the results of Baldwin[226] efforts now turned to the α-lithiation of (63). All attempts to prepare (71) were uniformly unsuccessful. Solvents systems of tetrahydrofuran, diglyme, diethyl ether, hexamethylphosphoramide either as pure solvents or mixtures of such were all unsuccessful using either deuterium oxide, methyl iodide or acetyl chloride as quenching agents. Addition of alkali-metal chelating agents e.g. diazobicyclooctane, N,N,N,N-tetramethyl-ethylenediamine, 18-crown-6, to increase the reactivity of the t-butyl lithium, in the solvent systems studied also gave no successful lithiation. In all attempts, some 30 in all, the enol ether was always recovered in ca. 90% yield with the isomer distribution unperturbed. From these studies it appears that deprotonation of the solvent was taking place in preference to the formation of the lithio species (71). Baldwin in studies on the α-lithiation of E- and Z-methylpropenyl ether (75) had to use 1 equivalent of N,N,N,N-tetramethylethylenediamine to prepare (76).[226]



(75)

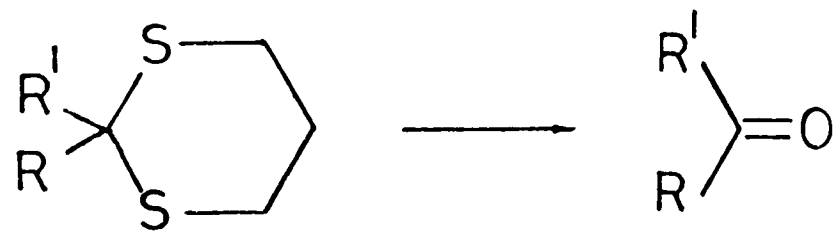


(76)

It appears that as the alkyl chain length increases, the reactivity of the α-proton in the enol ether is markedly reduced, perhaps by aggregation phenomena.

The use of sulphur umpolungs was now attempted. Considerable effort has been expended on the use of such reagents and their unmasking to the parent carbonyl functionalities. Such umpolungs have shown a high reactivity towards a wide range of substrates. After reaction however the removal of the masked functionality, to release the required carbonyl group has not always been straightforward. For example, in 2-alkyl-1,3-dithianes the removal of the dithianyl moiety has been the subject of a great deal of effort, such is their synthetic utility.[232]

Methods such as hydrolytic medium with transition metals e.g. Hg(II), Cu(II), Ag(I), alkylation e.g. methyl iodide, amination e.g. chloroamine-T, and oxidation e.g. peracids, N-halosuccinimides, have been used to date to effect the transformation shown in equation (24)

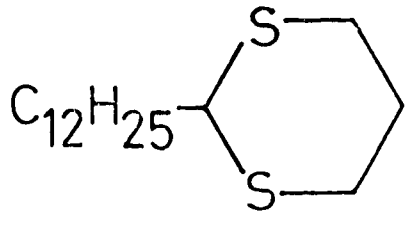


equation (24)

R = alkyl, aryl R' = H, alkyl, aryl

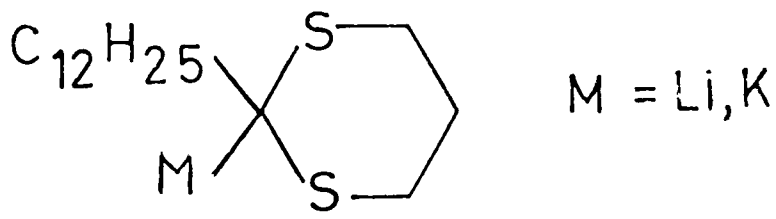
An excellent recent review by Seebach has critically examined this field.[233]

The dithiane (77) was obtained as a low melting solid in 95% yield, by reaction of propane-1,3-dithiol with (70) in the presence of boron trifluoride etherate, by adaptation of Eliel's method.[234]



(77)

Whilst giving consistent i.r., ^{1}H- and ^{13}C-n.m.r., and mass spectra, (77) only gave correct microanalytical data after repeated recrystallisations at low temperature and a final short-path distillation. Attempts to quench the anion (78) quantitatively

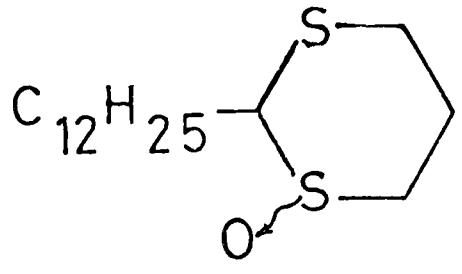


(78)

derived by metalation of (77), with a number of electrophiles e.g. deuterium oxide, methyl iodide and acetyl chloride, at either -70° or $0^{\circ}C$, were unsuccessful. In a series of experiments, using deuterium oxide as the quenching electrophile in a number of solvent systems, the highest incorporation of deuterium was found to be ca. 40%,

by n.m.r. analysis. Use of metal chelating agents *e.g.* N,N,N,N-tetramethylethylenediamine, gave no increase in the deuterium incorporation under the optimum conditions found previously.

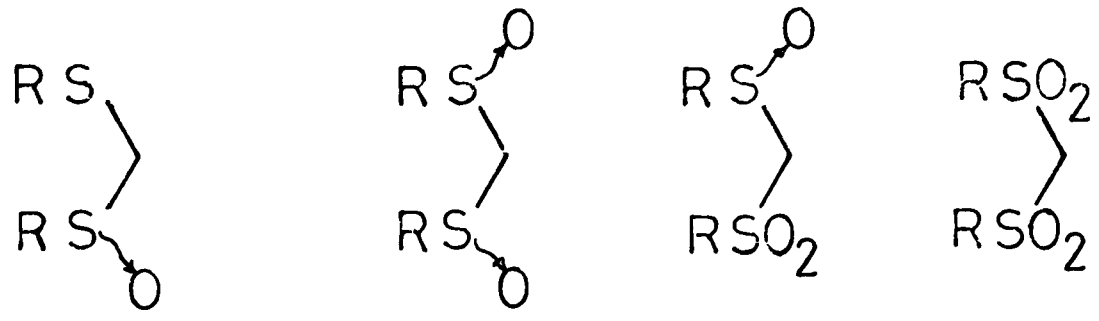
Since deprotonation of (77) was not apparently quantitative it was felt that oxidation of (77) to the more acidic 1,3-dithiane oxide (79).



(79)

(79) on metalation would generate the required acylation agent. Reaction of (77) with oxidising agents e.g. metaperiodate, hydrogen peroxide, m-chloroperbenzoic acid gave either recovery of (77) or decomposition to a number of products, as analysed by t.l.c. None of these decomposition products contained the 1,3-dithiane or 1,3-dithiane oxide moiety.

Although the 1,3-dithiane (77) had so far been ineffective, a number of other sulphur umpolungs were available, based on the activating properties of the sulphoxide or sulphone functionalities, as shown in Figure 33.

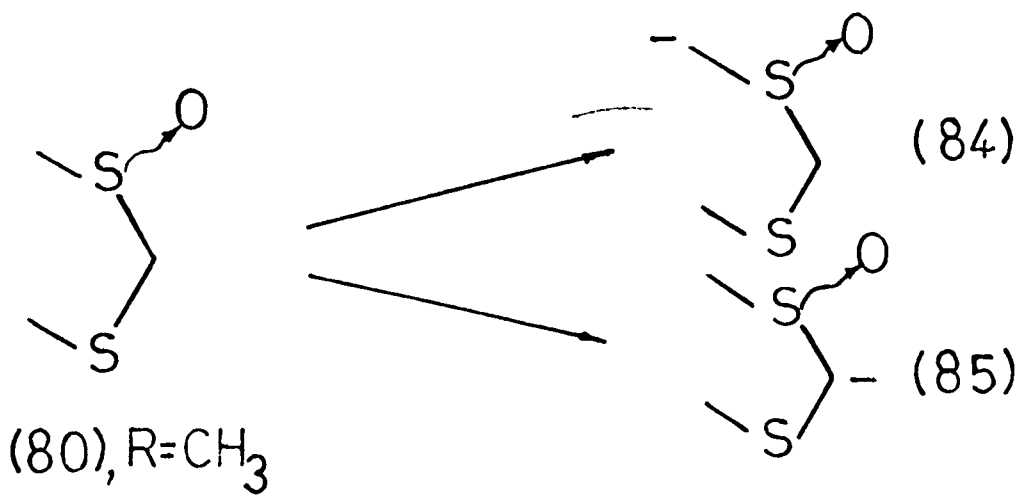


(80) (81) (82) (83)

Figure 33. Possible sulphur umpolungs, which on metalation can function as masked formaldehyde anions

In theory compounds such as (80)-(83) could be used in the same manner as a 1,3-dithiane, provided the sulphur oxidation levels could be adjusted, so that after reaction, the carbonyl precursor required could be obtained.

In terms of availability the obvious sulphur compound to utilise was ethanethiol, C_2H_5SH. Methanethiol was not preferred due to the possibility of forming e.g. the anion (84) rather than (85) by competitive deprotonation in S,S-acetal S-oxides such as (80,R=Me)



To this end the use of bisthioacetal (86) to prepare derivatives (87)-(90), shown in Figure 34, was investigated.

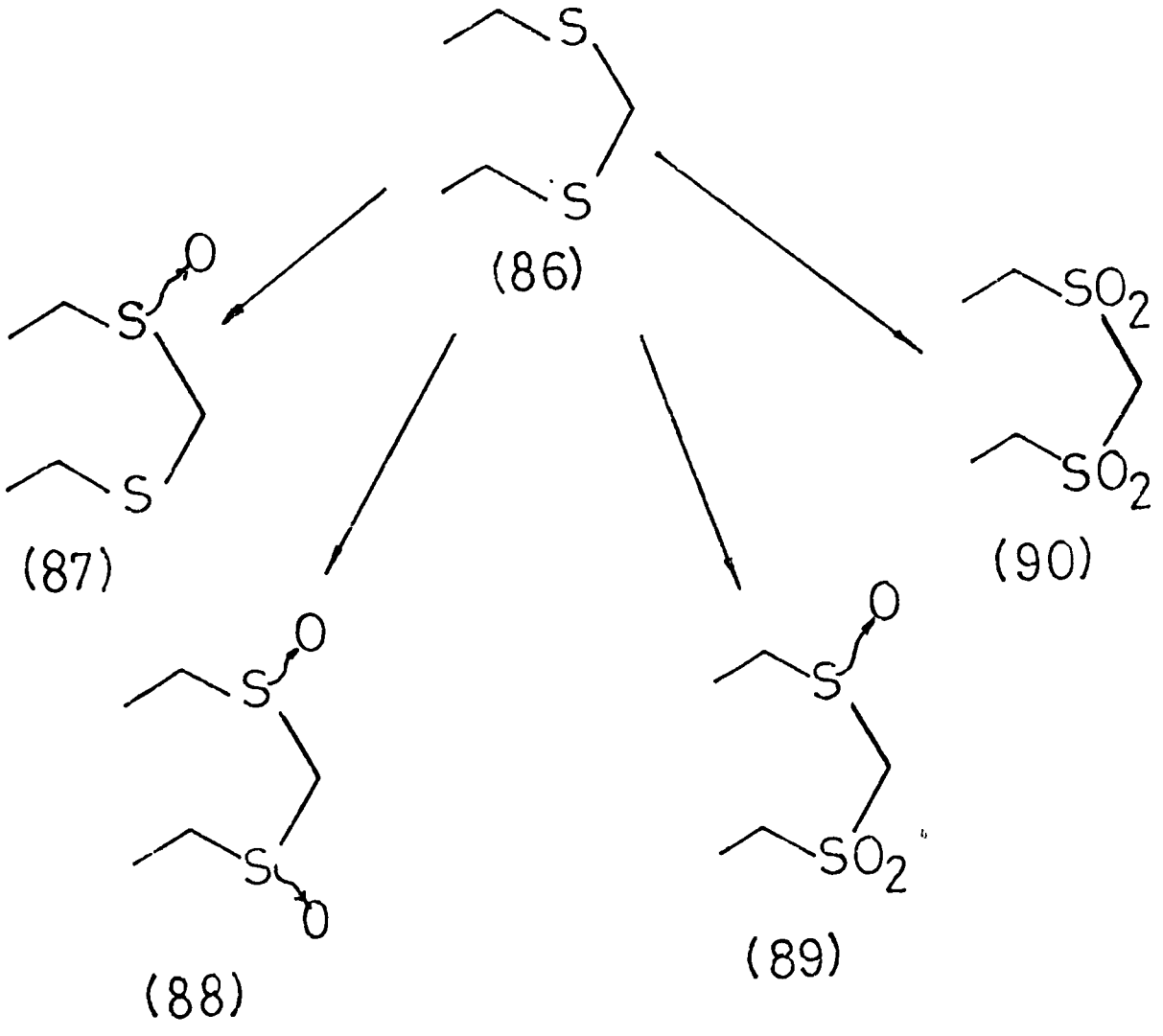
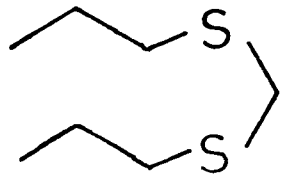


Figure 34. Bis(ethylthio)methane as a relay synthon for prospective sulphur umpolungs

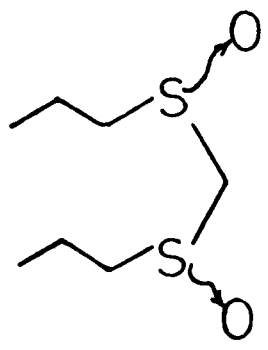
(86) was prepared in almost quantitative yield by the reaction of ethanethiol with a slight excess of paraformaldehyde in the presence of boron trifluoride etherate. Oxidation to (87)[235] was best achieved on a large scale by oxidation of crude or distilled (86) with 30% aqueous hydrogen peroxide in glacial acetic acid, monitoring the reaction by n.m.r. Oxidation of (86) to (87) by either aqueous sodium metaperiodate or peracid was found to be slower and prone to variation in yield. Attempts to prepare (88) by oxidation of (87) with one equivalent of oxidant gave a mixture of products,

apparently (88) and (89). These mixtures were obtained under a number of conditions and thus attention was turned to the bisthioketal (91) as an alternative to preparing the derivatives (80)-(83), R = Pr.

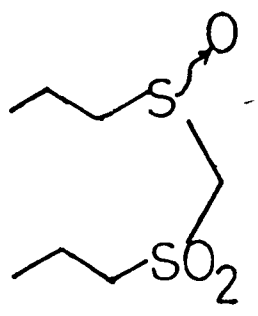


(91)

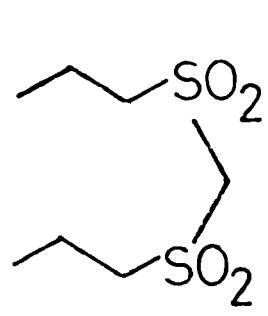
(91) was again prepared in high yield using the the same method as described for (86). In contrast to (86), however, (91) was found to be much more resistant to oxidation with e.g. hydrogen peroxide or peracid in refluxing solvents. Initial attempts to oxidise (91) with hydrogen peroxide-t-butanol-vanadium pentoxide[236] to (92), (93) or (94) at room temperature were unsuccessful giving a mixture of products.



(92)



(93)



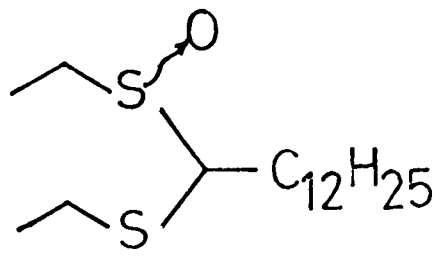
(94)

The mixture of products obtained, apparently containing (91), (92), (93) and (94) by n.m.r., was, no doubt, a direct consequence of the violent exothermicity observed for this reaction, under a number of conditions. Since cooling

would result in solidification of the solvent, a slight modification in the conditions was required. It was found that a 4:1 $^{v}/_{v}$ ratio of t-butyl alcohol and water was ideal for the purpose in hand. While the homogeneity was sacrificed to a small extent, (91) could be effectively titrated at 0°C with hydrogen peroxide to either (92), (93) or (94), as originally proposed, by the colour changes observed. Addition of sufficient 30% aqueous hydrogen peroxide to the vanadium pentoxide and dithioketal (91) in aqueous t-butanol produced a red-orange solution, which faded to a yellow colour on oxidation of (91). (92), (93) and (94) were easily identified by mass, i.r. and n.m.r. spectroscopy. The disulphoxide (92) as expected, was obtained as a 1:1 mixture of the cis- and trans-isomers and accordingly exhibited a singlet, at 4.0 p.p.m., for the trans-isomer and an AB quartet, at 3.75 and 4.1 p.p.m., for the cis-isomer. With (87), (92), (93) and (94) prepared, the deprotonation of such species to the nucleophilic umpolung reagents was desired. Standard conditions for each of the species i.e. n-butyl lithium in tetrahydrofuran with deuterium oxide quenching, indicated that (87) was the most efficient carbanion forming species. By careful experimentation 95% deuteration of (87), as analysed by n.m.r., was routinely obtained. (87) had previously been extensively used in synthetic reactions because of its high reactivity and the ease in which the carbonyl

functionality was generated after subsequent alkylation with electrophiles.[233,237]

The next stage involved the preparation of (95) by alkylation of (87)



(95)

It was found that the lithio species of (87) was most efficiently quenched with n-dodecyl bromide at 0°C in a 3:1 v/v mixture of tetrahydrofuran-hexamethylphosphoramide. With careful experimentation (95) could be obtained in 63% isolated yield, after centrifuging the crude material, at -30°C, and chromatography on activated alumina. Attempts to chromatograph (95) on silica gel caused decomposition to a number of products, which were not identified. Whilst (95) was found to be stable for at least 3 months when stored as a solid at 0°C, upon standing at room temperature e.g. in chloroform, decomposition took place. Initially this unexpected occurrence was thought to be the hydrolysis of (95) to tridecanal, by the fortuitous presence of acid in the n.m.r. solvents. However on continued monitoring a complex multiplet appeared at 5.5 - 6.3 p.p.m., as shown in Figure 35 and increased in intensity with time; such a n.m.r. resonance indicated the presence of a vinyl compound.

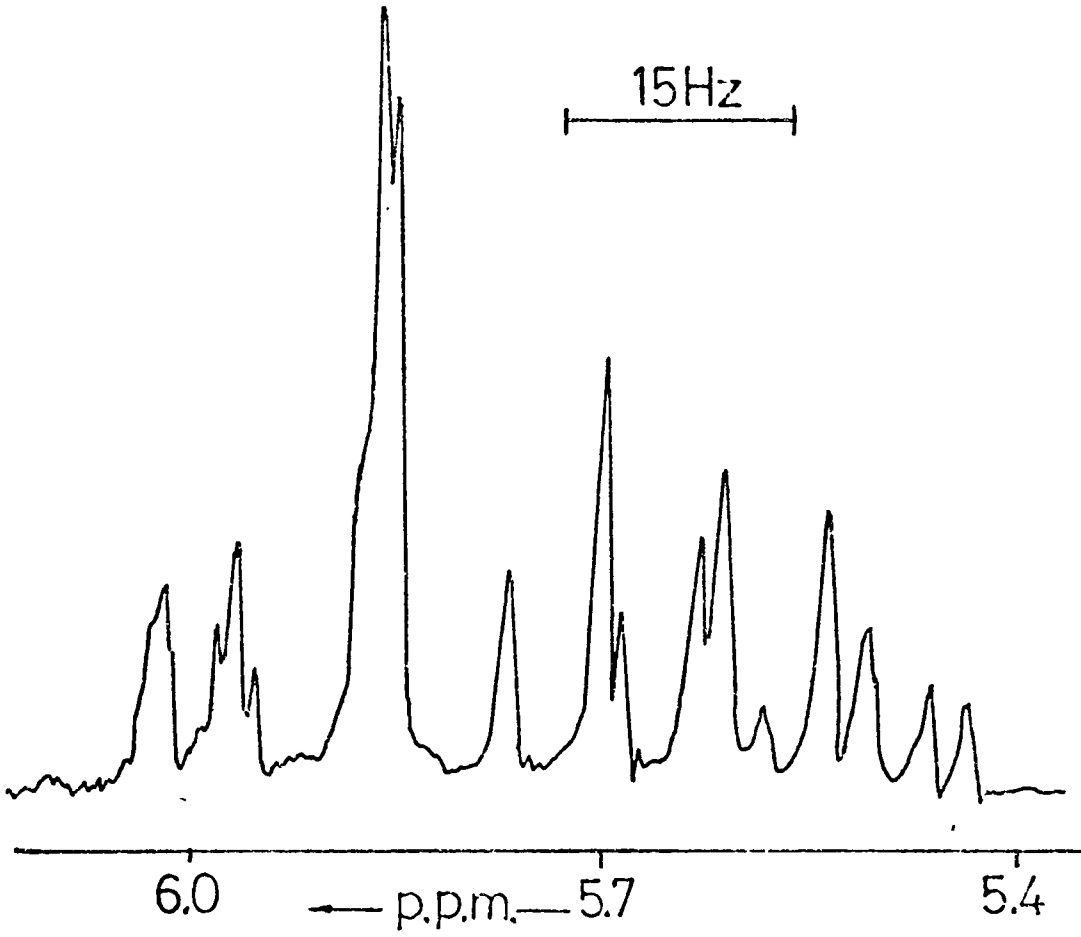
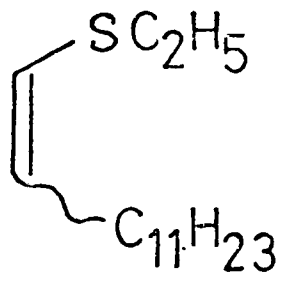


Figure 35. Expansion of the vinyl proton multiplet, 5.5 - 6.1 p.p.m., seen in the decomposition of (95)

An explanation of this observation is that the formation of a mixture of E- and Z-isomers of vinyl sulphide (96), by the elimination of ethanesulphenic acid from (95), had occurred.



(96)

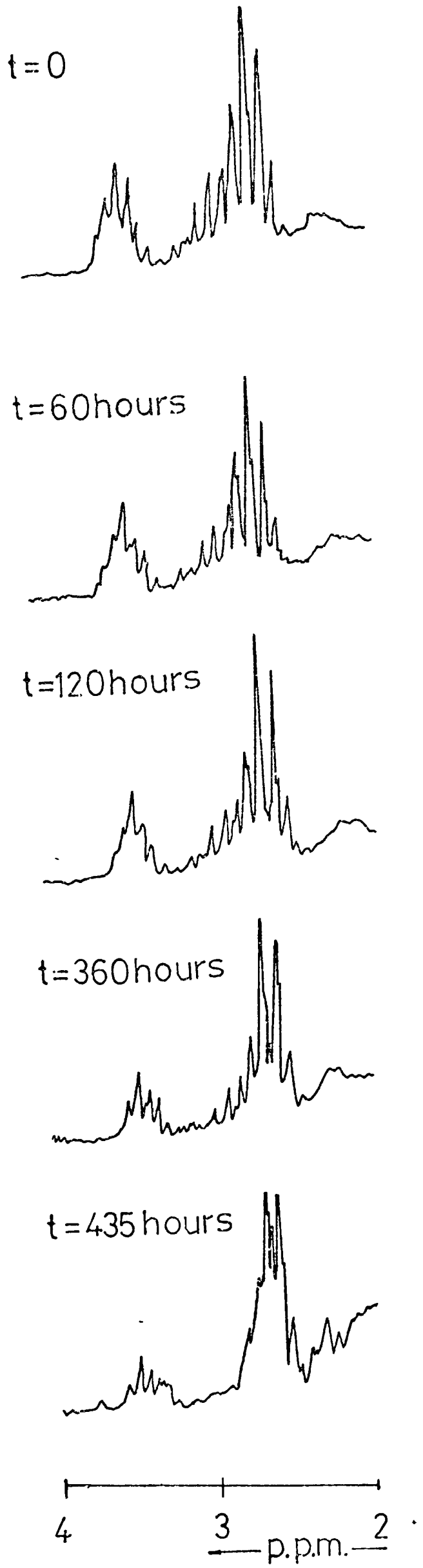
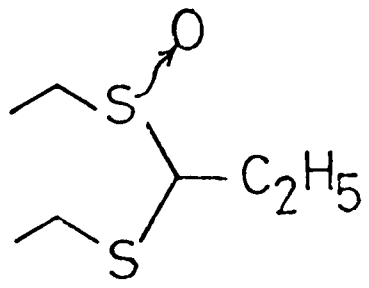


Figure 36. Changes in the 2.0-4.0 p.p.m. spectral region of the 90MHz ^{1}H-n.m.r. of (95) on heating in $CDCl_3$

Attempts to follow this reaction by n.m.r. at room temperature were unsuccessful due to the slow nature of the elimination ($t_{\frac{1}{2}} > 14$ days). The half-life of the reaction in refluxing chloroform was ca. 72 hours as indicated from the n.m.r. spectrum between 2 and 4 p.p.m., shown in Figure 36. Upon careful distillation of chloroform from potassium carbonate the reaction rate was clearly retarded, $t_{\frac{1}{2}} \simeq 100$ hours, indicating the need for acid catalysis to drive the elimination. It was found that (95) on being refluxed in hydrogen chloride-saturated toluene for 6 days afforded a 1:1 mixture of E- and Z- (96) in ca. 90% crude yield, as determined by g.l.c. (10% SE-25 on 100-120 mesh Celite). Careful g.l.c./m.s. indicated that tridecanal and tridecyne were also present in the crude mixture (ca. 10%). Whilst an analytically sound sample of (96) could not be obtained, a $\simeq$ 95% pure sample was prepared by chromatography on silica gel, which gave a mass spectrum consistent with the expected structure on g.l.c./m.s. analysis.

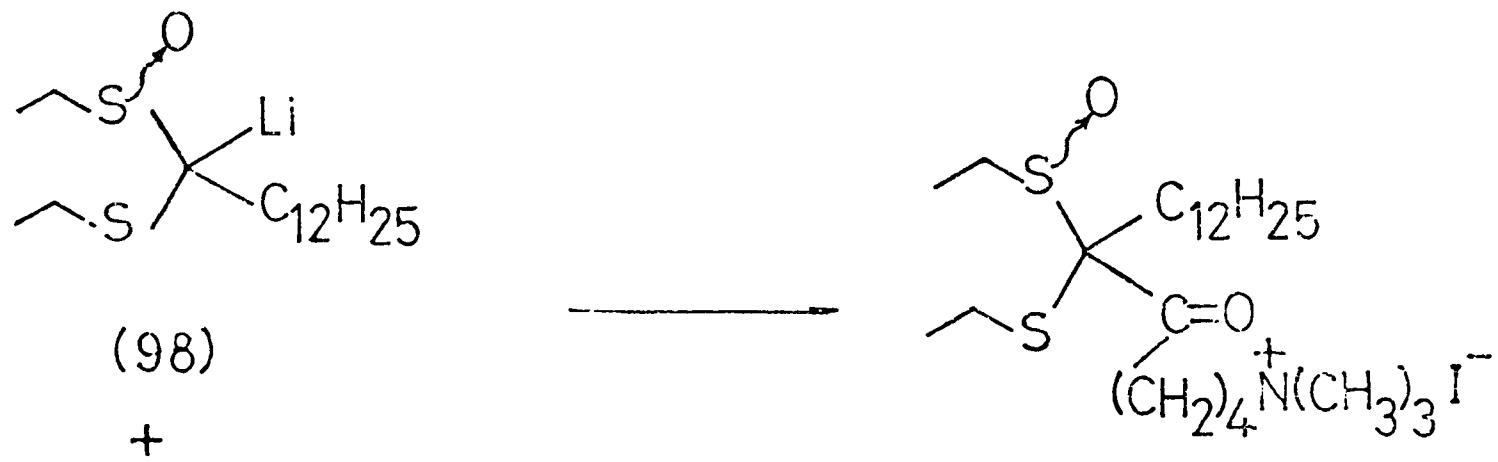
A number of workers had previously shown that analogues of (95) e.g. (97)



(97)

could be efficiently deprotonated by n-butyl lithium, potassium hydride or lithium diisopropylamide, at 0°C and quenched by deuterium oxide, with 90% deuterium incorporation.[233] An examination of all these reagents at 0°C in tetrahydrofuran-hexamethylphosphoramide, showed that n-butyl lithium was the most efficient. The anion obtained from (95) using such a base could be quenched to ca. 80% efficiency using either methyl iodide or deuterium oxide as electrophiles.

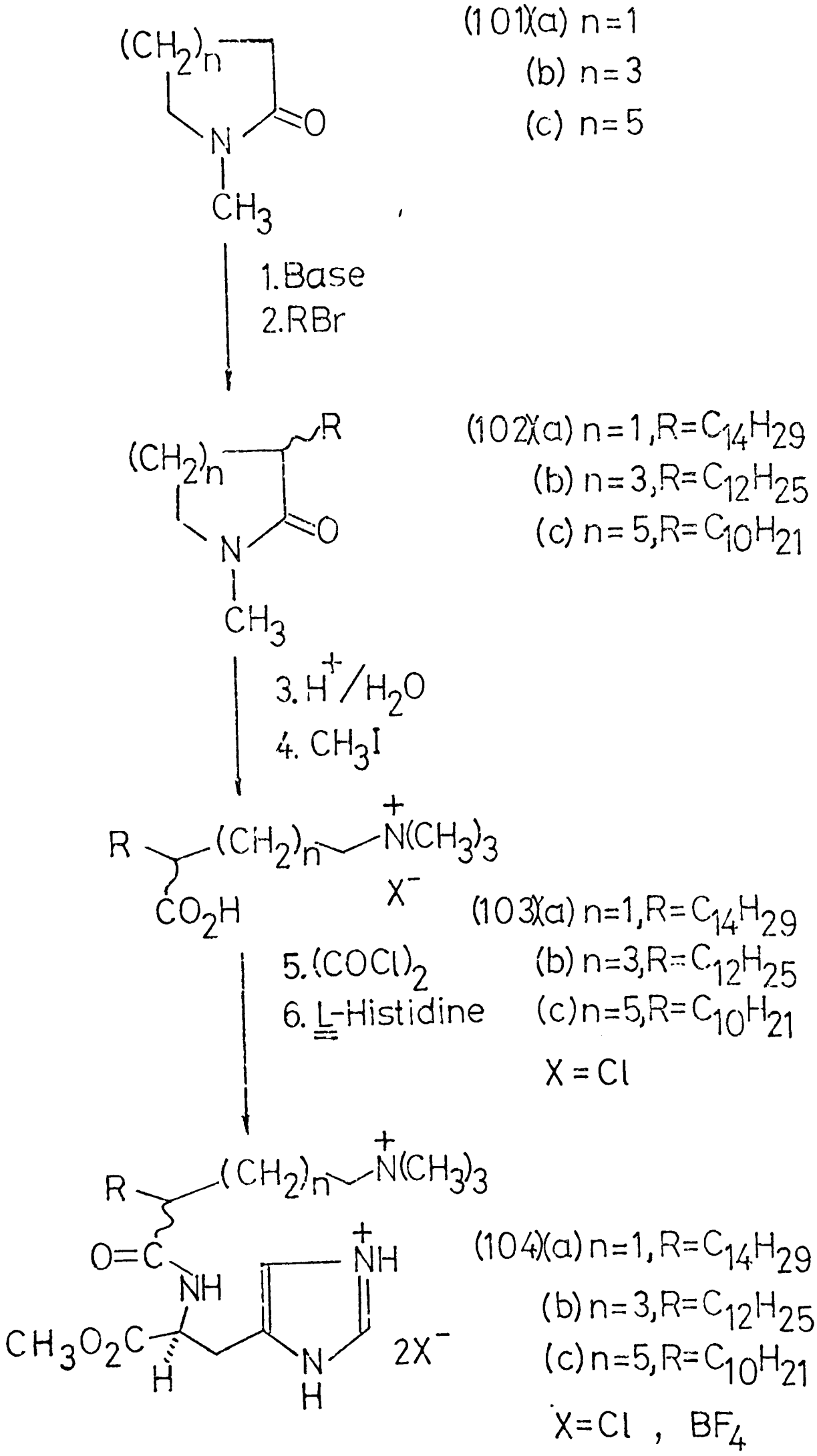
Having now prepared the two "halves" for the desired synthesis and examined their reactivity, the crucial coupling of the anion (98) with (57), (61) or (99) to give (100), as shown in equation (25) was attempted.



equation (25)

Since anion (98) was found to be stable at 0°C for 24 hours and ca. 12 hours at 25°C, such a coupling was investigated at these two temperatures. Numerous attempts to effect such a reaction, after forming (98) at 0°C, with either (57), (61) or (99) in a number of solvent systems at 0° or 25°C were unsuccessful. In all cases a high recovery (>80%) of (95) was obtained on work-up. No trace of (100) could be detected in the final reaction work-up by n.m.r. or i.r. No other reaction product could be detected by t.l.c. in a number of solvent systems. Whilst the anion (98) can be formed, its nucleophilic qualities were obviously diminished with respect to reaction with the desired electrophiles. Addition of lithium chelating agents e.g. N,N,N,N-tetramethyl—ethylenediamine, to increase the nucleophilic character of (98), also gave a high recovery of (95) on work-up.

The coupling reaction shown in equation (25) again highlights the adverse reactivity encountered in reactions involving long chain compounds. This has already thwarted previous synthetic attempts to prepare a metal-binding surfactant. Thus while anion (98) can be quenched with low molecular weight electrophiles e.g. methyl or ethyl iodide, deuterium oxide, reaction with electrophiles of slightly lower reactivity results in vastly diminished yields. Such an effect may be due to aggregation phenomena of long chain compounds, resulting in diminished reactivity



(101)(a) n=1
(b) n=3
(c) n=5

(102)(a) n=1, R=$C_{14}H_{29}$
(b) n=3, R=$C_{12}H_{25}$
(c) n=5, R=$C_{10}H_{21}$

(103)(a) n=1, R=$C_{14}H_{29}$
(b) n=3, R=$C_{12}H_{25}$
(c) n=5, R=$C_{10}H_{21}$
X = Cl

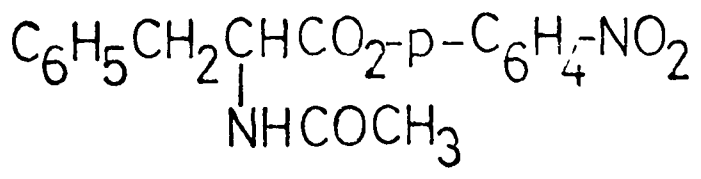
(104)(a) n=1, R=$C_{14}H_{29}$
(b) n=3, R=$C_{12}H_{25}$
(c) n=5, R=$C_{10}H_{21}$
X=Cl , BF_4

Scheme 9. Synthesis of diastereomeric functional surfactants from lactams

to anything except highly reactive electrophiles at low temperatures. The use of higher temperatures (25°C) is not always possible due to the sensitivity of carbanions to temperature.

2.4 Synthesis of a chiral surfactant

The stereochemistry of micellar reactions is of some interest.[107] In this context Brown et al. synthesised a series of optically active functional surfactants from cyclic lactams, as shown in Scheme 9.[121] In the preparation of (104(b)) a single crystalline salt was isolated having the characteristics of a single diasteromer. Most notable was a ^{13}C-n.m.r. spectrum with the expected number of resolved peaks and no evidence of pairwise splittings. Hydrolysis of (104(b)) in 6M hydrochloric acid gave the carboxylic acid (103(b)), possessing a negative circular dichroism at short wavelength. This diastereomer, isomer A, proved to be effective in the hydrolysis of p-nitrophenyl esters, as was the second diastereomer, isomer B, which was isolated by fractional crystallisation of the tetrafluoroborate salts. Separation of the diastereomers of (104(a)) and (104(b)) was unsuccessful after a number of attempts. Consequently a mixture of isomers had to be used for hydrolysis studies of the p-nitrophenyl esters of (R)- and (S)- phenyl alanine (13).



(13)

None of these studies enabled the effect of chain configuration to be examined, although it appears that one diastereomer is an efficient asymmetric catalyst, as previously shown in Table 8.

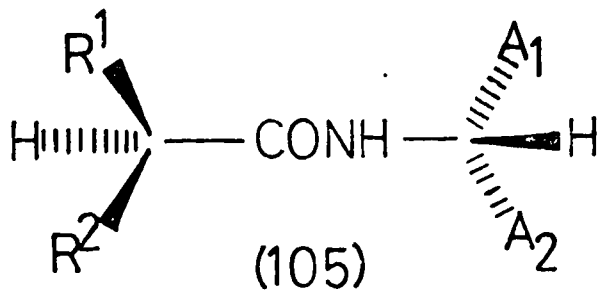
Surfactant	$k_{relative}$ ((S)-13)	k_s/k_r
(104(a)) mixed isomers	0.92	1.50
(104(b)) isomer A	1.00	3.10
(104(b)) isomer B	0.21	1.04
(104(c)) mixed isomers	0.51	1.67

Table 8. Stereoselectivity in the hydrolysis of p-nitrophenyl esters of (R)- and (S)-N-acetylphenylalanine (13) with chain-histidine surfactants at pH 7.3

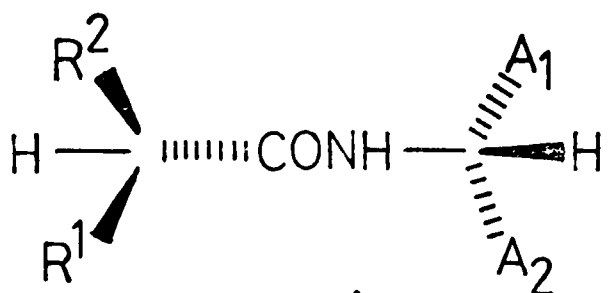
Thus it is of some interest to prepare a surfactant carboxylic acid of known configuration.

In recent years the ease of separation of diastereomers has been greatly improved by the application of high-pressure liquid chromatography.[238] Often, assignment of absolute configuration in these studies has relied on comparison of optical data with structural analogues and/or chemical degradation to compounds of known configuration. More recently Helmchen et al.[239] have used high performance liquid chromatography on silica gel, for the "directed resolution" of diastereomeric amides of general formula (105) and (106) and of defined

absolute configuration.



(105)

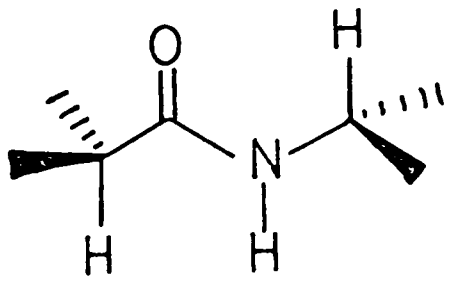


(106)

In particular the diastereomeric amides (105) and (106) with hydroxyl groups located in the $\underline{\gamma}$- or $\underline{\delta}$-position to the carbonyl group (R^1 or R^2 = $(CH_2)_nOH$ and/or A^1 or A^2 = $(CH_2)_{n-1}OH$, n = 2,3) show high separation factors upon liquid absorption chromatography. Such a phenomena, coupled with a large amount of additional data, enabled Helmchen to postulate four simple rules which can be used as guidelines in the search for structural features necessary for high separation factors:-[239]

(a) the conformations of diastereomeric amides in the dissolved state and in the absorbed state are the same i.e. the conformation is determined by the planar

structural element (107) (provided that neither R^1 nor R^2 in the diastereomer forms a hydrogen bond to the amide group)



(107)

(b) binding to the silica gel absorbent preferentially takes place <u>via</u> hydrogen bonding. Hence the contribution of the amide group, which could be bound as shown in Figure 37, is particularly high.

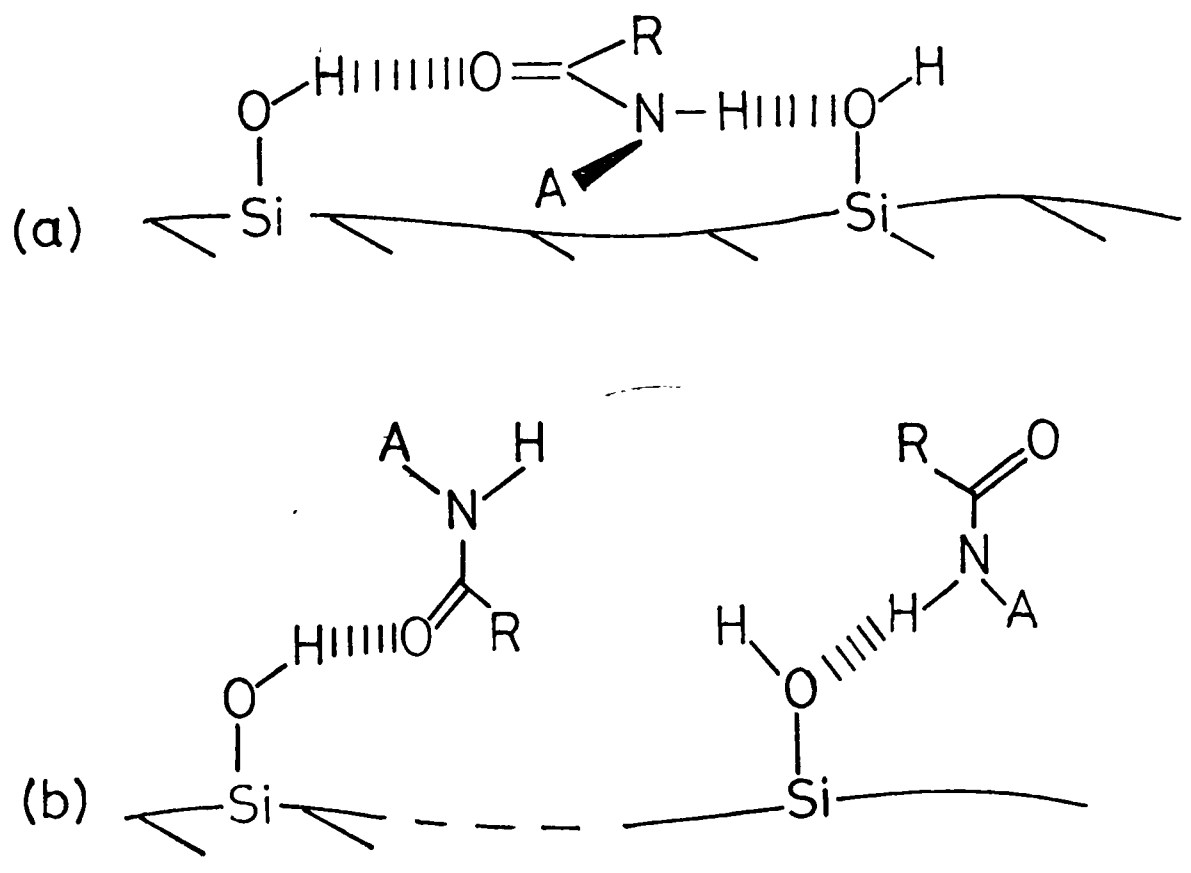
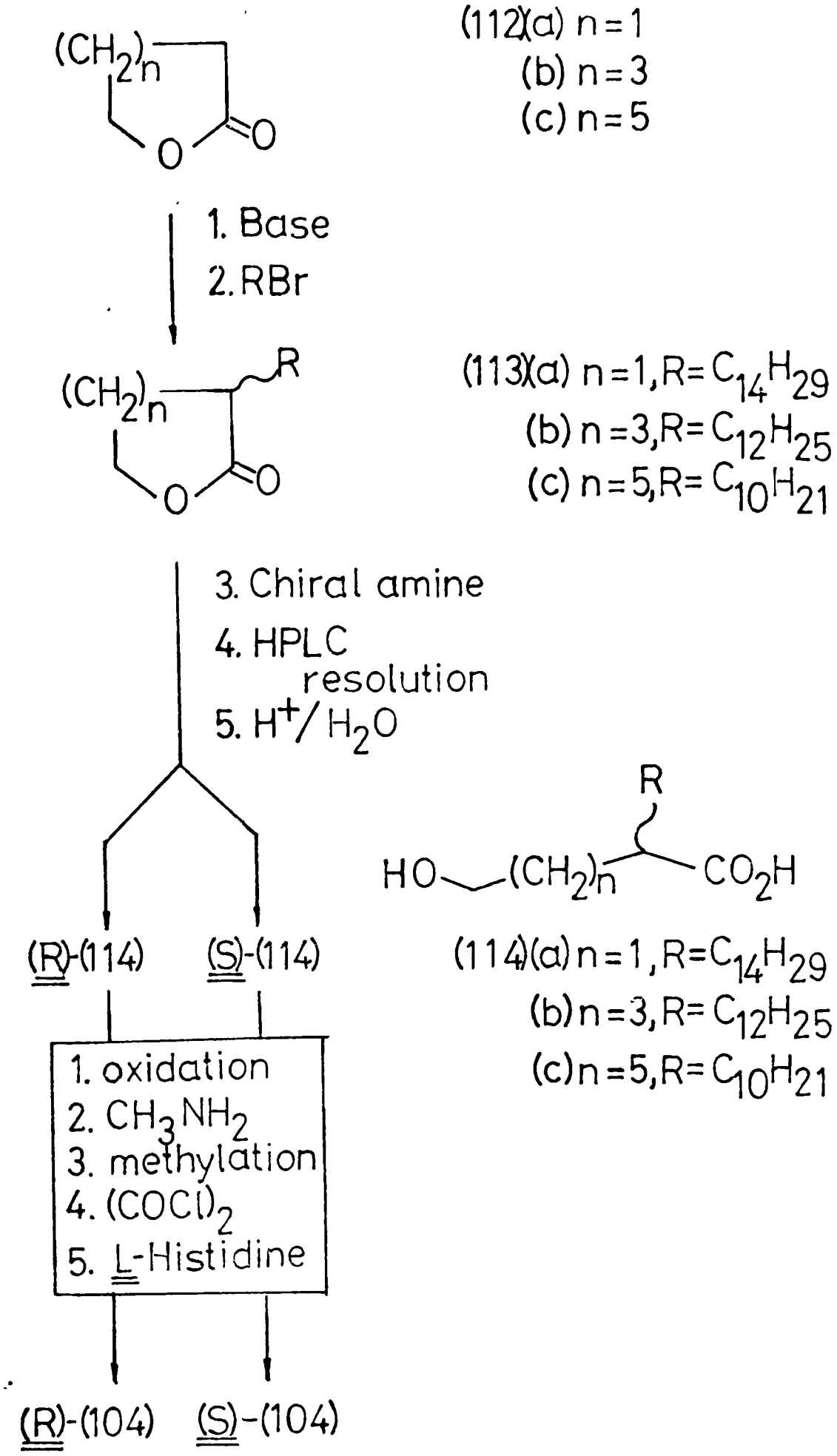


Figure 37. <u>Possible binding modes of diastereomeric amides with silica gel</u>

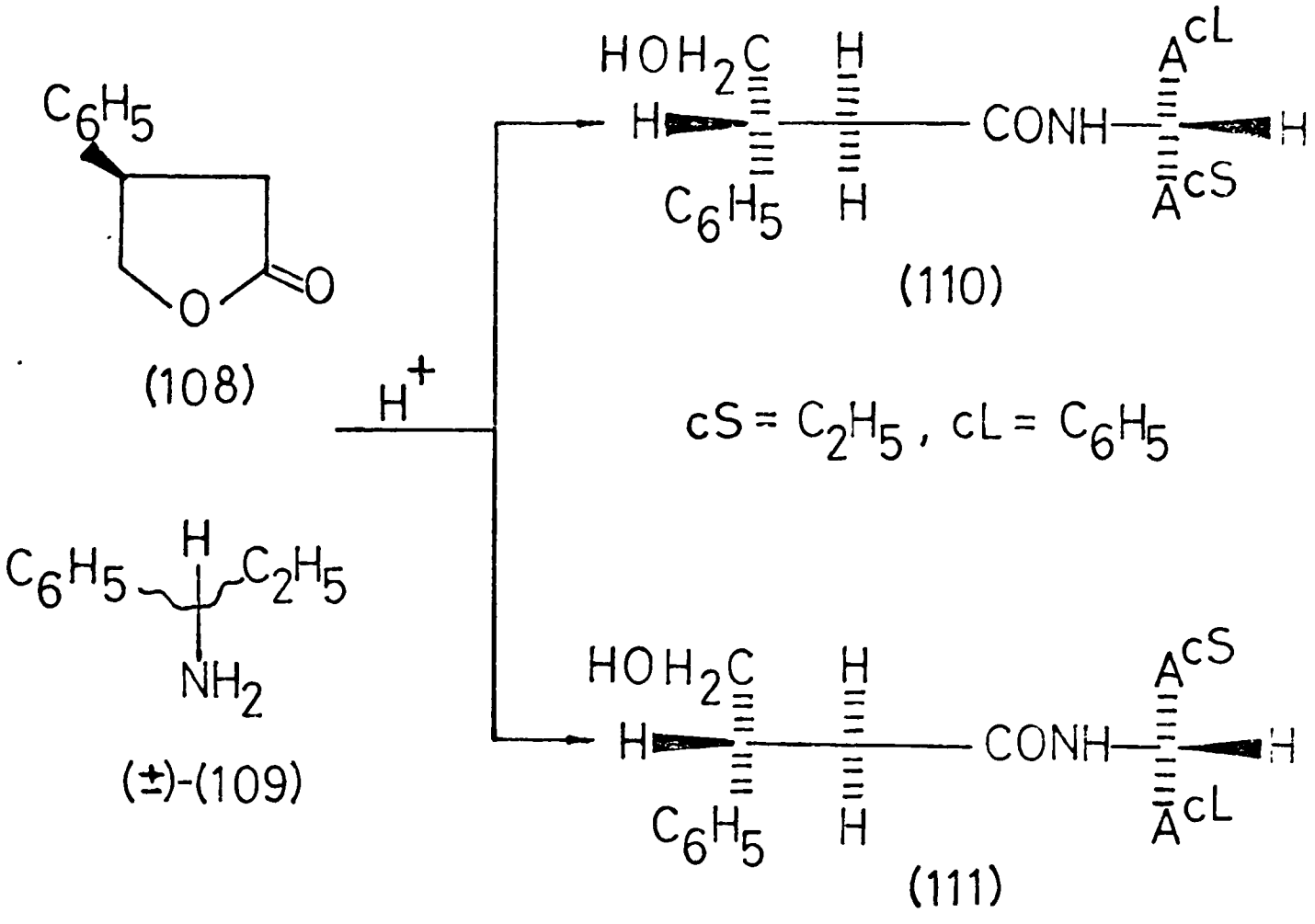
(c) significant diastereoselectivity is only expected in absorbed states such as those shown in Figure 37a. The perturbing effects of R and A in (105) and (106) affect the bound and unbound states by their affinity for the silica gel, and this perturbing effect must be determined empirically.

(d) the groups R^1, R^2, A^1 and A^2 are classified according to their perturbing effect, referred to as chromatographically "small" or "large" i.e. "cS" or "cL", approximately parallels the steric bulk that is perpendicular to the amide plane.

Taking such rules into account, the diastereomer whose R^{cL}/A^{cL} groups are situated on opposite faces of the structural element (107) is eluted first due to the better shielding effect of the amide moiety. For example (-)-(R)-phenylbutyrolactone (108), upon reaction with (±)-1-phenylpropylamine (109) gave the diasteromeric amides (110) and (111).[239c]

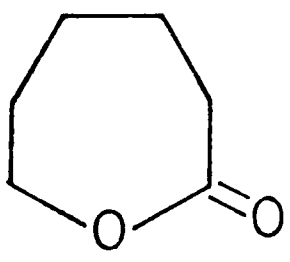


Scheme 10. Synthesis of chiral surfactants (104(a))-(104(c)) via directed resolution of diastereomeric amides

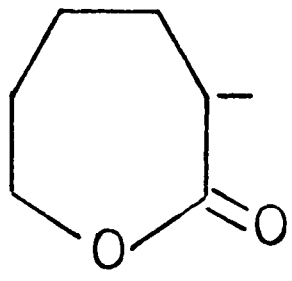


Of these two diasteromers, (110), with the "chromatographically large" phenyl groups diagonally opposed, was eluted first, as predicted by the rules. Thus a method for the directed resolution of enantiomeric carboxylic acids or amines was possible, as well as the separation of enantiomeric lactones.

It is possible to envisage the synthesis of chiral surfactants from α-alkylated lactones as indicated in Scheme 10. With the synthesis of (R)-(104(b)) in mind, alkylation of the 7-membered ring lactone (112(b)) was investigated via its lactone enolate (115).

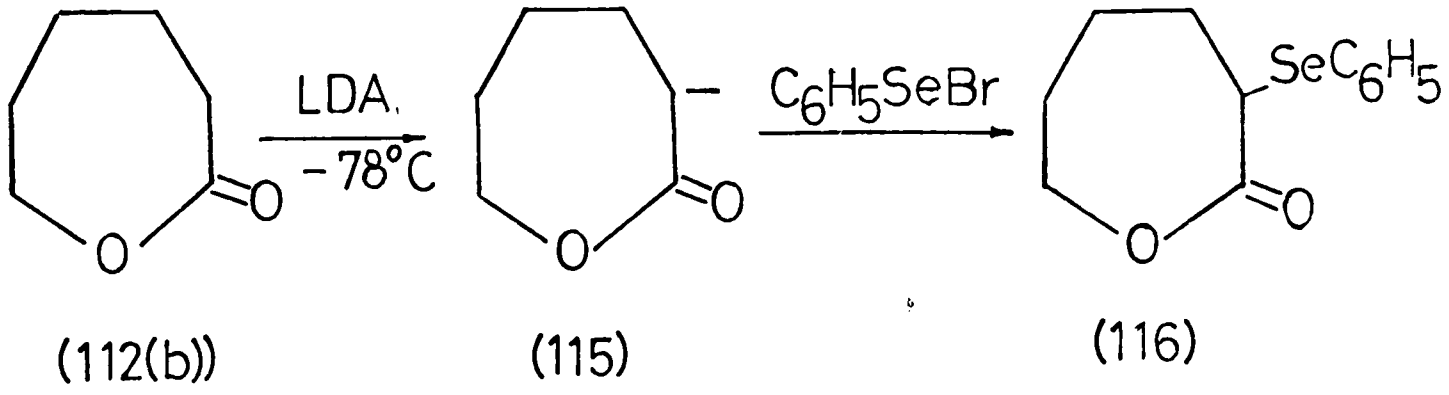


(112(b))



(115)

Examination of the literature revealed that there was only one example of alkylation of lactone (112(b)) by such a method. Reich et al.[240] had prepared the anion (115), by deprotonation of (112(b)) with lithium diisopropylamide (LDA) at -78°, and successfully quenched the anion with phenyl selenium bromide to give (116) in 70% yield.

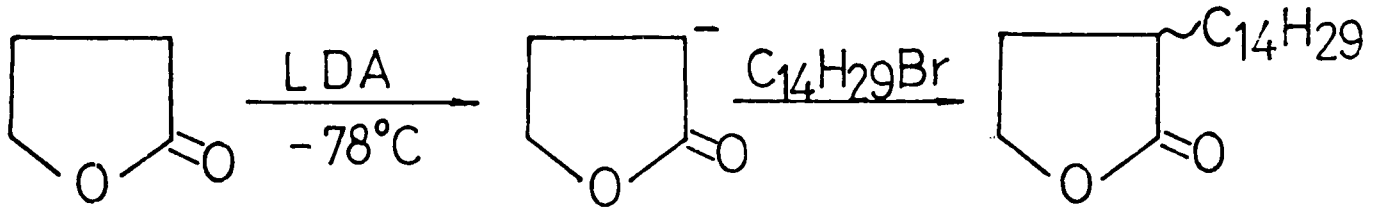


(112(b)) (115) (116)

Using exactly the same conditions to generate (115) its reaction with deuterium oxide, methyl and ethyl iodide was investigated at a number of temperatures. All attempts were unsuccessful. Under the conditions used ca. 60% of the starting material was recovered in each case as determined by n.m.r. No other identifiable product could be detected. No apparent rationale can be presented for the inability to quench (115) with the electrophiles studied. In the case of (116), the electrophile used, phenylselenyl bromide, is extremely reactive. Thus the anion (115) is quenched more efficiently than with the electrophiles studied in our investigations. Since all the attempts to alkylate (115) with reactive short chain alkyl halides failed, no

attempts to alkylate (115) with n-decyl halides were made. Attention was then directed to the 5-membered ring lactone (112(a)).

Due to the large amount of experimental detail on alkylations of γ-butyrolactone,[240,241] investigations under what were considered optimum conditions were instigated. Several attempts to quench the anion (117) with one equivalent of n-tetradecyl bromide to give (113(a)), gave yields of ≃ 5-10%, as analysed by n.m.r.



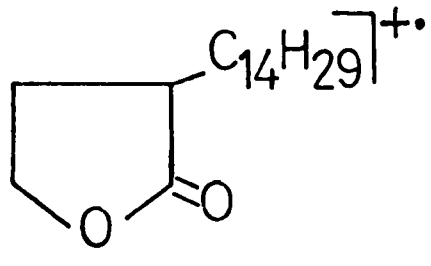
(112(a)) (117) (113(a))

Attempts using n-tetradecyl tosylate instead of the bromide gave very similar yields under the same conditions. Since the level of alkylation achieved was very low, the use of 2 equivalents of (117) to 1 equivalent of n-tetradecyl bromide was attempted. After considerable experimentation conditions were found that gave a product, in 55-60% yield, of a 1:1 mixture of (113(a)) and n-tetradecyl bromide, using 3:1 $^{v}/_{v}$ tetrahydrofuran-hexamethylphosphoramide as solvent. These conditions, upon scale-up, were found to give capricious yields unless the conditions were carefully controlled. In particular strict temperature control was required in

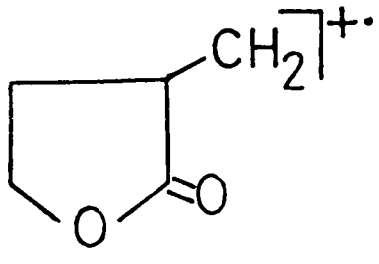
all stages of the reaction. For example, the temperature of electrophile addition had to be maintained between -40°C and -45°C. Lower temperatures than -50°C caused partial solidification of the reaction media, whilst above -30°C apparent polymerisation and/or decomposition of the anion (117) occurred.

Whilst the product, a low melting solid, could be purified by chromatography on silica gel, this was found to be a tedious procedure. Careful elution was required to prevent contamination of initial lactone fractions with starting alkyl halide. However Elad et al.,[243] in studying the photoalkylation of γ-butyrolactone with olefins, had used fractional crystallisation from cold pentane to isolate 2-alkylbutyrolactones. A slight modification of this method proved most useful in that dissolution of the crude product in pentane and cooling to -30°C gave a waxy solid after decantation. T.l.c. of the crude solid before and after this treatment showed a substantial reduction in the amount of alkyl halide present (as judged by the intensity of the spot). Three further recrystallisations from pentane at -30°C gave a white solid, m.p. 49-53°C, having two components (major R_f=0.49, minor R_f=0.31) by silica gel t.l.c. using 2:1 v/v diethyl ether/60-80° petrol. Upon chromatography the desired lactone (113(a)) was obtained as small white crystals. Physical data

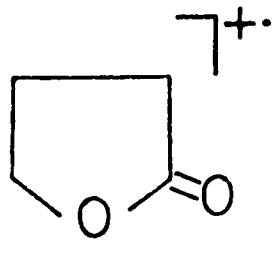
(i.r., ^{1}H-, ^{13}C- n.m.r., mass spectrum and microanalysis) supported the expected structure. In particular the mass spectrum of (113(a)) showed major peaks at m/e 282(11%), 99(100%), 86(83%) indicative of the species (118), (119) and (120) respectively.



(118)

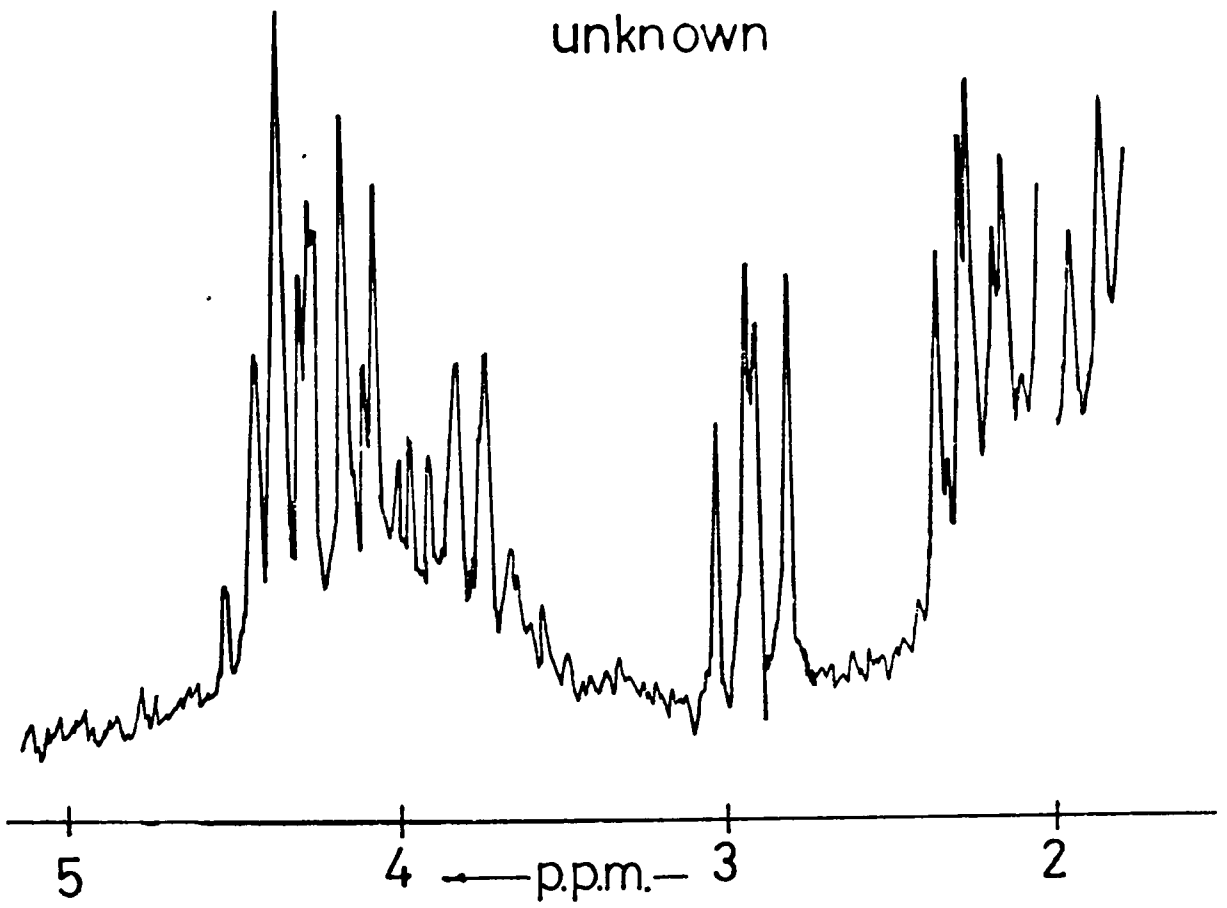


(119)



(120)

The minor product (R_f=0.31) was a pale yellow solid, m.p. 53.5-55°C, isolated after chromatography by crystallisation from pentane at -30°C. I.r. analysis indicated the presence of lactone (1755 cm^{-1}, very sharp band) and hydroxyl (3600-3400 cm^{-1}, broad medium band) functionalities. The hydroxyl band by its occurrence in the 3600-3400 region indicated, perhaps, the presence of an intermolecular hydrogen bond possibly to the lactone carbonyl group. This carbonyl group, at 1755 cm^{-1}, was outside the usual γ-lactone range (normally 1795-1760 cm^{-1}). Microanalysis showed that C=71.9% and H=11.1% indicating an empirical formulae of $C_{22}H_{40}O_4$. Attempts to observe the molecular ion (m/e 368) in the mass spectrum of this compound were unsuccessful, but the $M^{+}-H_2O$ ion at m/e 350 (18%) was



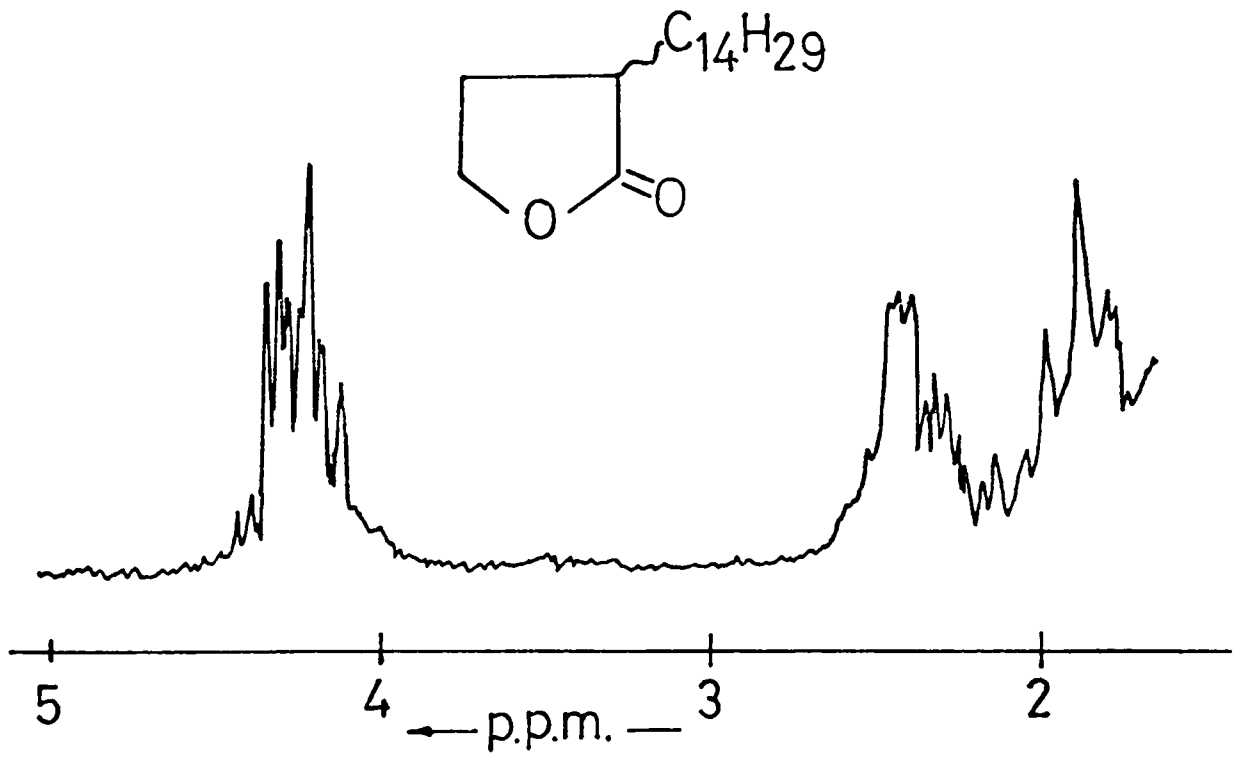


Figure 38. 2-5 p.p.m. region of the 90MHz ^{1}H-n.m.r. of the unknown material and (113(a)), illustrating the doublet of doublets (J=10 and 11Hz) at 2.9 p.p.m.

observed. This was another indication of a hydroxyl group, since loss of water is a principal mode of fragmentation in alcohols. Another high molecular weight peak was at m/e 283, corresponding to the loss of $C_4H_5O_2$ from the molecular ion, probably due to the loss of an ion such as (120). The 90MHz ^{1}H-n.m.r. of the unknown material exhibited resonances at 1.7-2.2 p.p.m. (m, 5H) and 3.5-4.4 p.p.m. (m, 5H) closely resembling the lactone resonances seen for (113(a)). The lower field multiplet decreased in intensity upon shaking with deuterium oxide, indicating the presence of the hydroxyl function under this multiplet. The spectrum showed a doublet of doublets at 2.9 p.p.m. (J=10 and 11Hz). This feature, indicative of a proton flanked by two electron withdrawing functions and a methylene group, is shown in Figure 38 with the same spectral region of (113(a)) as a comparison. While this spectrum did not totally clarify the identity of the unknown substance, it appeared that the compound was a derivative of (113(a)). The ^{13}C-n.m.r. spectrum of the unknown, shown in Figure 39, on comparison with the ^{13}C-n.m.r. spectrum of (113(a)), finally confirmed the structure. Resonances due to the γ-butyrolactone ring in (113(a)) i.e. 28.7, 39.3, 66.6 and 179.7 p.p.m. were also found in the unknown but occurred in pairs, (28.4, 28.6) (44.3,45.8) and (66.6,66.8), except for the carbonyl

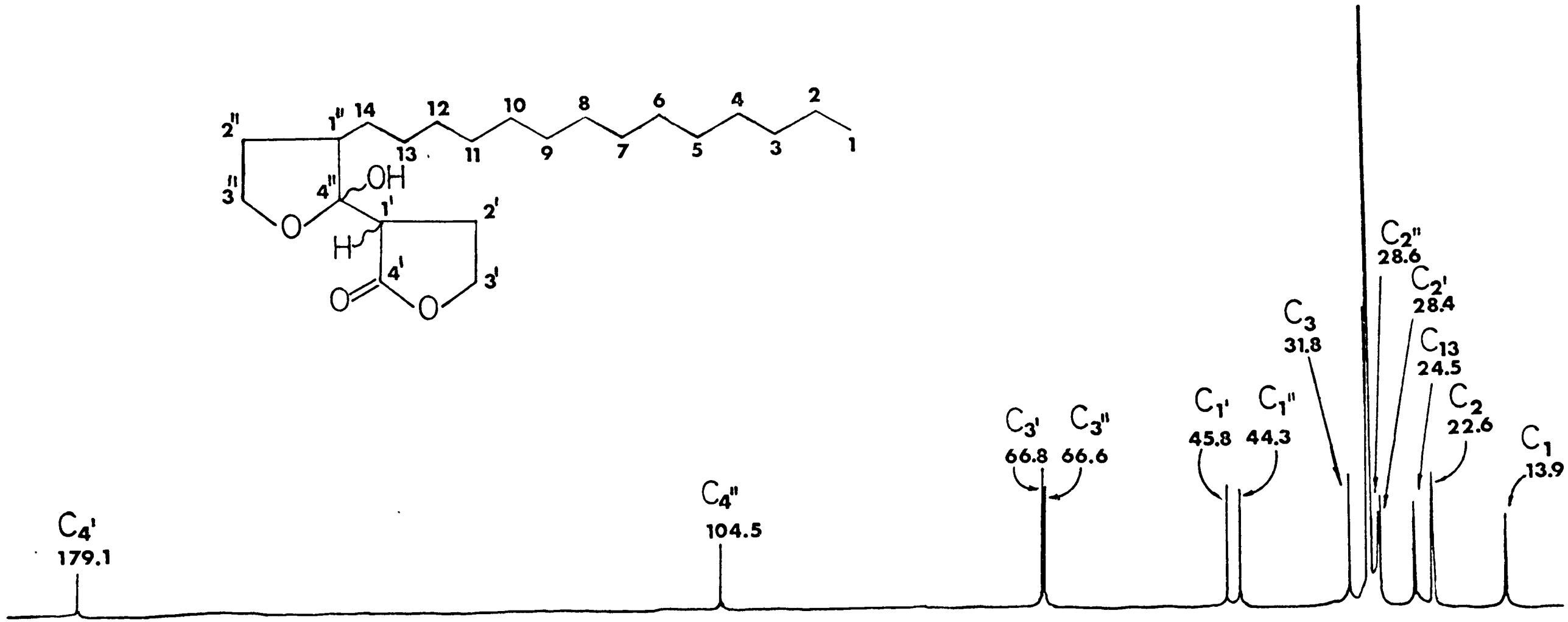
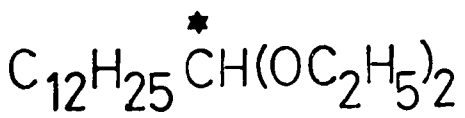


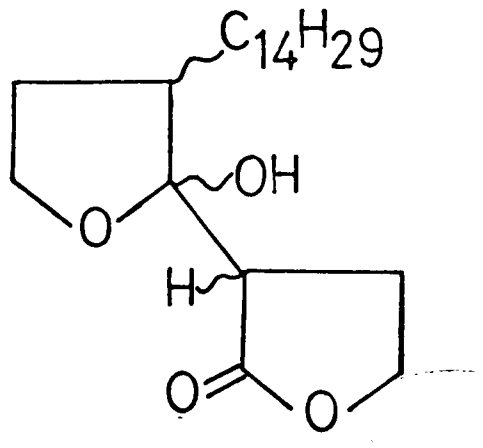
Figure 39. ^{13}C-n.m.r. spectrum of (121) with structural assignments in p.p.m.

carbon where only one peak, at 179.1 p.p.m., was observed. Additionally, a quaternary carbon at 104.5 p.p.m. was evident. Such a chemical shift had been previously observed for the carbon bearing the ethoxy functions in (70) i.e. C^{*}



(70)

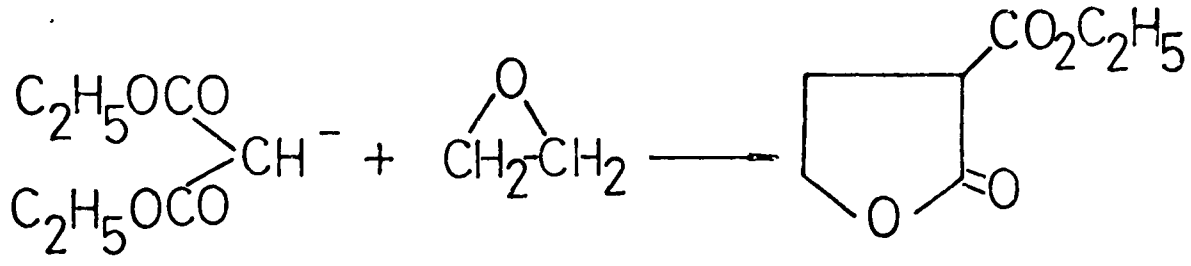
The chemical shift observed for (70) was 102.8 p.p.m. (see Experimental Section). With the data from the various spectroscopic techniques the general structure for the unknown was assigned as (121).



(121)

In order to confirm the general structure (121) and in particular simulate the doublet of doublets observed at 2.9 p.p.m. for (121), a model compound was synthesised. This derivative, (122), was synthesised,

as shown in equation (26), in 21% yield as a colourless, sweet-smelling liquid.



(122) equation (26)

The ^{1}H- and ^{13}C-n.m.r., i.r. and mass spectra of the lactone (122) provided confirmatory evidence of the structure. In particular the doublet of doublets at 3.59 p.p.m. in (123) (Figure 40) is very similar to that observed in (121), as expected.

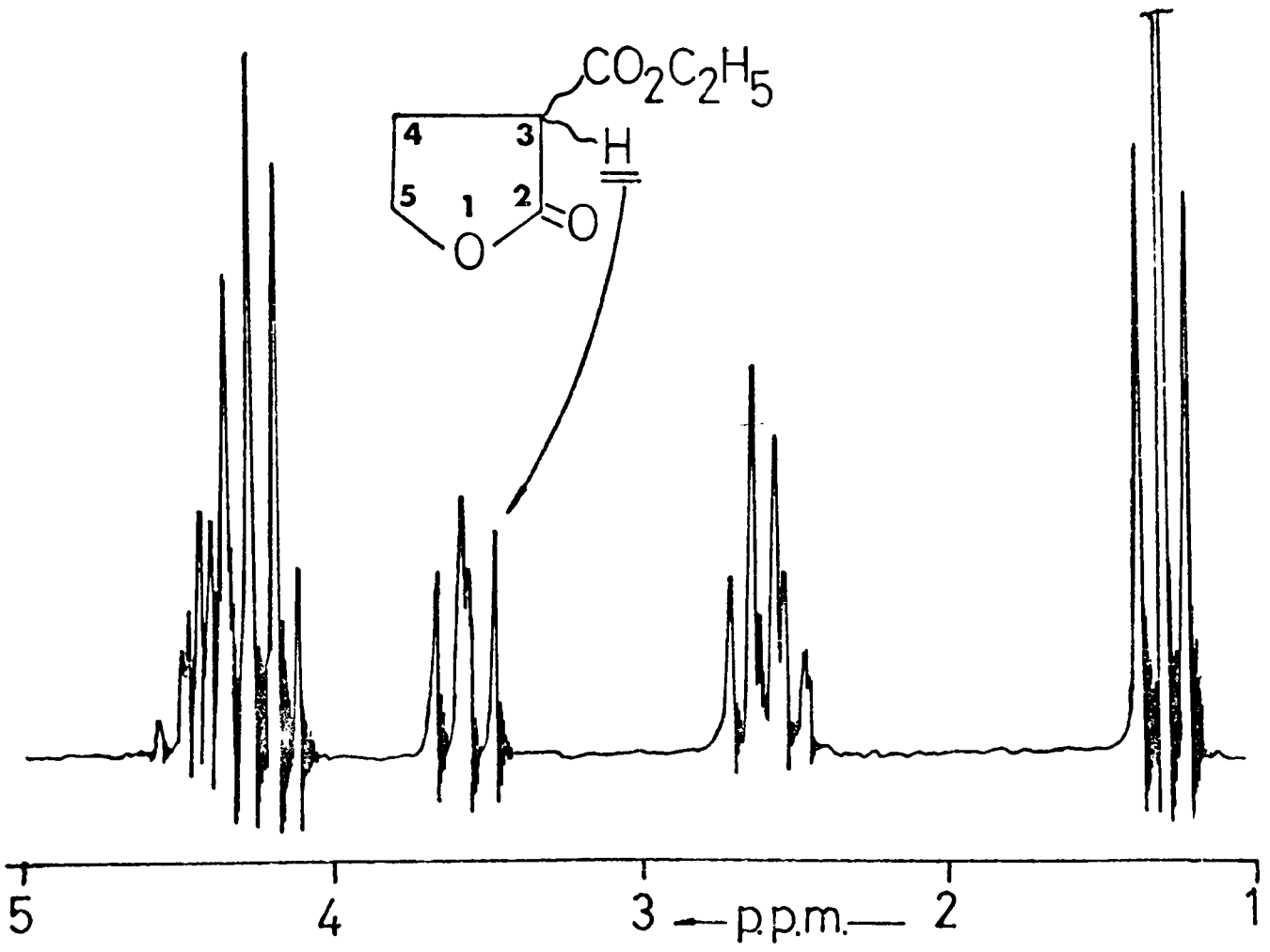


Figure 40. 90MHz ^{1}H-n.m.r. of (122) in $CHCl_3$ exhibiting a doublet of doublets at 3.59 p.p.m., due to the proton in the 3-position

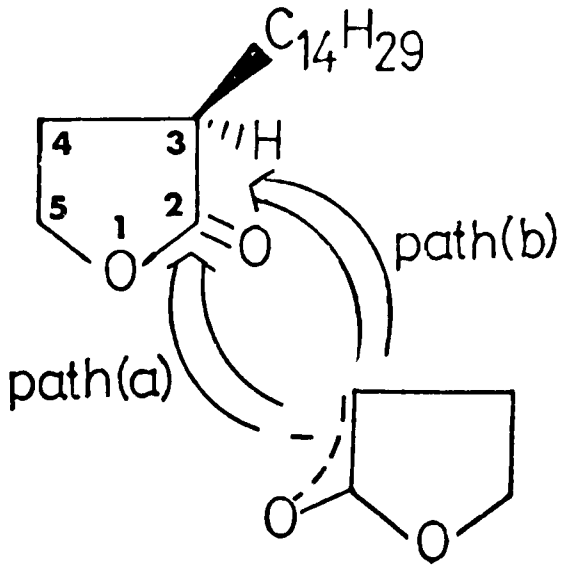


Figure 41. Possible addition pathways of lactone enolate (117) to (113(a)), considering steric interactions. Path (a), "trans"-addition, relative to the alkyl functionality would be favoured.

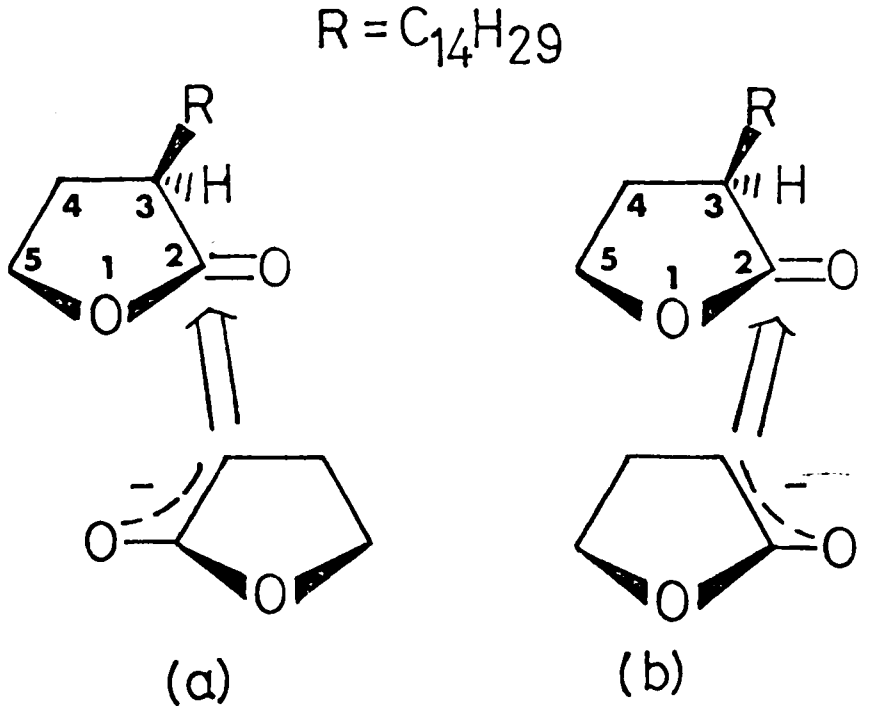
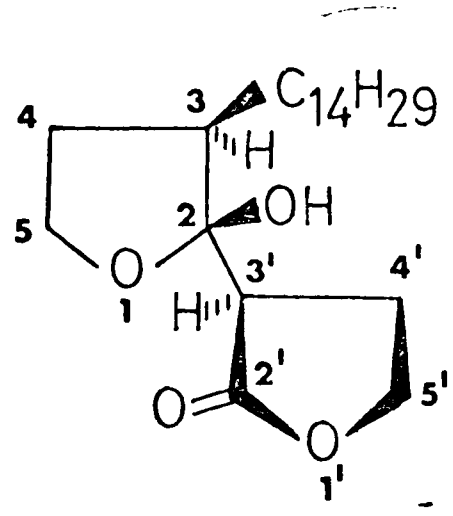


Figure 42. Possible addition pathways of lactone enolate (117) to (113(a)), taking into consideration dipole-dipole interaction

(121) is the product obtained by the addition of the γ-butyrolactone enolate to (113(a)). The fact that the ^{13}C-spectrum exhibited the expected number of resolved peaks, having no evidence of pairwise splittings, indicated that (121) was a single diastereomer. Upon examination of models it was felt that the lactone enolate would prefer to attack the carbonyl functionality from the opposite side to the alkyl function present in the 3-position of (113(a)) i.e. as shown in path (a), rather than path (b) in Figure 41. Path (a) would minimise the steric repulsion between the lactone enolate and the tetradecyl residue. To minimise the dipole-dipole interaction between the enolate and carbonyl functions, the addition would be expected to proceed by the trajectory shown in Figure 42a rather than Figure 42b.

Taking these considerations into account the relative stereochemical arrangement in (121) must be as shown in (123).



(123)

Examination of a model of (123), accurate to 0.1Å in scale, also indicated the probable existence of a hydrogen bond between the hydroxyl and the carbonyl function. Free rotation about the bond joining the 2- and 3'-positions in (123) brings the said hydroxyl in the 2-position to within 1.8-1.9Å of the carbonyl oxygen in the 2-position of (123), as shown in Figure 43.

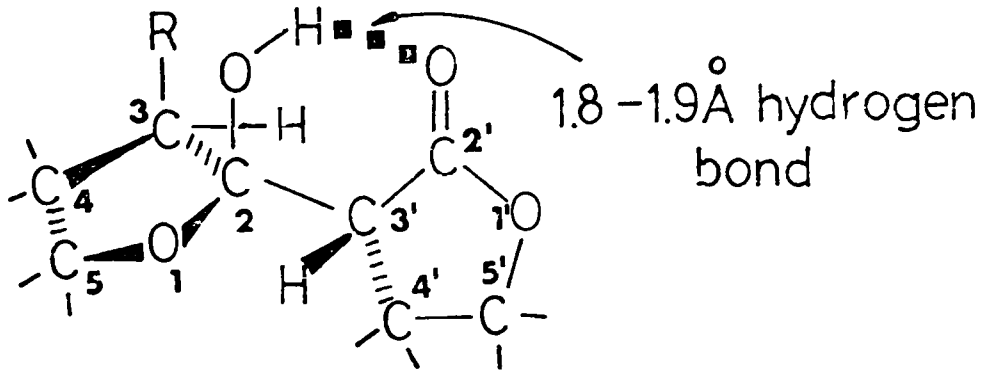


Figure 43. Possible stereochemical array in (123) to promote hydrogen bonding

Evidence for such a hydrogen bond had been seen in the i.r. spectrum of (123) in the hydroxyl and carbonyl stretching bands (3600-3400 cm^{-1} and 1755 cm^{-1} respectively). The carbonyl peak was lower than expected for γ-lactones in in the literature i.e. 1795-1760 cm^{-1}.

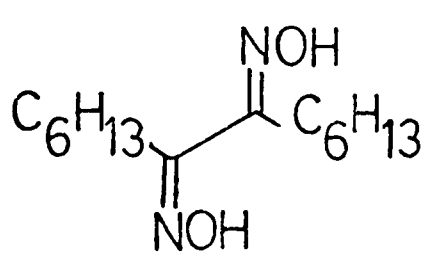
Having successfully isolated ca. 10g of racemic (113(a)) and unexpectedly obtained (123) from the alkylation reaction, the directed resolution of (113(a)) was then to be considered. The (R)- and (S)-forms of (114) were isolated by Dr. Helmchen and his

research group using (-)-(R)-phenylglycinol as the amine to prepare the diasteromers. Details of this separation are at present unavailable and are to be published elsewhere. (R)-(114), α_D=-8.13 (10.0,$CHCl_3$) and (S)-(114), α_D=8.17 (10.2,$CHCl_3$) are at present being investigated by Mr. R. Elliot in Oxford, who is attempting to prepare (R)-(104) and (S)-(104), by chemical transformation of the enantiomerically pure lactones.

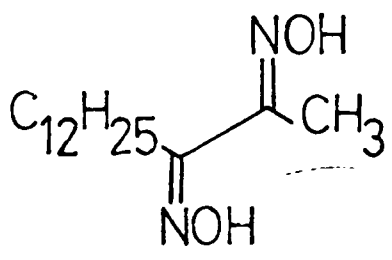
2.5 Reactions of simple α-dioximes in micellar media

2.5.1 Solubilisation of dioximes in aqueous surfactant solutions

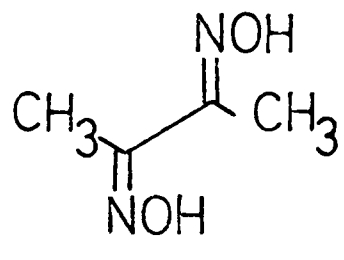
Preliminary experiments indicated that the dioximes (28), (29) and (34) had very little solubility in water, whether buffered or not.



(28)



(29)



(34)

Accordingly a co-micellar system was employed. In such a system the required substrate is solubilised in a micelle of a chemically inert surfactant. Injection of the respective α-dioximes (28), (29) and (34), in

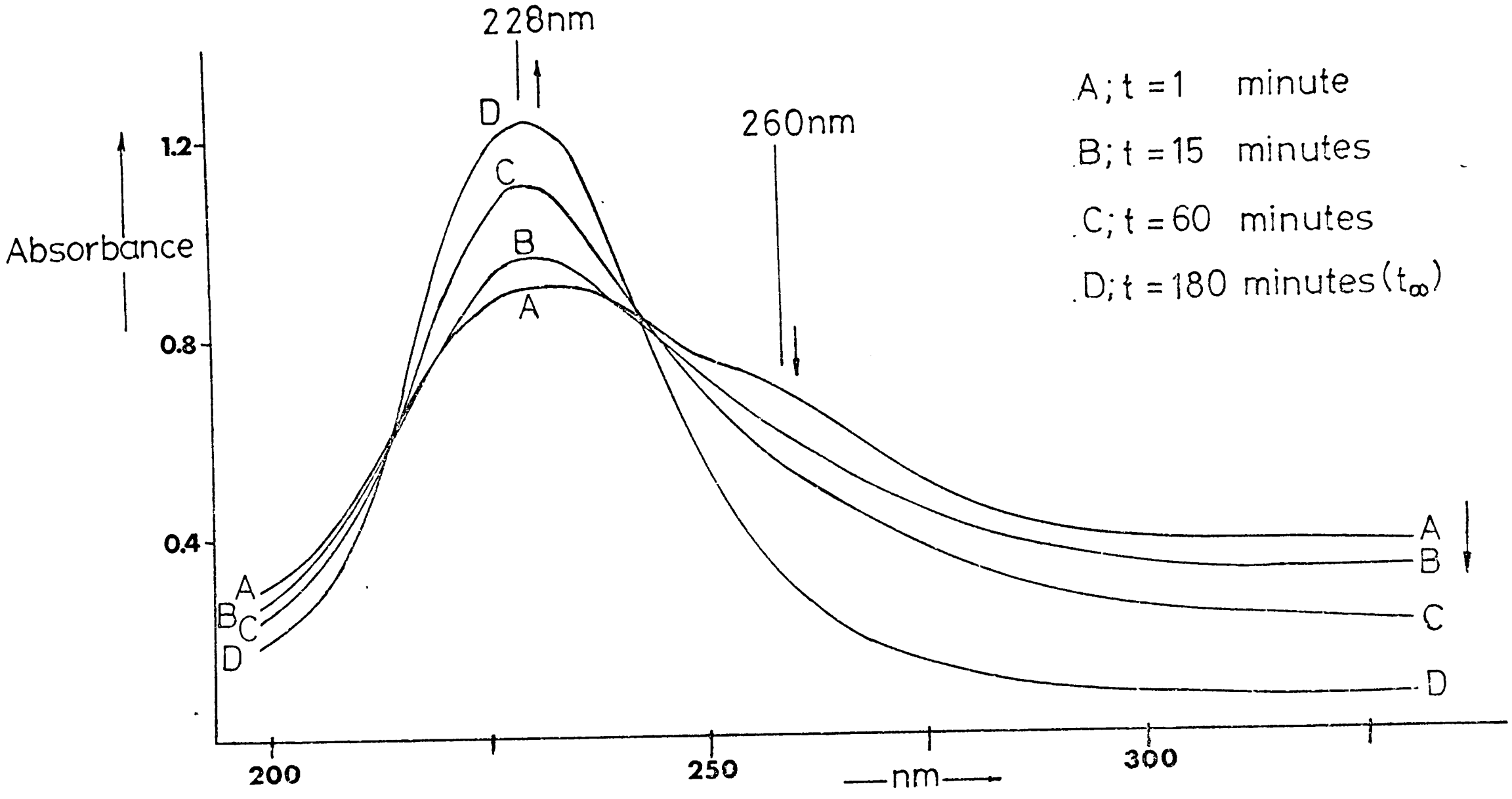


Figure 44. Spectral changes seen on preparing a solution of 10^{-4}M (28) or (29) in a buffered 10^{-2}M solution of (125) at pH=8.0

a water soluble solvent into a buffered surfactant solution was found to be most suitable. It was possible to prepare a 10^{-4}M solution of the dioximes in aqueous surfactant by injecting a tetrahydrofuran solution of dioxime (5×10^{-2}M) into the aqueous phase. Solutions formed in this manner ultimately exhibited a maximum at 228 nm, with an ε value exactly the same as that obtained for a methanol or tetrahydrofuran solution. This implied that the dioxime is bound to the surface of the micelle rather than its interior.

On dissolution of either dioxime (28) or (29) in 10^{-2}M surfactant solution an unusual equilibration phenomena was observed in the 200-350 nm region. On initial mixing the spectrum exhibited peaks at 228 and 260 nm (t=1 min) with considerable accompanying light-scattering. Further monitoring showed that the light scattering diminished markedly with time, with the peak at 228 nm increasing in intensity at the expense of the 260 nm peak, as shown in Figure 44. The final trace, t_∞, obtained after 3 hours was found to correspond to the u.v. maxima seen for dioximes (28) and (29) in methanol or tetrahydrofuran i.e. λ_{max}=228nm, logε=3.95. This equilibration phenomena was seen irrespective of the surfactant solubilisation system and the water soluble solvent used for studying (28) and (29). Attempts to obtain reproducible kinetic data on this equilibration

at 30°C were unsuccessful. First order kinetics were only observed over a short time (ca. 45 minutes) and the results obtained varied from run to run. In particular the kinetics were found to be dependent on the method of injecting the dioxime solution into the surfactant solution, although the rate of attaining the equilibrium was only very slightly affected. However from these attempts it was found that for the equilibration, $k_{obs} \simeq 2.0 \times 10^{-2}$ minute^{-1} ($t_{\frac{1}{2}} \simeq 35$ minutes) for both (28) and (29).

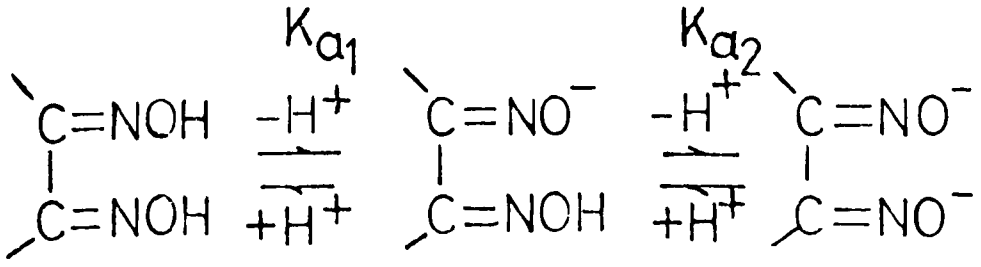
Since the light scattering diminished during the course of the above equilibration, the cause of this phenomena was thought to be a microemulsion of the dioxime dispersed in the surfactant. Initial experiments using ultrasonic techniques appeared to substantiate this theory, since on sonication the equilibrium was driven to completion at a faster rate. Attempts to obtain data at 30°C using sonication equipment were unsuccessful, due to the heating effect of the probe used. In order to eliminate the localised heating effects caused by the aforesaid probe, the equilibration was studied at 40°C for (29) in a 10^{-2}M solution of cetyltrimethylammonium chloride (125), using a water-cooled metal vessel (see Experimental Section).

$$C_{16}H_{33}\overset{+}{N}(CH_3)_3\ Cl^-$$

(125)

Under these conditions it was found that heating effects were eliminated. First order kinetics were observed over six half-lives and the equilibration rate constant at pH 8.0 and 9.0 was found to be 3.85×10^{-2} minute^{-1} ($t_{1/2}$=18 minutes). The reproducibility observed was a direct consequence of sonication, since investigations without sonication at 40°C gave spurious kinetic profiles, similar to those obtained at 30°C. No equilibrium phenomena was observed for (34) under these conditions. Attempts to eliminate the equilibration phenomena by dissolution of the dioximes (28) or (29), either as a solid or in lyotropic surfactant phases with further surfactant solution were unsuccessful since equilibration phenomena were still observed. The equilibration seen is probably a result of microemulsification of the dioximes upon injecting into the surfactant solution. As a result of this microemulsification, solutions of dioximes (28) and (29) in (125) solution were always equilibrated at 30°C for six hours before further reaction e.g. with a metal ion. Surface-tensiometry measurements indicated that (28) or (29) at 1 mole % did not appreciably perturb the cmc of (125).

In alkaline solutions, α-dioximes lose two protons sequentially according to equation (27)



equation (27)

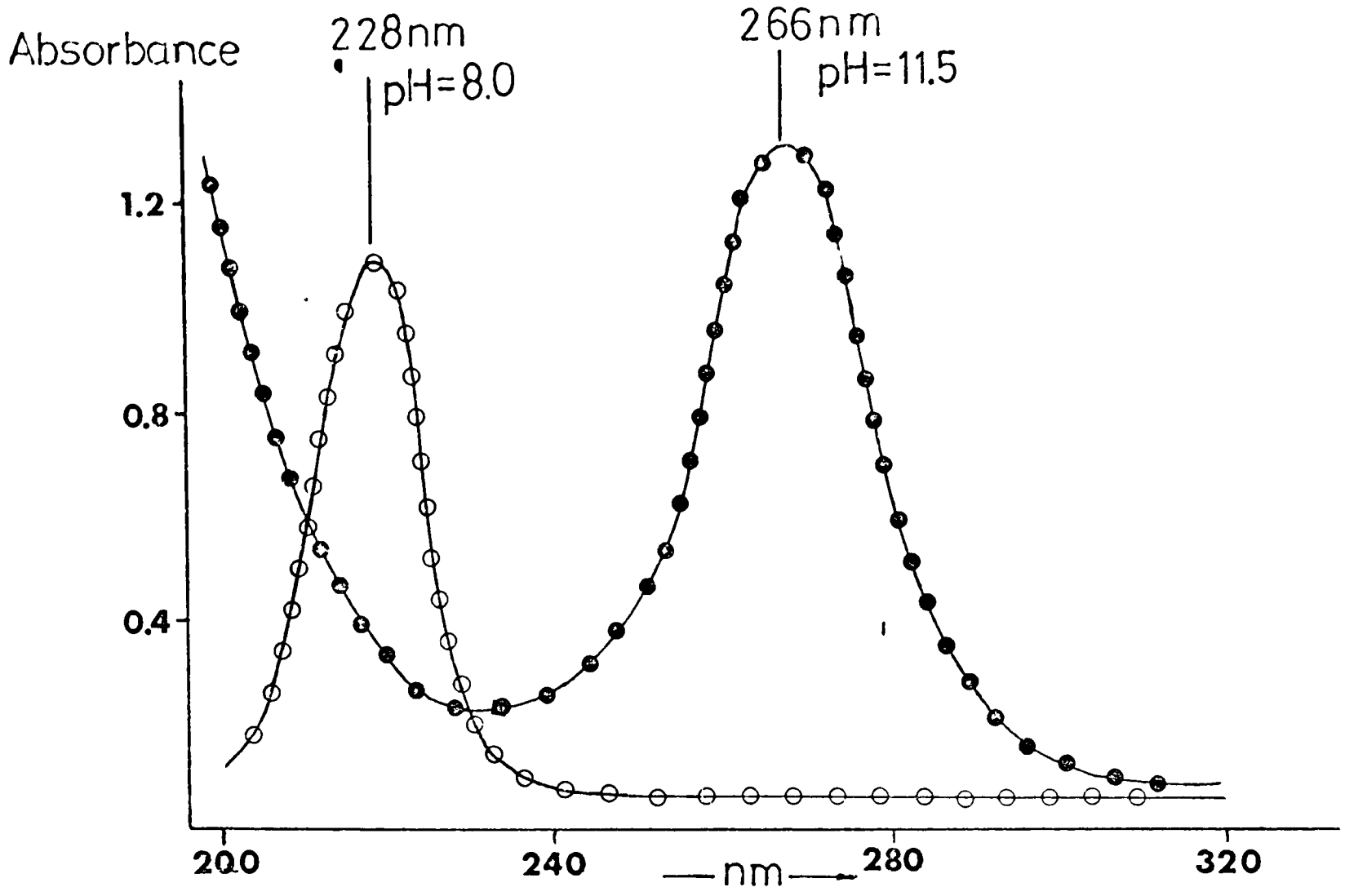


Figure 45. Spectral changes observed on adding sodium hydroxide solution to 10^{-4}M (29) in 10^{-2}M buffered solution of (125)

α-Dioxime	pK_a
Dimethylglyoxime	10.48
Diethylglyoxime	10.67
Di-n-propylglyoxime	10.81
Cyclohexane-1,2-dioxime	10.55
Cycloheptane-1,2-dioxime	10.71

Table 11. Acid dissociation constants of some α-dioximes in water, according to Banks[245]

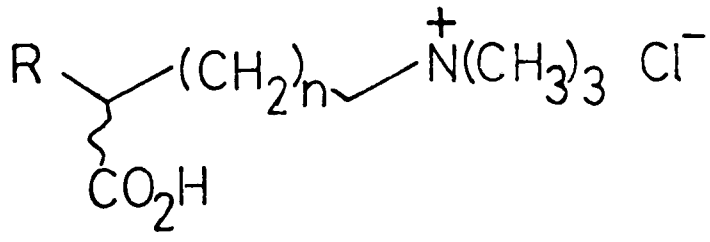
The first pK_a is generally about 10.5 and the second pK_a about 12.[244] The first pK_a, for both (28) and (29) in surfactant solution was found to be 11.0 at 30°C by spectrophotometric titration with sodium hydroxide. Addition of sodium hydroxide to dioxime (28) and (29) in surfactant solution resulted in a bathochromic shift, as shown in Figure 45. The peak obtained at 228nm for an equilibration solution, decreased as the pH was increased to 12.0, with a new peak appearing at 266nm and increasing in intensity as further base was added. The final solution obtained (pH 12) was found to give a single peak at 266nm for up to 4 hours, after which time hydrolysis of the dioxime occurred. Attempts to determine the pK_a's of (28) and (29) in water were unsuccessful, due to their lack of solubility and the apparent hydrolysis which occurred on addition of strong base. In methanol addition of small amounts of base caused precipitation of the dioximes.

The pK_a values for dioximes (28) and (29) are in fact similar to values obtained for the pK_a of some short chain dioximes investigated by Banks[245] (Table 11). As the length of the alkyl group increases so does the value of pK_a for (28) of 11.2-11.4, which is not far removed from the value obtained in surfactant solution. Thus the micelle only has a marginal effect

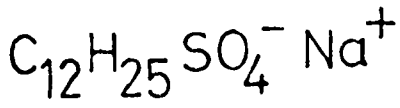
on the ionisation of the dioxime (28). In the surfactant solution the long chain of (29) might be taken up in the micellar interior rather than bound to the micelle surface.

2.5.2 Reaction of nickel with equilibrated dioxime-surfactant solutions

On adding one molar equivalent of a transition metal ion e.g. Ni^{2+}, Cu^{2+}, Fe^{2+} or Co^{2+}, to an equilibrated surfactant-dioxime solution, further changes occurred in the electronic spectra indicating metal-ion complex formation. These spectral changes were, however, found to be dependent on the surfactant system used for the solubilisation of (28) and (29). In the cases of cationic surfactants containing a free carboxyl group i.e. (103(a)), (103(b)), (103(c)) and an anionic surfactant (126), no reaction occurred and only the equilibrium spectrum, ε_{max}=228nm, was seen.



(103)(a) n = 1, R = $C_{14}H_{29}$
(b) n = 3, R = $C_{12}H_{25}$
(c) n = 5, R = $C_{10}H_{21}$



(126)

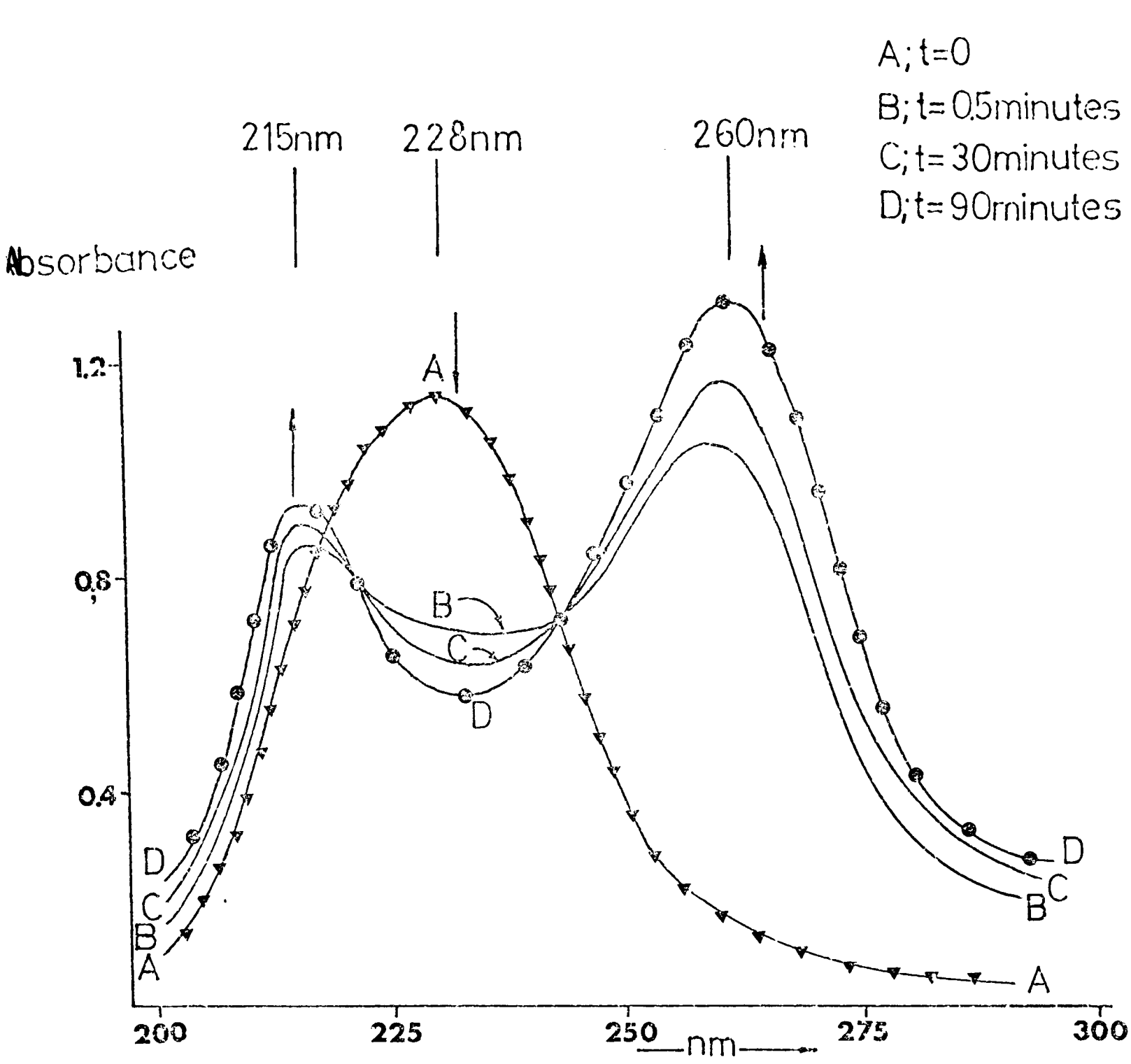
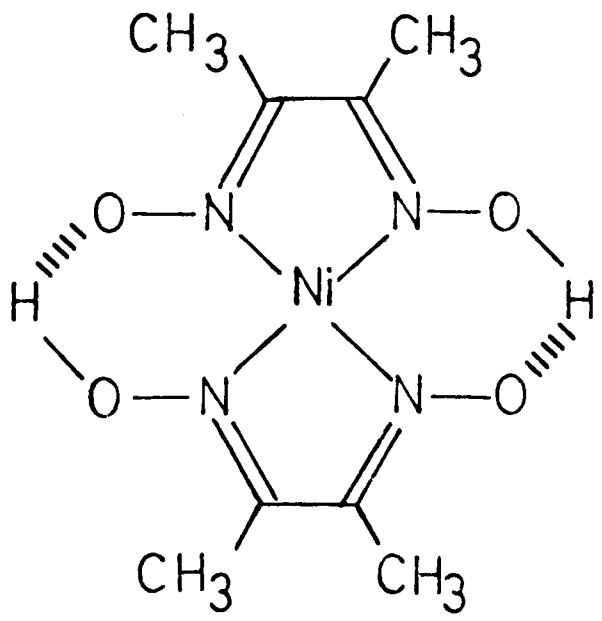


Figure 46. Spectral changes observed on reacting $5x10^{-5}$M Ni^{2+} with 10^{-4}M (28) or (29) in 10^{-2}M buffered (125), pH=8.0

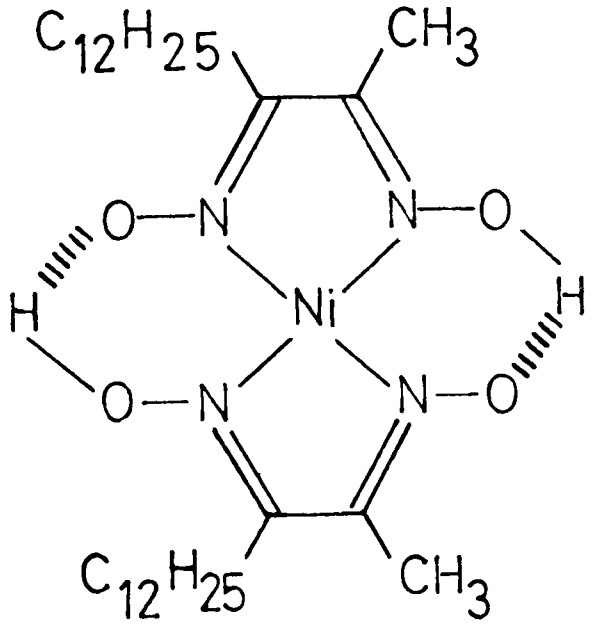
No reaction was seen on addition of vast quantities of metal ion (100 molar equivalents), even over a 7-day period. This lack of transition metal-ion incorporation is best explained by binding of the metal ion on the micelle surface in the case of (126) and for (103(a)), (103(b)) or (103(c)), or binding of the metal-ion to the carboxylate functionality. The fact that no reaction occurred under these conditions also suggested that the dioximes were solubilised in the micelle interior, shielded from the bulk solution. Further studies involving metal-ions thus employed (125) as the solubilising surfactant.

For metal-ion studies Ni^{2+} was chosen as a suitable ion for investigation since the chromophoric change is readily followed. Besides requiring no special experimental techniques e.g. anaerobic conditions, comparison could be made with the well documented nickel-dimethylglyoxime complex (127)



(127)

The spectral changes observed on addition of one molar equivalent of Ni^{2+} to either (28) or (29) in a solution of buffered (125) are shown in Figure 46. Peaks were obtained at 215 ($\log\varepsilon = 4.24$) and 260nm ($\log\varepsilon = 4.39$) in place of the 228nm peak seen in the equilibrated solution (trace A in Figure 46), as time increased; the time taken for equilibration was *ca*. 90 minutes. To confirm that the species observed was the nickel complex of the solubilised dioxime an authentic sample of such a complex was required. Complex (128) was synthesised from dioxime (29) by adaptation of the method used to prepare (127).



(128)

(128) was obtained as an orange-yellow microcrystalline solid, giving a similar u.v. spectrum to that described above, although it was of diminished intensity.

possibly due to difficulties in solubilisation. (128) gave physical data consistent with the proposed structure.

2.5.3 Kinetic studies on metal-ion dioxime-surfactant systems

Initial attempts to measure the rate of nickel oximation in surfactant were plagued by irreproducibility. This was due to the time taken to mix reagents efficiently in a standard spectrophotometer cuvette. Thus an improved cuvette mixer was designed (see Experimental Section), which gave reproducible kinetic data on reactions with $t_{\frac{1}{2}}$ = 1-2 seconds and monitoring at 260nm.

At fixed concentrations of dioxime, (28) or (29), the observed rate constant, k_{obs}, was found to increase linearly with the concentration of Ni^{2+} as shown in Figure 47 (Tables 12 and 13).

$[Ni^{2+}]/M$	k_{obs}/s^{-1}	$t_{\frac{1}{2}}/s$
2.5×10^{-4}	1.75×10^{-2}	39.6
5.0×10^{-4}	3.60×10^{-2}	19.3
7.5×10^{-3}	5.20×10^{-2}	13.3
1.0×10^{-2}	7.10×10^{-2}	9.8

Table 12. Values of k_{obs} for the reaction of Ni^{2+} with 10^{-4}M (28) in 10^{-2}M buffered solution of (125), at pH 8.4 and 30°C

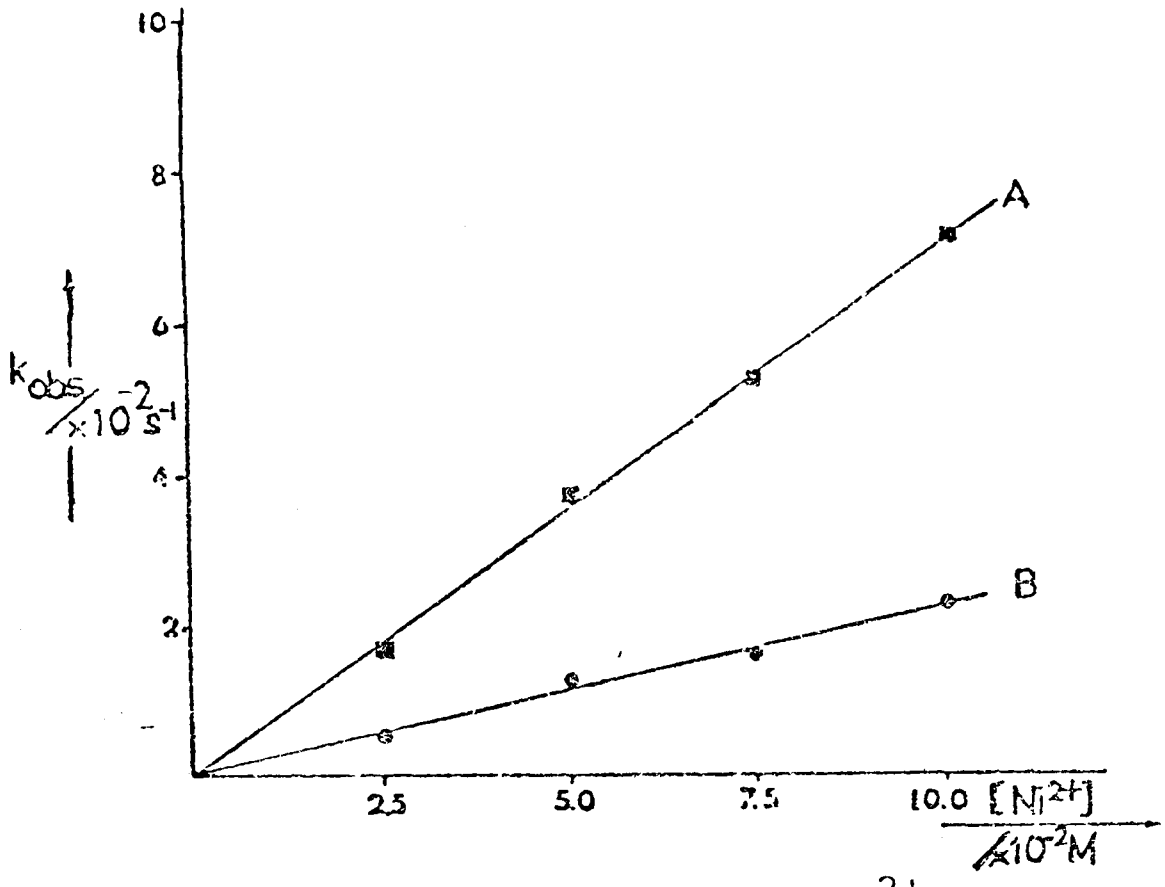


Figure 47. Dependence of k_{obs} on Ni^{2+}; (A) 10^{-4}M of (28) in 10^{-2}M (125) pH=8.4; (B) 10^{-4}M (29) in 10^{-2}M (125) pH=8.05

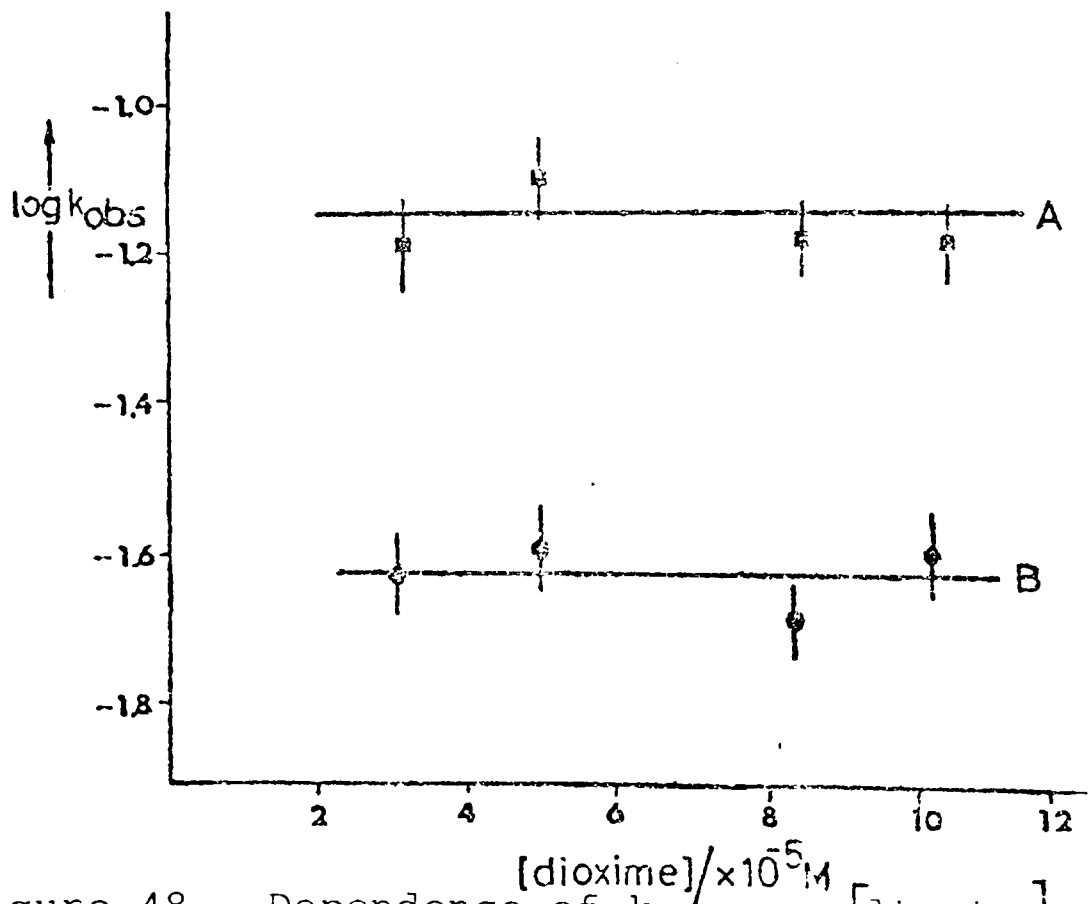


Figure 48. Dependence of k_{obs} on [dioxime] for reaction of 7.5×10^{-2}M Ni^{2+} in 10^{-2}M (125) at 30°C A (29) pH=8.28, B (28) pH=8.1

$[Ni^{2+}]$/M	k_{obs}/s^{-1}	$t_{1/2}$/s
2.5×10^{-4}	5.64×10^{-3}	123.0
5.0×10^{-4}	1.17×10^{-2}	59.5
7.5×10^{-4}	1.63×10^{-2}	42.5
1.0×10^{-3}	2.23×10^{-2}	31.1

Table 13. Values of k_{obs} for the reaction of Ni^{2+} with 10^{-4}M (29) in 10^{-2}M buffered solution of (125), at pH=8.05 and 30°C

The rate constant, k_{obs}, does not change when the dioxime concentration is varied whilst holding the pH, nickel and surfactant concentration constant. Data are presented in Tables 14 and 15 and plotted in Figure 48.

[28]/M	k/s^{-1}	$t_{1/2}$/s	logk
1.0×10^{-4}	2.41×10^{-2}	28.8	-1.62
8.3×10^{-5}	1.98×10^{-2}	35.0	-1.70
5.0×10^{-5}	2.60×10^{-2}	26.7	-1.59
3.3×10^{-5}	2.31×10^{-2}	30.0	-1.64

Table 14. k_{obs} for reaction of 7.5×10^{-3}M Ni^{2+} with variable concentrations of (28) in 10^{-2}M buffered solution of (125), at pH 8.1 and 30°C

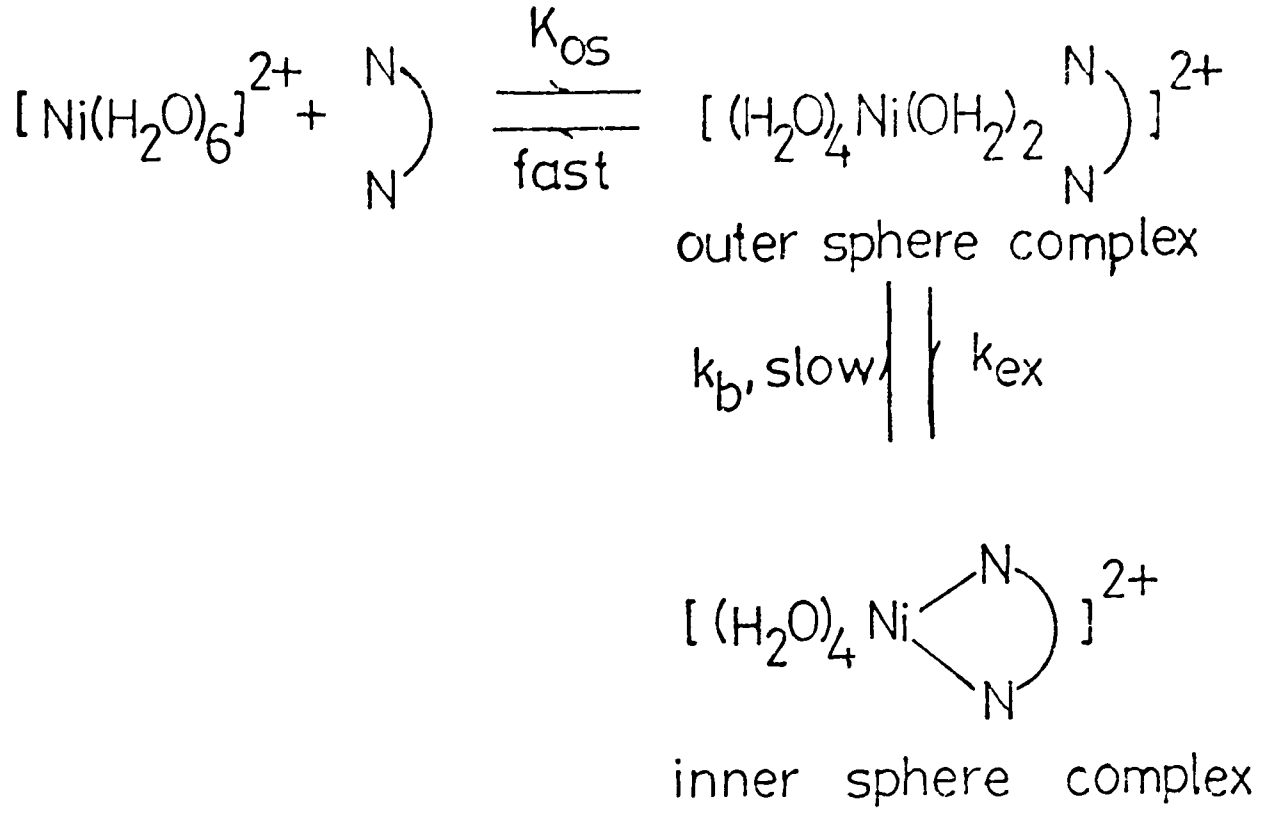
[29]/M	k/s^{-1}	$t_{1/2}/s$	logk
1.0×10^{-4}	6.37×10^{-2}	10.9	-1.196
8.3×10^{-5}	6.45×10^{-2}	10.7	-1.190
5.0×10^{-5}	7.97×10^{-2}	8.7	-1.099
3.3×10^{-5}	6.22×10^{-2}	11.2	-1.207

Table 15. k_{obs} for reaction of 7.5×10^{-3}M Ni^{2+} with variable concentrations of (29) in 10^{-2}M buffered solution of (125), at pH 8.28 and 30°C

This shows that there is a zero or first order dependence on [dioxime]. The first order dependence observed in $[Ni^{2+}]$ is consistent with a Eigen-Wilkins mechanism[245] for which the general expression is shown in equation (28) (where $[Ni^{2+}] >> [ligand]$),

$$k_{obs} = a\ [Ni^{2+}] + b \qquad \text{equation (28)}$$

In this mechanism the rate determining step of the reaction is the loss of water from the inner co-ordination sphere of the metal-ion, following the rapid formation of an outer sphere complex. Subsequent steps are usually rapid in aqueous solution e.g. ligand ring closure. The mechanism is presented for a bidentate system in Scheme 11.



Scheme 11. Proposed course for an Eigen-Wilkins mechanism

K_{os} is the equilibrium constant for outer sphere complex formation and k_{ex} is the first order rate constant for water loss. The first order rate constant for complex formation where $[Ni^{2+}] >> [ligand]$, and $K_{os} << [Ni^{2+}]^{-1}$, can be expressed as in equation (29)

$$k_{obs} = K_{os} . k_{ex} . [Ni^{2+}] + k_b \qquad \text{equation (29)}$$

where k_{obs} is the observed first-order rate constant for metal complex formation.

The value of k_{obs} is also dependent on pH. Preliminary experiments indicated little reaction below pH 7; indeed decomposition of dioximes in acidic media occurs and has been previously studied.[244] First-order kinetics were observed over the pH range 7.9-9.2 for (28) and (29) at constant Ni^{2+}, dioxime and surfactant concentrations. The results are shown in Tables **16** and **17**,

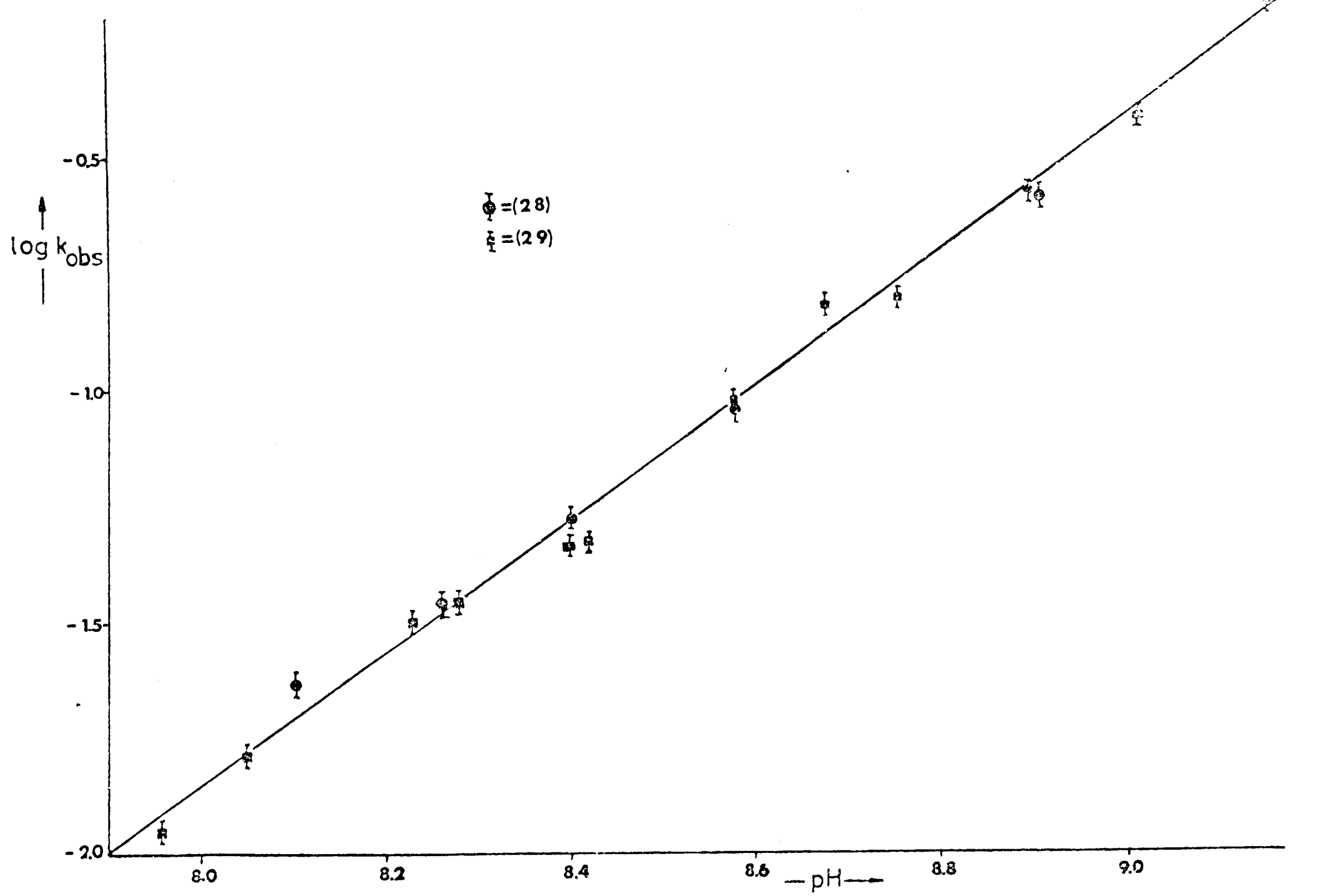


Figure 49. Dependence of k_{obs} on pH for the reaction of 7.5×10^{-2}M Ni^{2+} with 10^{-4}M (28) and (29) in buffered 10^{-2}M (125) at 30°C

and represented graphically in Figure 49.

pH	k/s^{-1}	$t_{1/2}/s$	logk
8.10	2.41×10^{-2}	28.80	-1.62
8.26	3.34×10^{-2}	20.70	-1.48
8.40	5.20×10^{-2}	13.30	-1.28
8.58	9.18×10^{-2}	7.55	-1.04
8.91	2.53×10^{-1}	2.74	-0.60

Table **16.** Dependence of k_{obs} on pH for reaction of 7.5×10^{-3}M Ni^{2+} with 10^{-4}M (28) in a buffered solution of (125) at 30°C

pH	k/s^{-1}	$t_{\frac{1}{2}}/s$	logk
7.96	1.14×10^{-2}	61.10	-1.945
8.05	1.63×10^{-2}	42.50	-1.788
8.23	3.19×10^{-2}	21.70	-1.496
8.28	3.44×10^{-2}	20.10	-1.463
8.40	4.58×10^{-2}	15.10	-1.339
8.42	4.70×10^{-2}	14.70	-1.326
8.58	9.34×10^{-2}	7.42	-1.030
8.68	1.49×10^{-1}	4.65	-0.827
8.76	1.55×10^{-1}	4.48	-0.811
8.90	2.55×10^{-1}	2.72	-0.593
9.02	3.69×10^{-1}	1.88	-0.433
9.15	5.03×10^{-1}	1.38	-0.298

Table 17. Dependence of k_{obs} on pH for reaction of 7.5×10^{-3}M Ni^{2+} with 10^{-4}M (29) in a buffered solution of (125), at 30°C

A linear relationship was again obtained for both (28) and (29). The rate constants, k_{obs}, for (28) and (29) at a given pH were found to be the same, indicating a common mechanism. The similarity of k_{obs} for these structurally different dioximes shows that they are not involved in the rate-determining stage. Although a linear relationship was observed in the pH range 7.0-9.2, above pH 9.2 the reaction rate was too fast to measure by standard spectrophtotmeric

techniques. Since $\log k_{obs}$ was found to increase linearly between pH 7.9-9.2 this indicated that a term $[H^+]^n$ was included in the rate law (where n is a negative integer). The negative dependence on $[H^+]$ can be attributed to a complex pre-equilibrium deprotonation step. The gradient of Figure 49 is 1.4 (correlation coefficient = 0.997) so that a single pathway is unlikely. Rather, there is a deprotonation of the divalent hexaquo nickel ion (129) at the micellar surface according to equation (30).[247,248]

equation (30)

(129) $[Ni(H_2O)_6]^{2+}$

$+H^+ \rightleftharpoons -H^+$

(130) $[Ni(OH)(H_2O)_5]^{+}$

$+H^+ \rightleftharpoons -H^+$

(131) $[Ni(OH)_2(H_2O)_4]$

All the work described to date was conducted in 10^{-2}M solutions of (125) i.e. an order of magnitude above the cmc of 10^{-3}M. The reaction rate was therefore

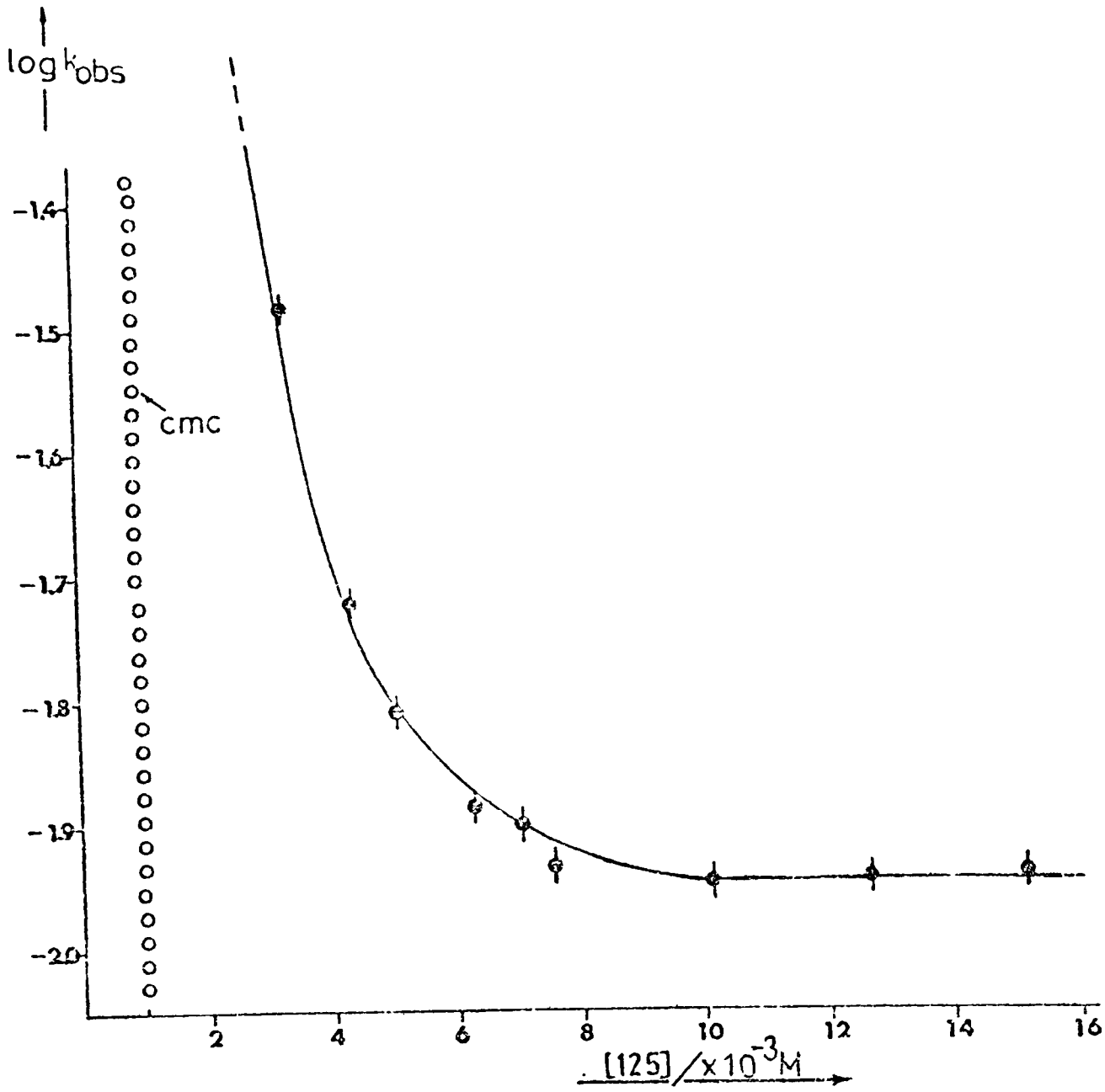


Figure 50. Dependence of k_{obs} on [surfactant] for reaction of 3.75×10^{-4}M Ni^{2+} with 5.00×10^{-5}M (29) in buffered solutions of (125) at pH 7.96 and 30°C

studied by varying the surfactant concentration whilst holding other parameters constant. The results for the study involving (29) are given in Table **18** and are shown in Figure 50.

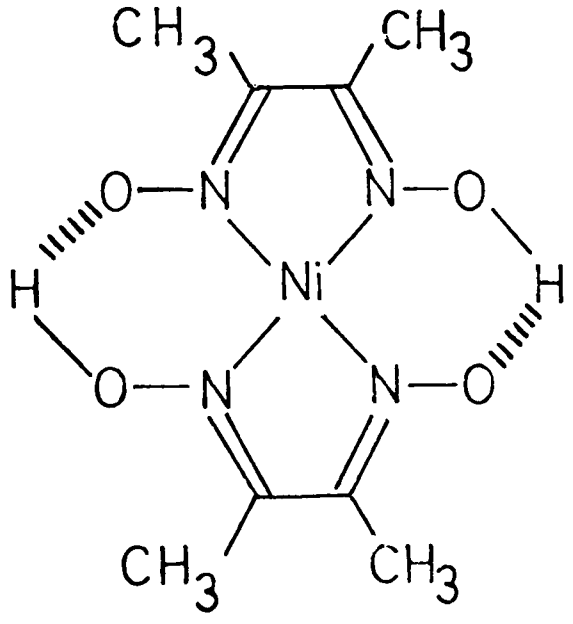
[125] /M	k/s^{-1}	$t_{\frac{1}{2}}$/s	logk
3.17×10^{-3}	3.24×10^{-2}	21.4	-1.490
4.16×10^{-3}	1.90×10^{-2}	36.5	-1.722
5.00×10^{-3}	1.54×10^{-2}	45.0	-1.812
6.26×10^{-3}	1.31×10^{-2}	52.7	-1.881
7.04×10^{-3}	1.26×10^{-2}	55.0	-1.900
7.50×10^{-3}	1.18×10^{-2}	58.7	-1.928
1.00×10^{-2}	1.14×10^{-2}	60.8	-1.943
1.25×10^{-2}	1.14×10^{-2}	60.8	-1.943
1.50×10^{-2}	1.15×10^{-2}	60.3	-1.939

Table **18**. Dependence of k_{obs} on surfactant concentration for the reaction of 3.75×10^{-4}M Ni^{2+} with 5.00×10^{-5}M (29) in buffered solutions of (125) at pH 7.96 and 30°C

In this particular study the concentration of (29) was maintained at 5.00×10^{-5}M to avoid solubility difficulties at low surfactant concentrations. As can be seen from Figure 50 the rate of complex formation is greatest just above the cmc determined from the buffered dioxime-surfactant system i.e. 1.00×10^{-3}M. Such a

rate decrease, as the surfactant concentration is increased can be explained in terms of the reaction of unbound dioxime at low surfactant concentrations. The shape of the rate-inhibition curve is the reverse of that normally observed in micellar catalysis when the reaction transition-state and head groups are of opposite charge types.

On reaction of (34) in buffered surfactant solution with Ni^{2+} at pH 8.05 a very different phenomena occurred. Rapid incorporation of Ni^{2+} was seen with $t_{1/2} \gg 0.5$ seconds and complex kinetics. Precipitation of the nickel complex (127) i.e.



(127)

began with 10-15 seconds. Precipitation continued until after ca. 60 seconds 90% of (127) had been deposited.

A typical trace is shown in Figure 51, showing the precipitation procedure as a fall in the absorption at 260nm.

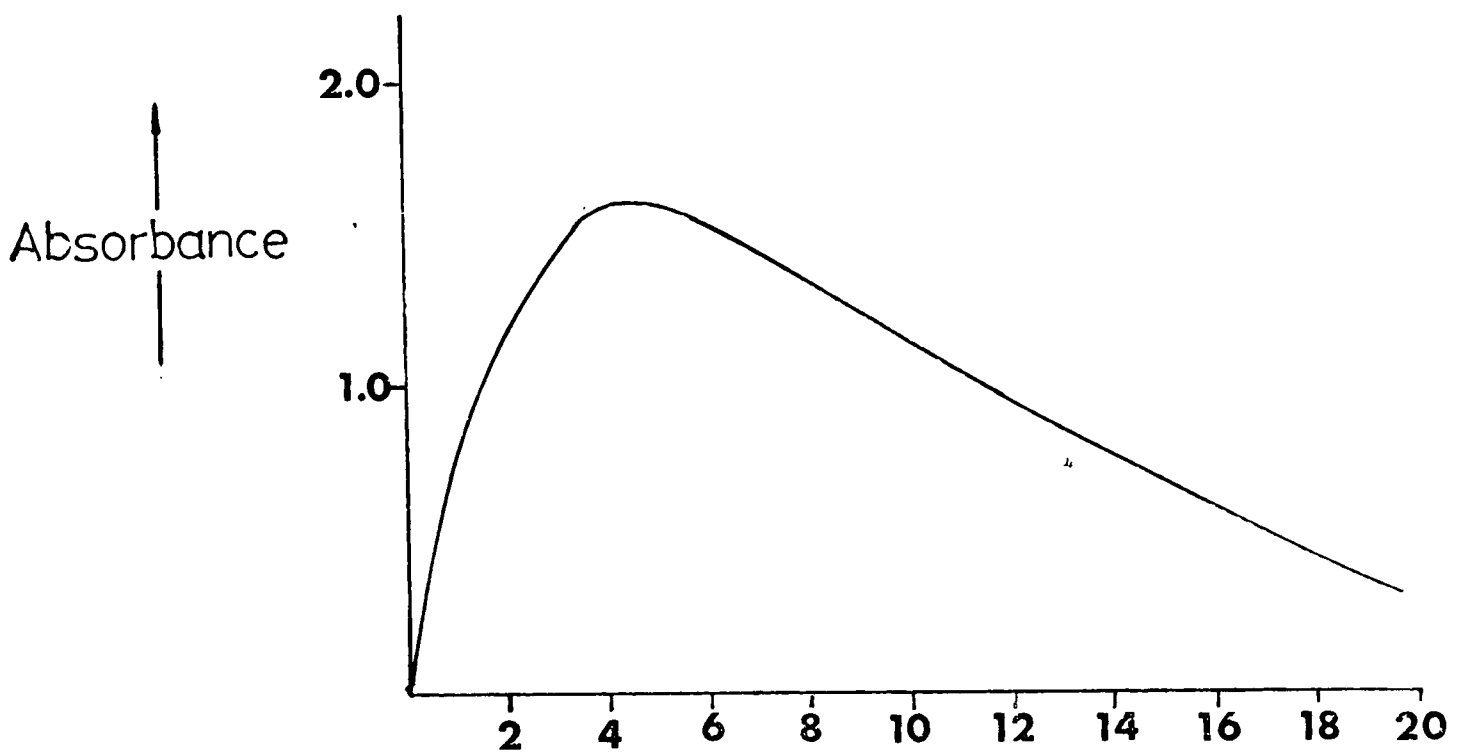


Figure 51. Typical spectrophotometer trace for the reaction of 7.5×10^{-4}M Ni^{2+} with 5×10^{-5}M (34) in a buffered solution of 10^{-2}M (125) at pH 8.05

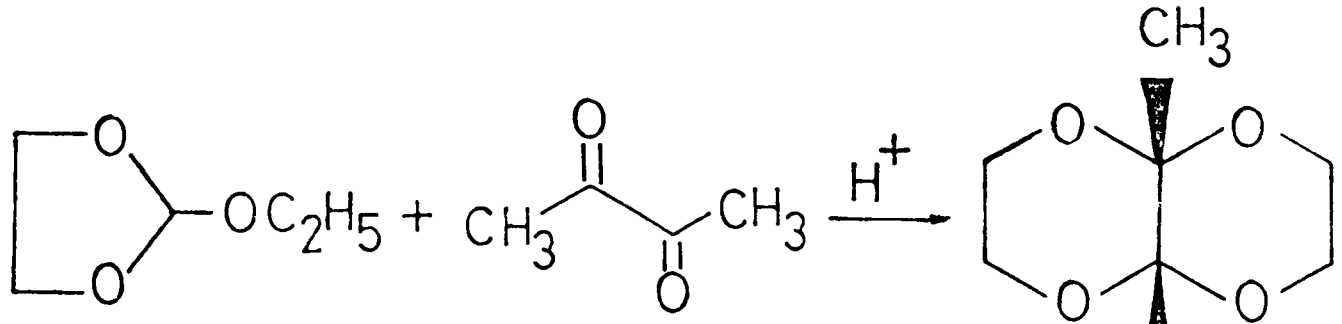
The complex formed was found to be identical with an authentic sample of (127). Obviously micelles have no overall effect on the rate of reaction since complex formation appears to arise mainly in bulk solution.

These studies demonstrate that metal-ion complexation can be profoundly affected in both rate and mechanism by micellisation.

2.6 Dynamic n.m.r. studies on a substituted 1,4,5,8-tetraoxadecalin

With the recent upsurge in the study of conformational analysis of heterocyclic systems[220] the ketalisation products of α-diketones have attracted considerable attention. Reasons for this special attention have been due to the ease of synthesis, their use in industrial processes and unusual properties.[249] In particular the interplay of C-O bond dipoles, results in enhanced "anomeric" effects.[250-252] In the course of studies on possible protecting groups for α-diketones, the reaction of 2-ethoxy-1,3-dioxolane (49) with butan-2,3-dione was investigated.

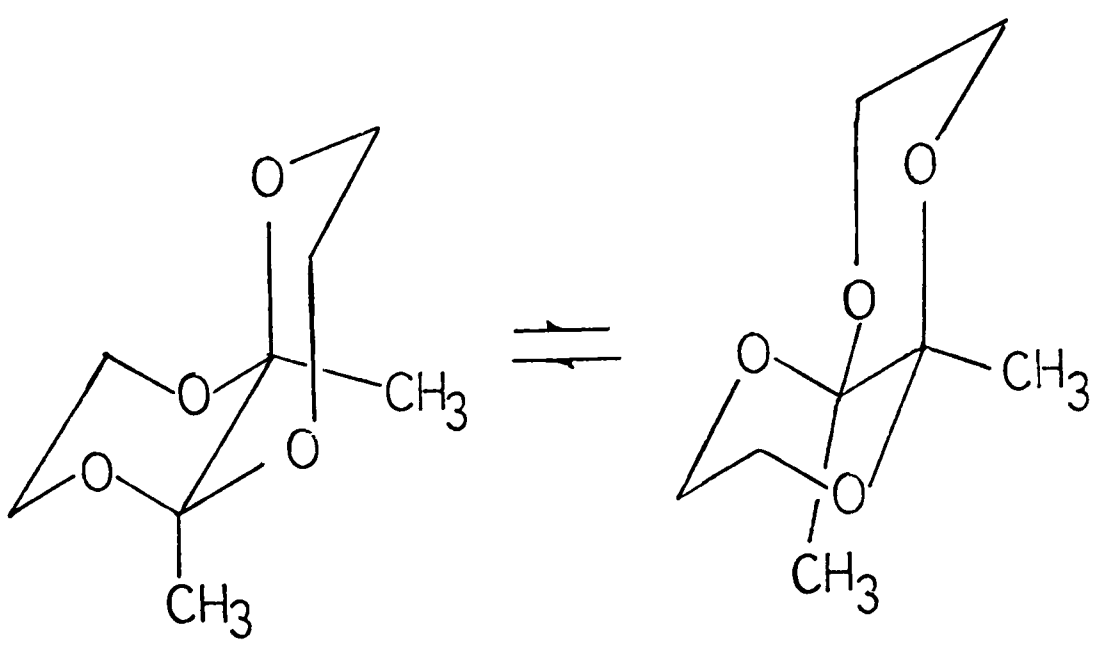
Under a number of conditions the reaction always gave the tetraoxadecalin (51) as the exclusive product, in >90% isolated yield after recrystallisation from hexane i.e.



(49) (51)

No trace of the bisketal (48, R=Me) or any other product could be detected by t.l.c. or n.m.r. of the crude reaction mixture. In an attempt to prove the

cis-configuration of (51), the variable temperature ^{1}H-n.m.r. was investigated. For a cis-isomer, a "flipping" between enantiomeric forms of (51), as indicated below, would produce a temperature dependent n.m.r. spectrum.



In the case of a trans-isomer, no such behaviour would be observed due to the "locked" configuration.

At room temperature (51) was found to be very soluble in many solvents, exhibiting a single peak for the methyl groups at the bridgehead positions, and an AA'BB' multiplet for the methylene protons of the $-OCH_2CH_2O-$ portion. The chemical shift for the AA'BB' multiplet was found to be strongly dependent on the solvent i.e. CCl_4, $CDCl_3$, CD_2Cl_2 3.5-4,2 p.p.m., d^8-$PhCH_3$ and d^6-C_6H_6 3.2-4 p.p.m. An upfield shift was observed in the aromatic solvents. The application of different solvents assisted in the interpretation of the spectra since changes in $\Delta\nu_{AB}$ altered the line positions

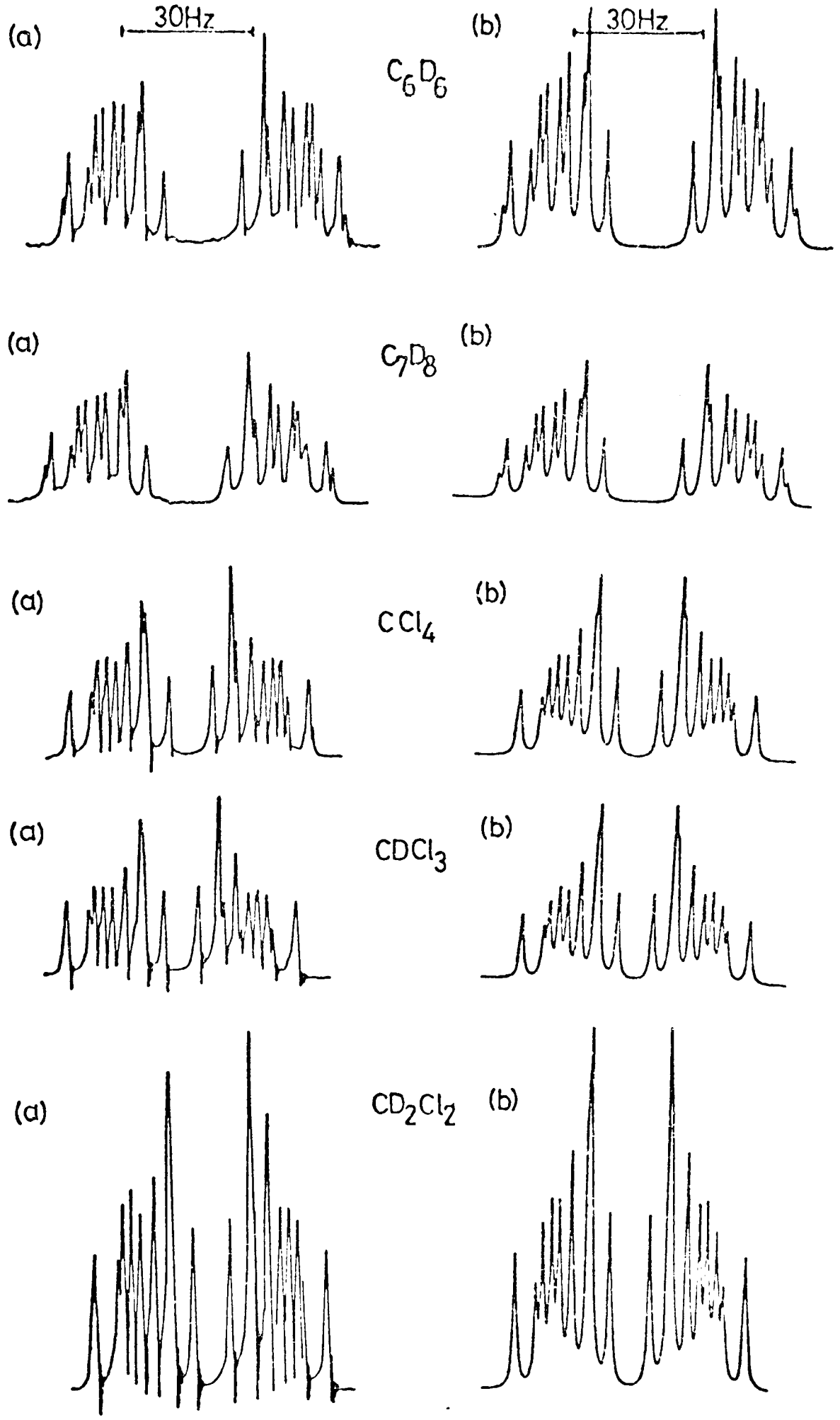


Figure 52. Actual (a) and simulated (b) spectra for the AA^1BB^1 multiplet obtained in the 90MHz ^1H-n.m.r. of cis-(51) in various solvents

and intensities. The agreement between actual and computed spectra was found to be better than 0.2Hz, as shown in Figure 52. The spectral parameters, displayed in Table **19**, were calculated by computer simulation using standard techniques.[253]

Solvent	δ_{AA}	δ_{BB}	$\Delta\nu_{AB}$	$J_{ee}=J_{aa}$	$J_{ea}=J_{e'a'}$	J_{gem}	$W_{1/2}$
CCl_4	355.93	322.00	33.93	6.60	3.16	-11.53	1.6
$CDCl_3$	365.78	333.08	32.7	6.81	3.04	-11.60	1.6
CD_2Cl_2	361.23	329.61	31.62	6.67	3.16	-11.68	1.6
C_6D_6	346.54	301.83	44.71	6.62	3.32	-11.73	1.6
C_7D_8	344.44	300.77	43.63	6.63	3.35	-11.68	1.6

Table **19**. Chemical shifts, coupling constants and $\Delta\nu_{AB}$ values, in Hz, for the iterated spectra shown in Figure 52 for the $AA'BB'$ multiplet of (51) at room temperature

From Table **19** it can be seen that the two vicinal coupling constants J_{ea} and $J_{e'a'}$ are equal. Such a result is only reasonable if (51) possesses the cis-configuration and undergoes a rapid chair-chair interconversion at room temperature. The values obtained for J_{ea}, J_{ee}, J_{aa} and J_{gem} are in good agreement with the coupling constants previously obtained for inverting chair-forms of other cyclic heteroatom compounds,[249b] as indicated in Table **20**.

Compound	$J_{aa}+J_{ee}$	J_{ea}	J_{gem}
cis-2,3-Dichloro-1,4-dioxan	12.6	3.1	-12.2
cis-2,3-Diphenyl-1,4-dioxan	12.7	3.0	-11.9
cis-Naphthodioxan	12.6	2.9	-11.7
1,4-Dioxan	13.0	2.7	-
cis-2,5-Dimethyl-1,4-dioxan	11.4	2.6	-11.8
Morpholine	13.1	3.0	-

Table **20.** Coupling constants for a series of inverting saturated heterocyclic ring compounds[249b]

From Table **19** it can also be seen that the geminal coupling constants are negative and are typical for protons attached to sp^3 hybridised carbon atoms. The existence of boat or twist-boat forms in measurable quantities can be excluded for a number of reasons. Firstly the i.r. spectrum of (51) in solution is practically identical to that of the solid. Secondly, the couplings for 1,4-dioxane and (51) are very similar and the former is known to exist exclusively in the chair form.[249b] Finally, the J values are independent of the solvent used; if any other forms were present discrepancies would occur on changing solvents. Recently Fuchs *et al.*[251] have studied, by X-ray crystallography and dynamic

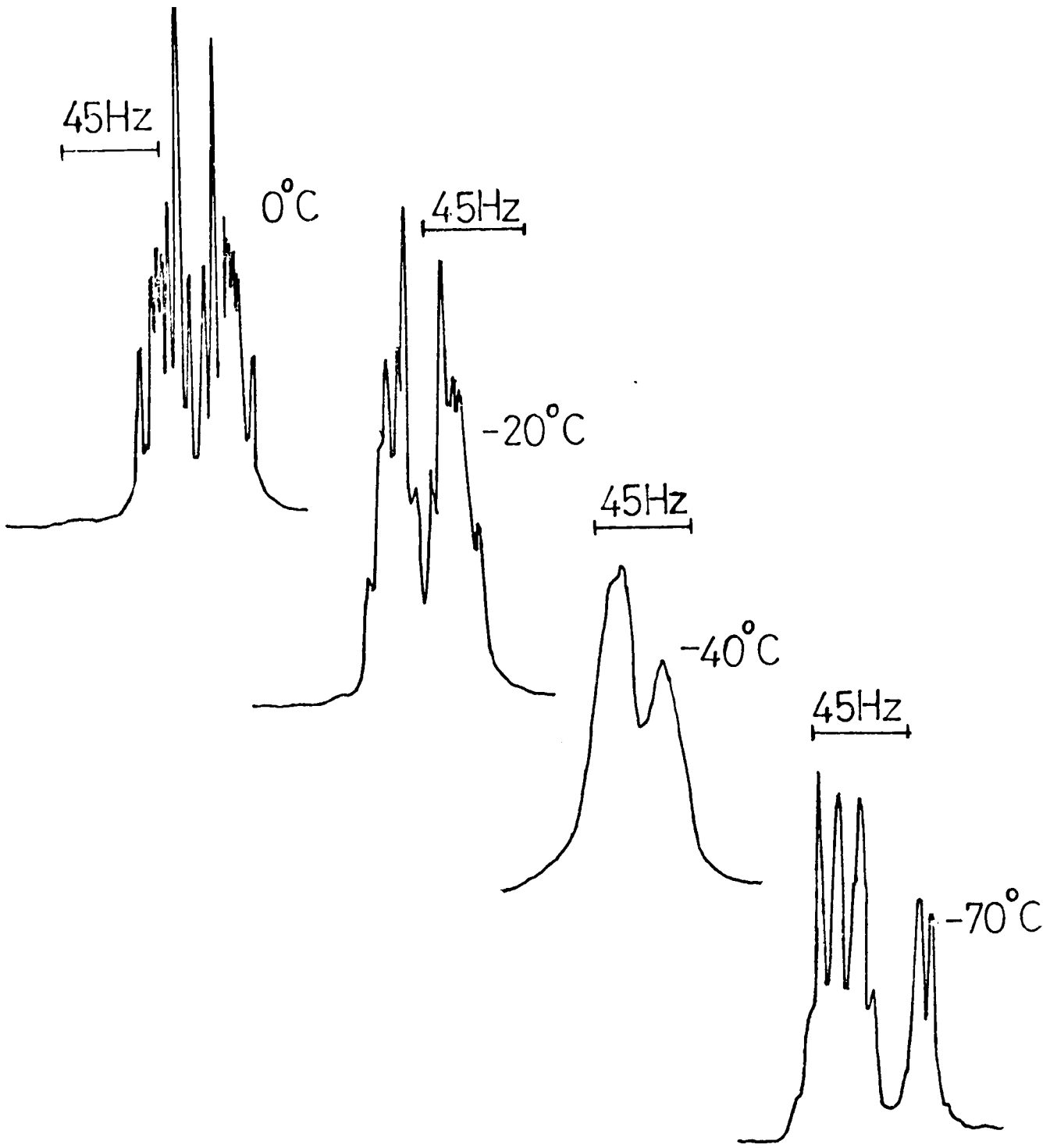
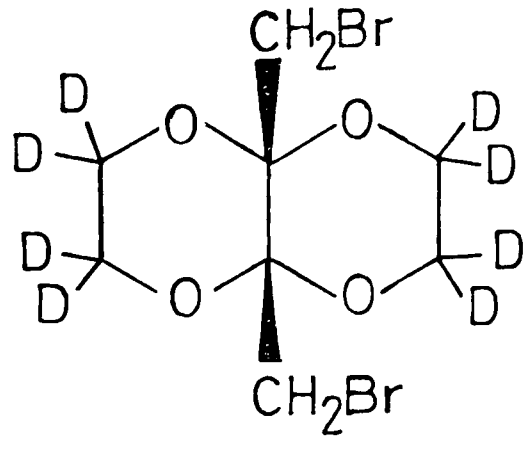


Figure 53. Variable temperature 90MHz ^{1}H-n.m.r. for (51) in CD_2Cl_2, showing the collapse of the AA^1BB^1 multiplet between 3.5 and 4.15 p.p.m.

n.m.r., (132), which is structurally very similar to (51)



(132)

In this study it was found that the structure at room temperature was a double chair conformation and the temperature dependent ^{1}H-n.m.r. was consistent with flipping between the two enantiomeric forms.

A variable temperature n.m.r. study was undertaken on (51). On studying (51) in CD_2Cl_2 at low temperatures i.e. below 20^{o}C, dramatic changes occurred in the AA'BB' multiplets on lowering the temperature, as shown in Figure 53. It can be seen that the multiplet fine structure completely collapses to give, at -70^{o}C, two diffuse multiplets at 3.3-3.6 and 3.7-4.4 p.p.m., in a ratio of 1:3 respectively. A slight broadening of the bridgehead methyl signal was observed, but no evidence of dynamic behaviour i.e. doublet formation, could be detected. On cooling below -70^{o}C it was found that crystallisation of (51) occurred. Such a temperature dependent n.m.r. behaviour confirms that

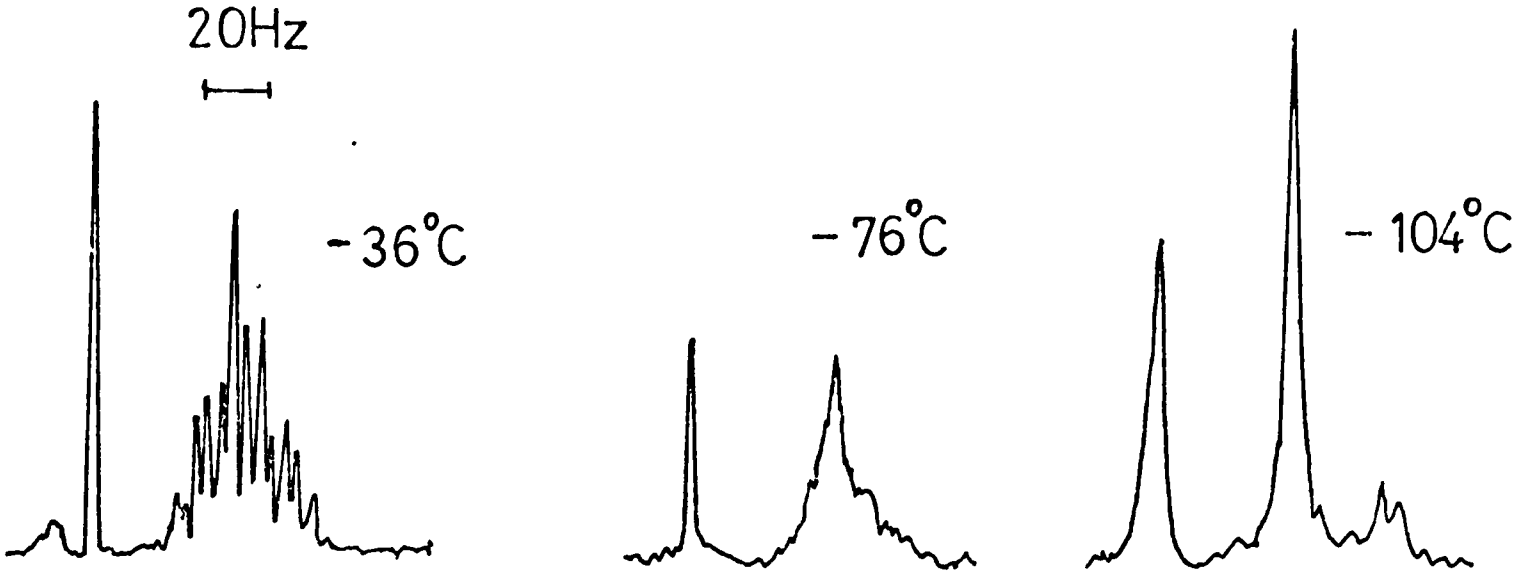


Figure 54. Temperature dependent ^{1}H-n.m.r. of the $AA^{1}BB^{1}$ multiplet at 3.77 p.p.m. of cis-(133)[254]

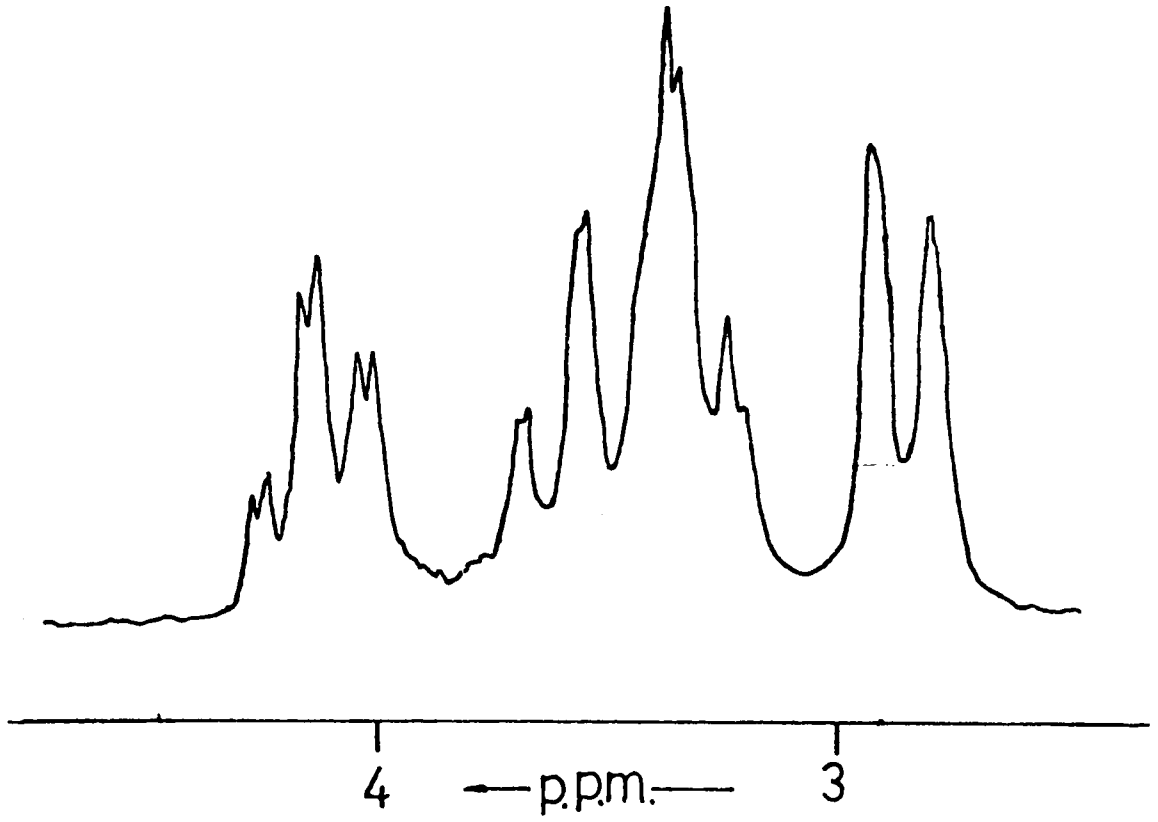
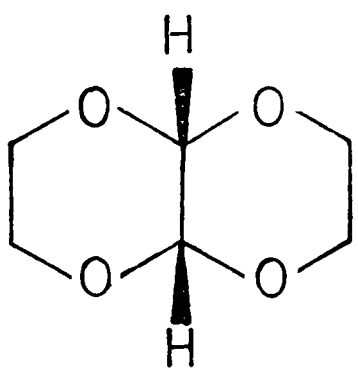


Figure 55. Low temperature (-70°C) 90MHz ^{1}H-n.m.r. spectrum obtained for (51) in d^{8}-toluene

(51) has the cis-configuration already suggested from the analysis of the room temperature spectrum. Of more interest is the spectrum obtained at -70°C. Similar dynamic behaviour has been observed for the tetraoxadecalin (133)[254]



(133)

For (133) the AA'BB' multiplet pattern at 3.77 p.p.m. changed to an apparent unsymmetrical two peak pattern of intensity 1:3, at -104°C, as shown in Figure 54. The actual spectrum lacked well resolved lines and this was attributed to the complexity of the inhererent ABCD pattern and the decreased resolution at low temperatures. As can be seen from comparing the spectra a single conformer is always obtained. This behaviour is accompanied by three of the four protons in the AA'BB' multiplet having similar chemical shifts at low temperature.

A far simpler spectrum for (51) was obtained in toluene at -70°C, as shown in Figure 55. The AA'BB' multiplet at ambient temperature changed at -70°C to

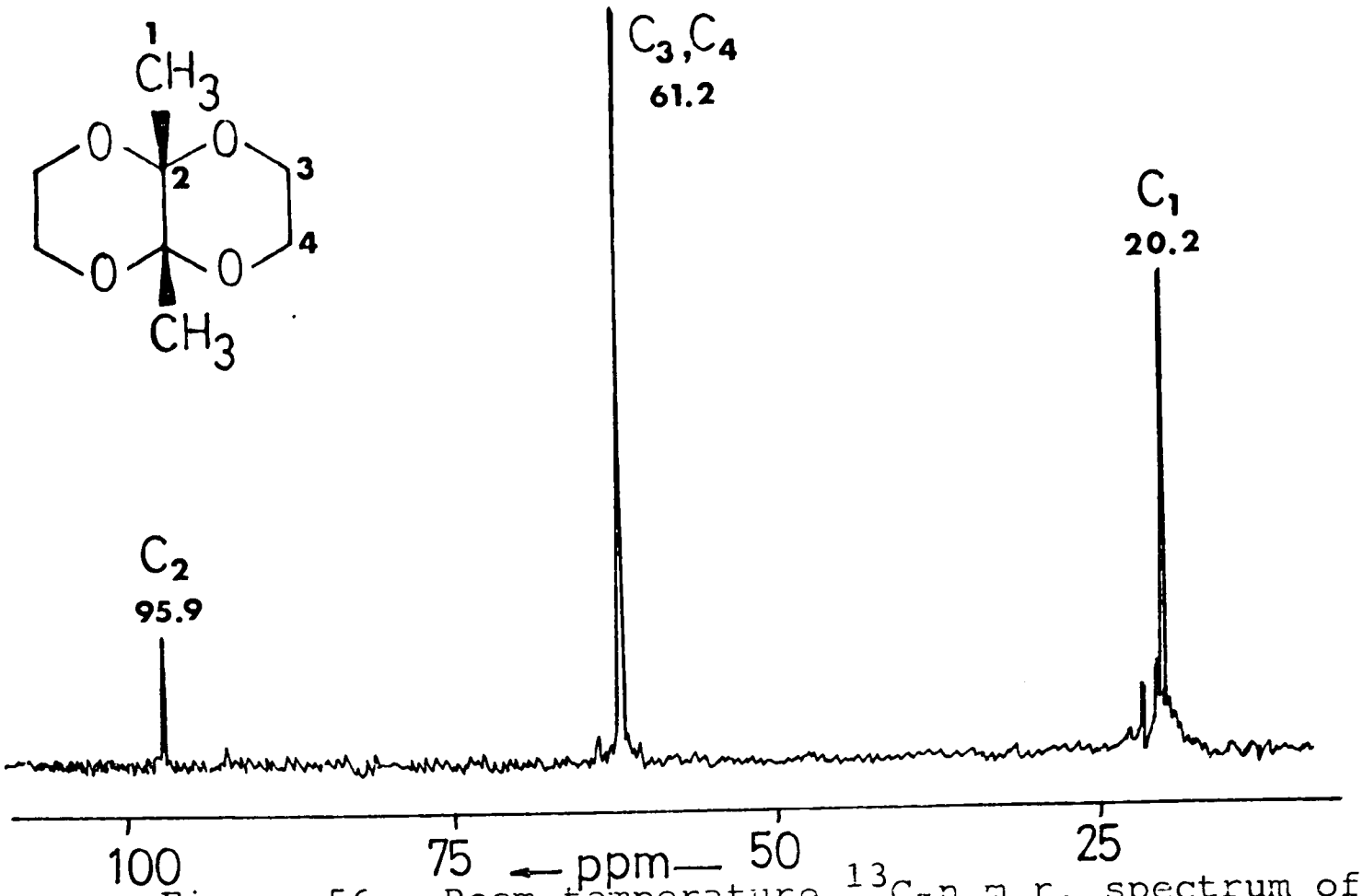


Figure 56. Room temperature ^{13}C-n.m.r. spectrum of (51) in d^8-toluene (assignments in p.p.m.)

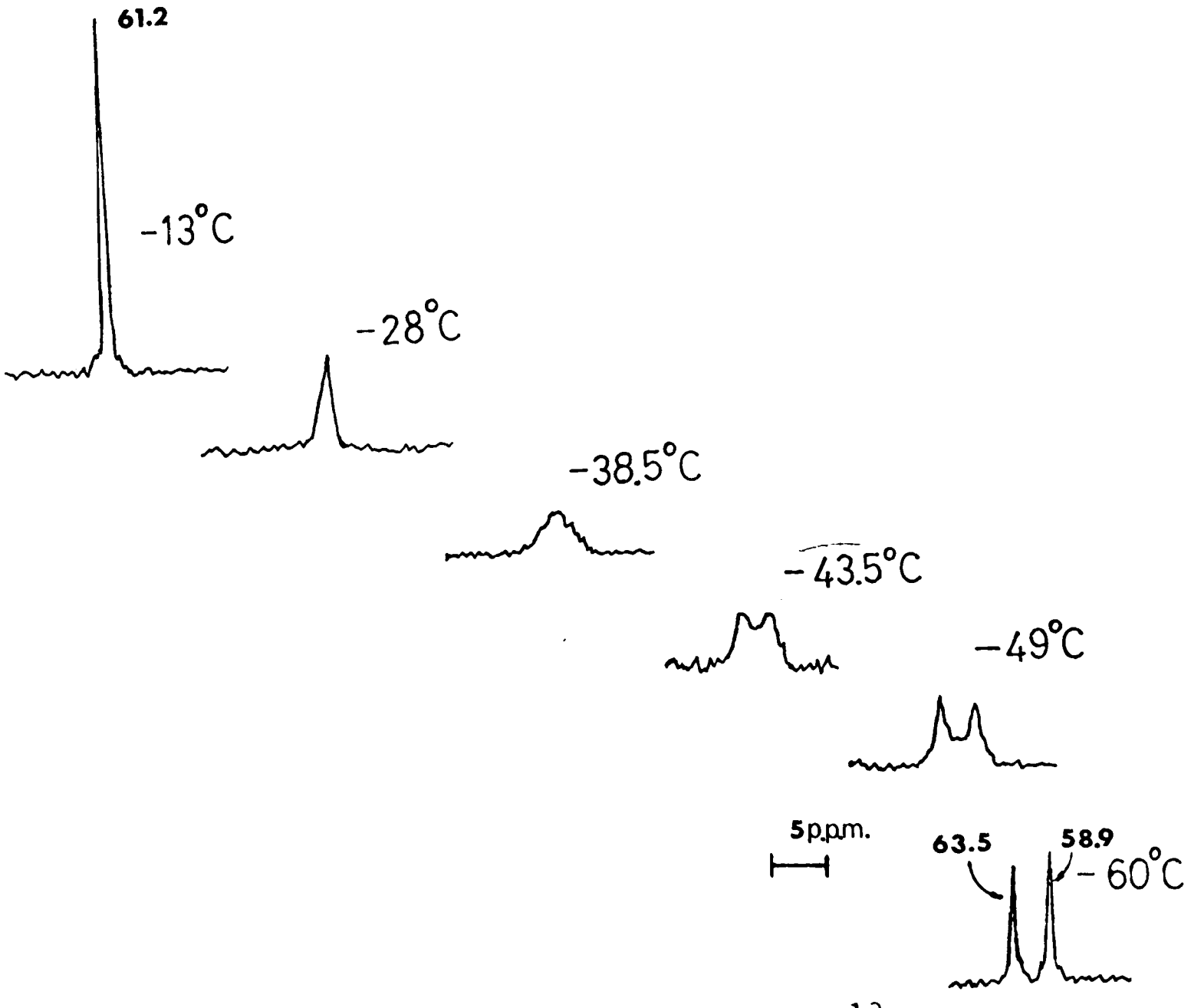


Figure 57. Variable temperature ^{13}C-n.m.r. behaviour of (51), for methylene carbons (C_3, C_4 shown in Figure 56)

three multiplets of an ABCD system in the 2.65-4.4 p.p.m. region. The relative intensities of these multiplets were found to be 1:2:1. Such dynamic behaviour was best accounted for by the occurrence below coalescence of an ABCD $\rightleftharpoons$ BADC exchange system.

At room temperature the ^{13}C-n.m.r. of (51) exhibited three resonances at 20.2, 61.2 and 95.9 p.p.m. (Figure 56). On cooling the peak at 61.2 p.p.m. broadened, to a broad hump centred at 61.2 p.p.m. before producing a doublet of peaks at 63.5 and 58.9 p.p.m. at $-53^{o}C$ (Figure 57). This appearance of this doublet is a consequence of freezing out the enantiomeric forms of (51). At room temperature the two methylene carbons, labelled C_3 and C_4 in the enantiomeric forms (Figure 57) exchange at such a high rate that only a singlet is observed, since C_3 equivalences with C_4 in the interchange of enantiomers. Spectral analysis was by line shape fitting, which was a simple task of solving a two site problem. The line shape analysis of the spectra obtained at $-28^{o}C$ (245K), $-38.5^{o}C$ (234.5K), $-43.5^{o}C$ (229.5K), $-49^{o}C$ (224K) and $-60^{o}C$ (213K) were accomplished and their respective rate constants are given in Table **21**.

Temp. °C	Temp. K	k/s^{-1}	lnk	$^{1}/Tx10^{3}$
-28.0	245.0	1155	7.05	4.08
-38.5	234.5	462	6.14	4.26
-43.5	229.5	247.5	5.51	4.36
-49.0	224.0	125	4.83	4.46
-60.0	213.0	27	3.30	4.69

Table 21. Exchange rates for enantiomers of (51) afforded by line shape analysis of variable ^{13}C-n.m.r. spectra as shown in Figure 57

Using regression analysis the data given in Table 21 afforded values of rate constants which were subsequently used to simulate the ^{1}H-n.m.r. spectra. By this method all unnecessary simulations were minimised. The simulated and actual spectra obtained are illustrated in Figure 58. For the low temperature spectrum the ABCD multiplet when analysed gave the following parameters:- υ_D=2.85 p.p.m., υ_C=3.29 p.p.m., υ_B=3.53 p.p.m., υ_A=4.12 p.p.m., J_{CD}=-0.1, J_{BD} =1.1, J_{AD}=-10.7, J_{BC} =-12.9, J_{AC} =3.0 and J_{AB}=11.7Hz. The large negative J_{AD} and J_{BC} values are the respective geminal coupling constants. Since all the other couplings are small except for J_{AB} this can be assigned to the axial-axial coupling. Thus the resonances of the axial protons appear downfield of the equatorial protons, which is the

reverse of that normally observed for the cyclohexane system. Such a phenomena has been observed in other heterocyclic systems but no explanation has been forwarded.[255] The assignment of $H_A - H_D$ as shown in Figure 59 is based on the precedence that a 1,3-diaxial interaction between a hydrogen and a bridgehead methyl would be more pronounced than a 1,3-diaxial interaction with oxygen axial functionality;[220] models also indicate a direct steric effect from the methyl group in (51).

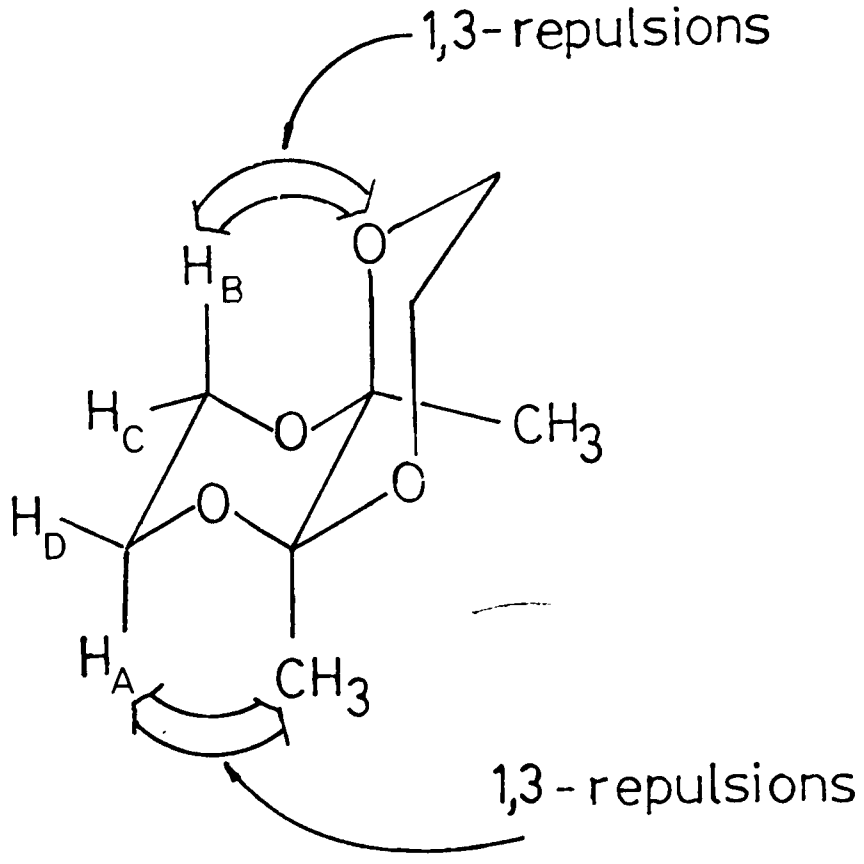


Figure 59. Assignment system used in variable temperature analysis, obtained from analysis of the $-70^{\circ}C$ spectrum

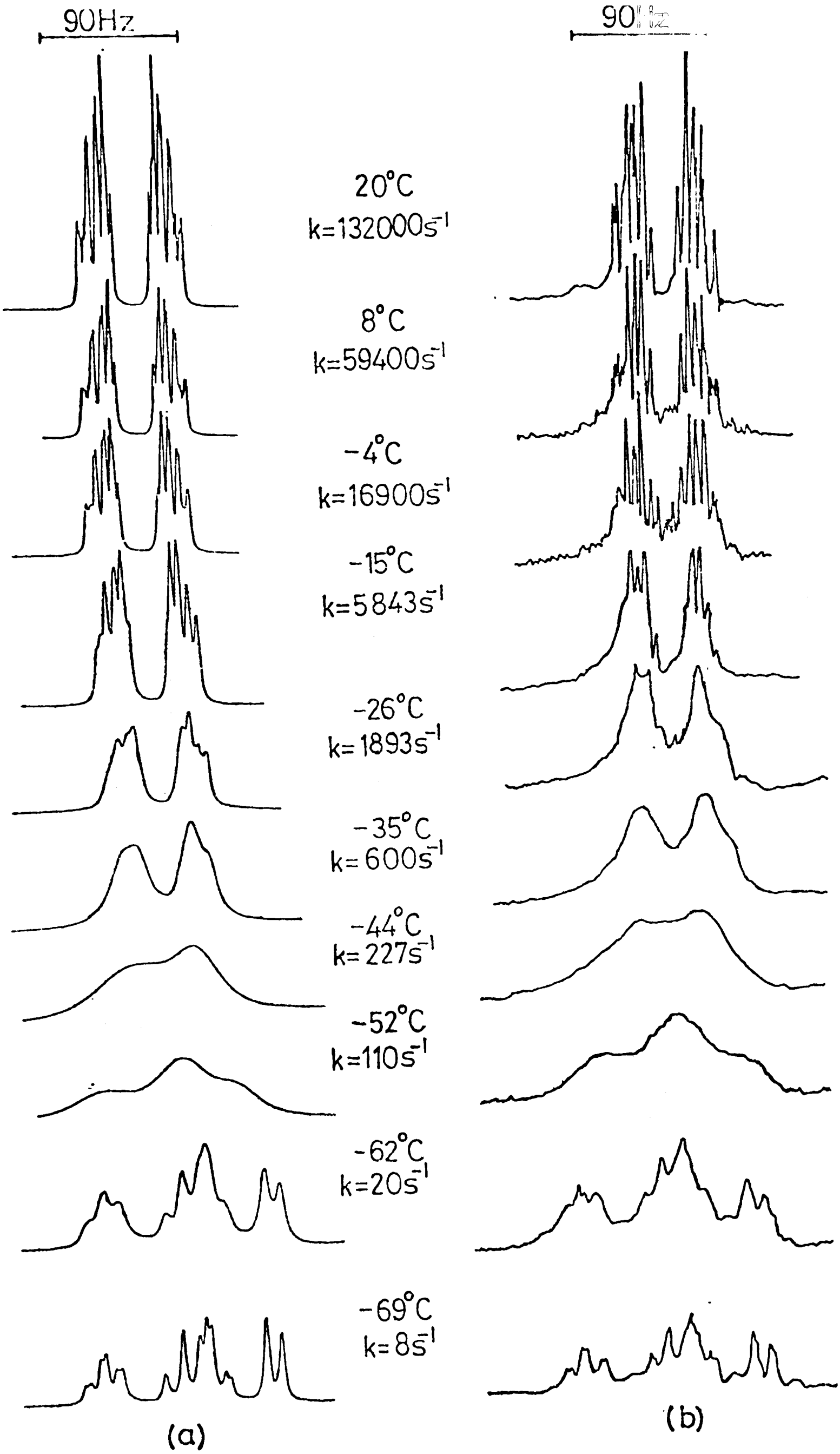


Figure 58. Simulated (a) and actual (b) spectra obtained for the variable temperature ^{1}H-n.m.r. of (51) in d^8-toluene

From the simulations[256] shown in Figure 58, it was found that the agreement between actual and calculated spectra was better than 0.2Hz. However the simulated spectra at high exchange rates i.e. $> 15000s^{-1}$ are not a good test of the simulations. At high temperature the error of $\pm$5% can be accommodated in the simulation easily without any loss to the computed profile. The agreement obtained at high temperature for the spectra concerned confirms the general approach that has been employed. Moreover the fact that the AA'BB' multiplet was in fact produced at high exchange rates from the ABCD system indicates that the proposed process is correct for the dynamic behaviour observed. The room temperature spectra obtained at $k_{ex}=132{,}000s^{-1}$ was in fact superimposable on the spectrum obtained from data for d^8-toluene listed in Table **19**. Whilst there was a slight drift in the absolute positions of the AA'BB' multiplet, ca. 15Hz, from the high temperature simulations, the $\Delta\nu_{AB}$ value was exactly the same as shown in Table **19**. This slight drift may occur since such simulations do not take into account any temperature-induced chemical shifts which may occur.

From the values of the reaction rate for the "flipping" of the enantiomers of (36), one can obtain thermodynamic parameters apertaining to the ring inversion process. The reaction rate constant k is related to

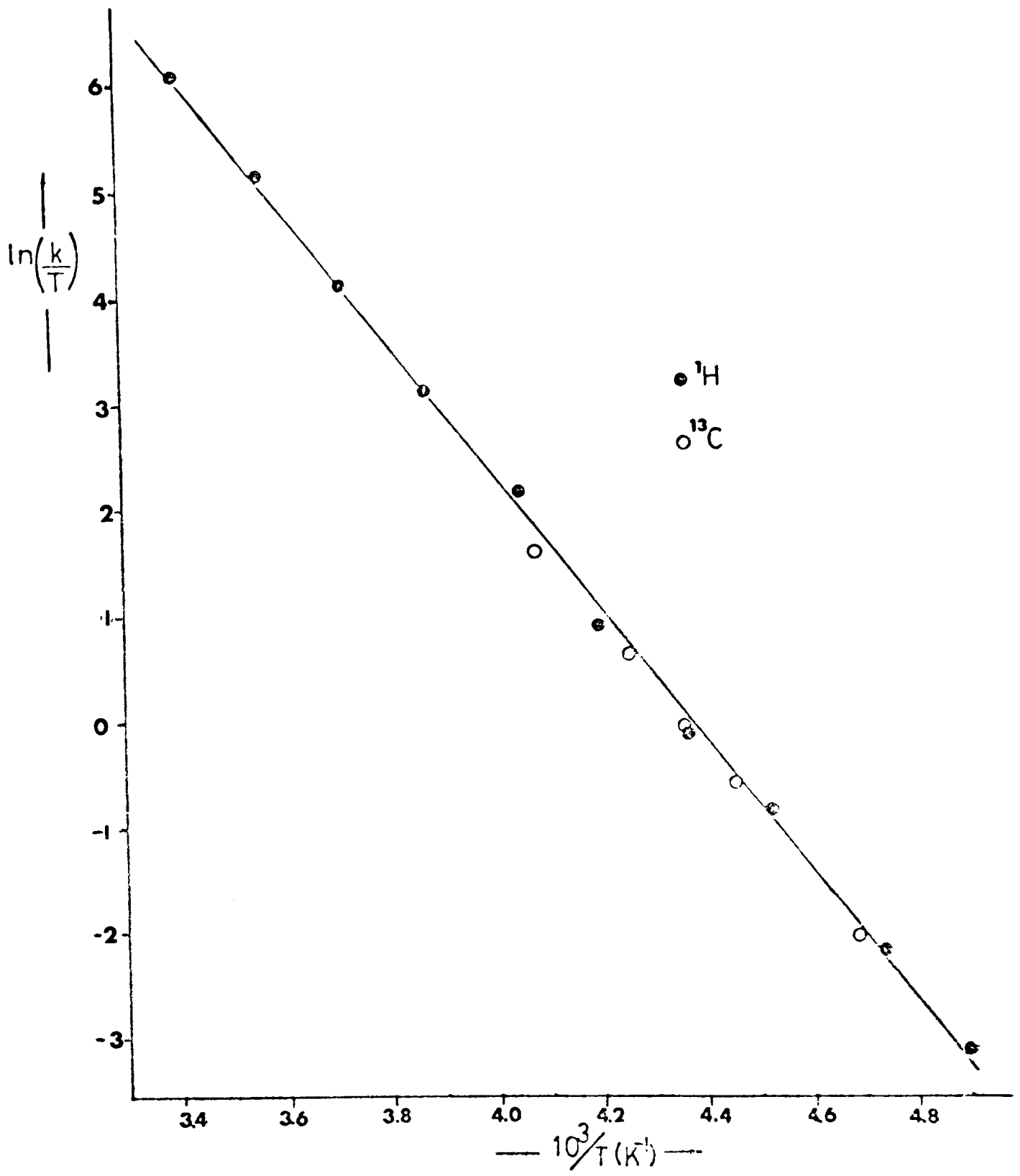


Figure 60. Evaluation of thermodynamic parameters using the absolute rate expression (equation (31)) and the data in Table 21 and 22.

the enthalpy and entropy of activation, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ respectively through the Eyring equation (equation (31))[257]

$$k = \frac{k'T}{h} \exp\left(\frac{\Delta S^{\ddagger}}{R}\right)\exp\left(\frac{-\Delta H^{\ddagger}}{RT}\right) \qquad \text{equation (31)}$$

In equation (31) k' is the Boltzmann constant, h is Planck's constant and R the gas constant. To obtain $\Delta H^{\ddagger}$, the data in Table **21** and **22** were evaluated by plotting $\ln(k/T)$ against $^{1}/T$, as shown in Figure 60.

Temp		$^{1}/T$	k	$\ln(^{k}/T)$
^{o}C	K	$/x10^{-3}$	$/s^{-1}$	
20	293	3.41	132000	6.11
8	281	3.56	59400	5.35
-4	269	3.72	16900	4.14
-15	258	3.88	5843	3.12
-26	247	4.05	1893	2.04
-35	238	4.20	600	0.92
-44	229	4.37	227	-0.01
-52	221	4.53	110	-0.70
-62	211	4.74	20	-2.36
-69	204	4.90	8	-3.24

Table **22**. Kinetic data for the analysis of variable temperature H-n.m.r. of (51) as shown in Figure 58

From the plotted data given in Figure 60 a very good linear correlation was obtained (correlation coefficient =0.9991). The value of $\Delta H^{\ddagger}$ was evaluated from the slope and found to be 12.5 ± 0.8kcalmol^{-1}, whilst the intercept afforded $\Delta S^{\ddagger}=7\pm3$ e.u. Using the absolute reaction rate expression the value of $\Delta G^{\ddagger}_{229}$ was found to be 10.8kcalmol^{-1} at the coalescence temperature of 229K. Such a value of $\Delta G^{\ddagger}_{c}$ is very similar to that observed for (132)[251] i.e. $\Delta G^{\ddagger}_{226}$ 11.2kcalmol^{-1}. The coalescence temperature for (132), 226K, is also similar to that of (51) i.e. 229K. The inversion barrier of (51) is very similar to that of 1,4-dioxane, 9.7kcalmol^{-1} but is conspicuously lower than the barriers in decalin and its substituted derivatives[257] e.g. cis-9,10-bis(bromomethyl)decalin $\Delta G^{\ddagger}_{c}$ 14.7kcalmol^{-1}.

The reason why only cis-(51) is isolated in preference to the trans-isomer is due to the "anomeric effect". This effect, long known in carbohydrate chemistry,[250] has been defined in terms of preference of an axial polar substituent[220] e.g. OR, in a position alpha to the heteroatom over an equatorial one. Such a proposal is contrary to the expected order of conformational stability in other systems. Several explanations have been offered for the origin of the anomeric effect e.g. "rabbit-ear" effects, which cause the destabilisation of conformations with parallel lone-pair orbitals

(dipole-dipole interactions).[258] For (51) the absence of the trans-isomer may be due to its destabilisation by a double lone-pair/bond interaction of the oxygen lone pairs with the methyl group, as well as the occurrence of "rabbit-ear" effects, as shown in Figure 61.

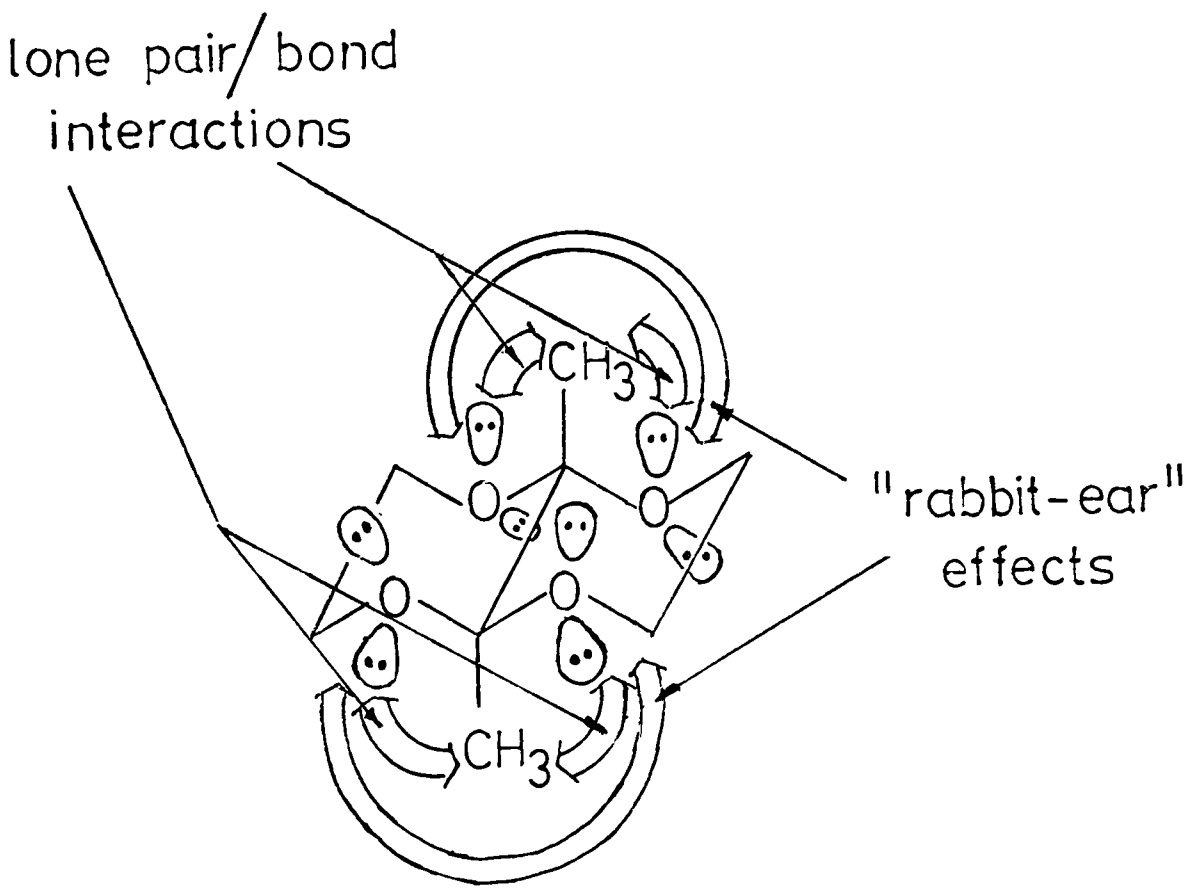


Figure 61. Possible destabilisation effects in trans-9,10-dimethyl-1,4,5,8-tetraoxadecalin

Such interactions, as indicated in Figure 61, could account for the lack of the trans-isomers in analogous systems.[251,252,254] In (51) rabbit-ear effects are minimised, due to the cis-configuration unlike the trans-isomer.

EXPERIMENTAL

Instrumentation

^{1}H-Nuclear magnetic resonance (n.m.r.) spectra were obtained on either a Perkin-Elmer 24B (60MHz), a Perkin-Elmer R32 (90MHz) or a Perkin-Elmer R14 (100MHz) instrument. Chemical shifts are expressed in parts per million (p.p.m.) from either tetramethyl silane (TMS) or the sodium salt of 2,2-dimethyl-4-silapentyl sulphonate (DSS) as the internal standards (0 p.p.m.). All coupling constants are in Hertz(Hz). The following abbreviations in spectral analysis are used:- s=singlet, d=doublet, t-triplet, q=quartet, m=multiplet and br=broad. ^{13}C-n.m.r. spectra were recorded on a Bruker WH90 (22.63 MHz) operating in the Fourier Transform mode.

Infra-red spectra were recorded either as thin films, on potassium bromide discs or in chloroform solution, using a Perkin-Elmer 257 infra-red spectrometer. The following abbreviations used are:- v.s.=very sharp, s=strong, m=medium and w=weak. Ultra-violet spectra were recorded on a Unicam SP 800A spectrophotometer in 1cm cells as solutions in the solvents indicated. Extinction coefficients are quoted in parentheses after the absorption. Mass spectra were determined on a V.G. Micromass spectrometer by the direct insertion technique. All mass peaks are expressed in terms of the largest peak (parent=100%). All melting points are uncorrected and were determined using a Kofler Block, hot-stage,

melting point apparatus.

Analytical gas-liquid chromatography (g.l.c.) data were obtained on a Pye 104 series instrument using 10 feet, 2mm internal diameter, glass columns using the following stationary phases:- Column A, OV17 15% on Chromosorb-G (100-120 mesh); Column B, OV101 10% on Chromosorb-G; Column C, 10% SE25 on Celite (100-120 mesh). Microanalyses were performed by Dr. Strauss and his staff at the Dyson Perrins Laboratory. Analytical samples were obtained by either evaporative short-path distillation *in vacuo* or by recrystallisation from the indicated solvent and drying *in vacuo* at 0.01mm Hg for several hours.

Surface tension measurements were carried out at 30°C with an A. Krüss Model **8600** De Nouy tensiometer equipped with a platinium ring. Measurements of pH were made on a Pye-Unicam 297 pH meter at 30°C, using a glass electrode. The pH meter prior to use was standardised with commercial buffers (as supplied by BDH) at pH 4.0 and pH 10.0. All kinetic runs were carried out using a Perkin-Elmer SP1800 spectrophotometer, monitoring at a fixed wavelength. Pseudo first order rate constants were obtained by calculation on a Hewlett-Packard HP-97 programmable desk-top calculator, using a least squares regression analysis.

Computer simulations of experimental spectra was

performed on an adaption of the LAOCOON III programme.[253] Line shape analysis was performed using the DNMR III program of G. Binsch and D. Klein.[256] Both programmes were adapted by I. Field for use on the Oxford University computer.

Techniques and materials

Alumina used for column chromatography was Laporte Industries' activated aluminium oxide (type II) of ungraded particle size. Silica gel for column chromatography was BDH 60-120 mesh. Thin layer chromatography (t.l.c.) was performed on 0.2mm thick E. Merck silica plates 60F-254, or on 0.3mm thick alumina plates prepared by Mr. R. Prior in the Dyson Perrins Laboratory. Components in the developed chromatograms were detected either by their own u.v. fluorescence or by their reaction with iodine vapour.

All reactions were conducted under an inert gas pressure unless otherwise stated. All transfers of liquids and solutions of any air sensitive materials were carried out with dried, inert gas purged syringes fitted with stainless steel needles or by the double tipped needle technique.[259] Schlenck glassware, previously dried at 60°C, then assembled whilst hot, being evacuated and cooled under a purge of inert gas, was extensively used for the manipulation of air sensitive compounds.[259,260] Inert gases, argon or nitrogen, were

prepurified by passage through liquid paraffin, concentrated sulphuric acid, potassium hydroxide pellets and glass wool.

Commercial solvents were distilled prior to use as either chromatography, recrystallisation or reaction solvents. Anhydrous solvents were always distilled shortly prior to use from an appropriate drying agent, according to standard procedures.[261] Dichloromethane, chloroform, carbon tetrachloride and ethyl acetate were distilled from phosphorus pentoxide. Ethanol and methanol were distilled from magnesium turnings. Pentane, hexane, toluene, 30-40° and 60-80° petrol were distilled from phosphorus pentoxide and then sodium wire. Triethylamine, diisopropylamine and tetramethylethylenediamine were distilled from calcium hydride. Diethyl ether was distilled from phosphorus pentoxide and then sodium metal using benzophenone ketyl as an indicator. Tetrahydrofuran was filtered through activated alumina, distilled from calcium hydride and then sodium wire using benzophenone ketyl as an indicator. Hexamethylphosphoramide was distilled at 0.5mm Hg from pulverised calcium hydride and stored over 4A molecular sieves. Acetone was distilled from pulverised potassium permanganate. Dimethylformamide was distilled at 0.5mm from barium oxide. Drying agents for solvent extracted products were either anhydrous magnesium sulphate or potassium

carbonate and were of reagent grade. 4A Molecular sieves were activated by heating them to 200°C and cooling to room temperature under a stream of dry inert gas, and then adding them to the solvent required under an inert gas stream.

Alkyl lithium reagents were obtained from Pfizer Chemicals and Aldrich and used directly from the bottle. n-Butyl lithium in hexane and t-butyl lithium in pentane were ca. 2.0 and 1.8M respectively, and were stored at 0°C, prior to use, in air-tight containers.[259] The molarities of the alkyl lithium reagents were determined by a double titration procedure.[262]

Commercial alkyl halides were always filtered through activated alumina, distilled and stored over activated 4A molecular sieves. Before use the alkyl halides were examined by n.m.r. to ensure that no decomposition had occurred upon storage.

All water used in the reactions was distilled from an all-glass apparatus. Brine was a saturated aqueous solution of sodium chloride. "Concentration in vacuo" refers to solvent removal under reduced pressure (water aspirator) using a rotary evaporator either at 40°C or steam bath temperature. Ion-exchange was carried out on Dowex^{R} 2-X4 anion exchange resin which had been previously charged by washing with a saturated aqueous solution of the sodium salt and then washing the

exchange resin with distilled water and then methanol until free of excess anion. This resin exchanged 5 milliequivalents of anion for every 1g of resin used.

Surfactants used were of the highest purity obtainable and purified according to standard methods.[107] Boric acid, used to buffer surfactant solutions, was BDH Analar grade. Surfactant solutions were always prepared using doubly distilled water which had been degassed by purging with an inert gas. Buffered surfactant solutions were always made up immediately before use with M/50 borate buffer (pH = 8.0 - 9.25).

Determinations of pK_a's of dioximes in surfactant solutions were obtained by addition of a concentrated sodium hydroxide solution, with stirring, to the surfactant solution in a thermostatically controlled bath held at 30°C. Whilst monitoring the changes in pH, aliquots were withdrawn and the changes in the ultra-violet spectrum (226nm) were measured in a thermostated spectrophotometer cuvette (1cm). Data obtained was used in the Henderson-Hasselbach equation[263]

$$pH = pK_a + \log \frac{(A^-)}{(HA)}$$

to obtain the apparent pK_a.

Kinetic data for the equilibration of of dioxime-surfactant solutions was conducted at 40°C, using the metal reactor shown in Figure 62. The

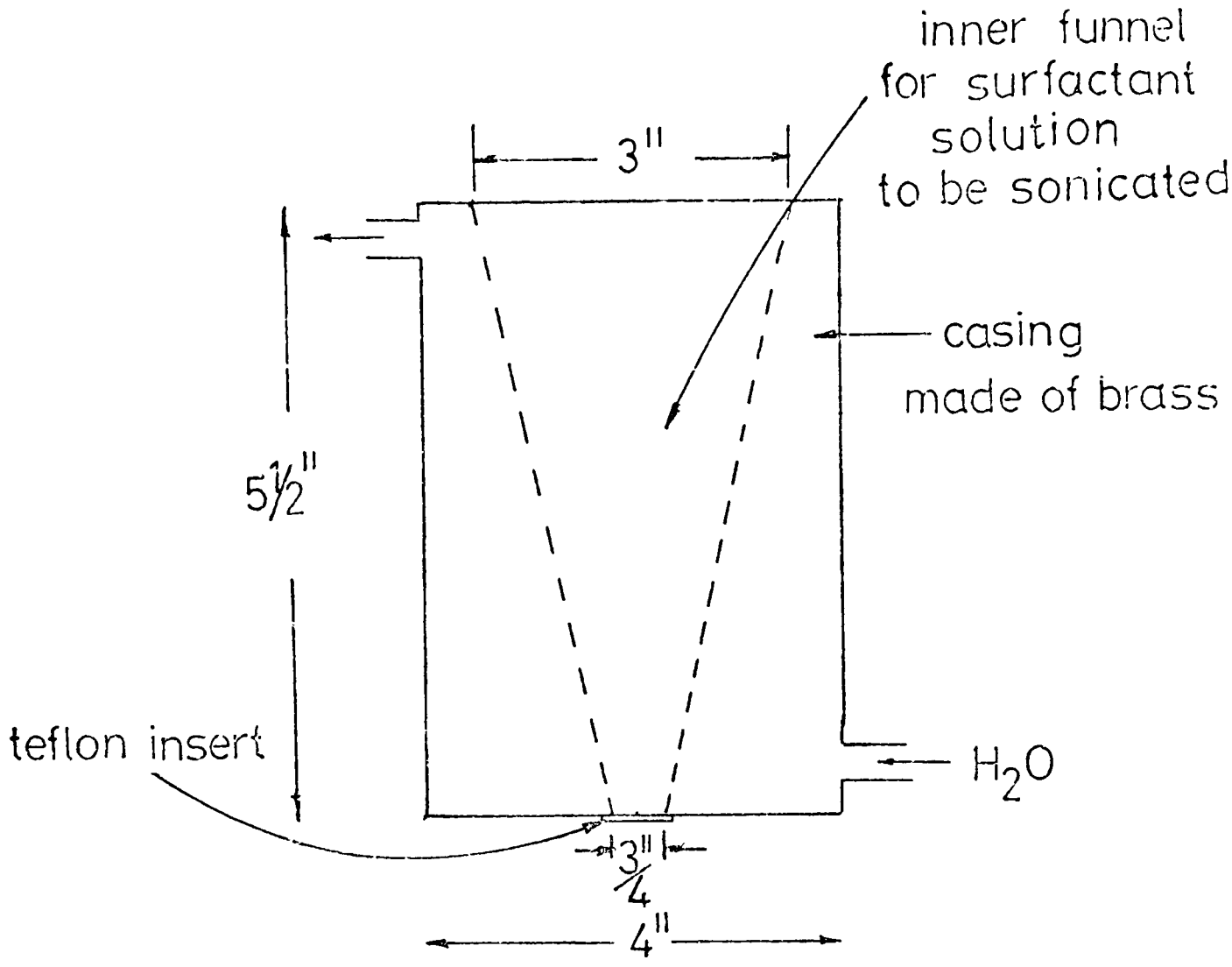


Figure 62. Metal container used for studying the equilibration of dioximes in surfactant solution by ultrasonic probe at 40°C

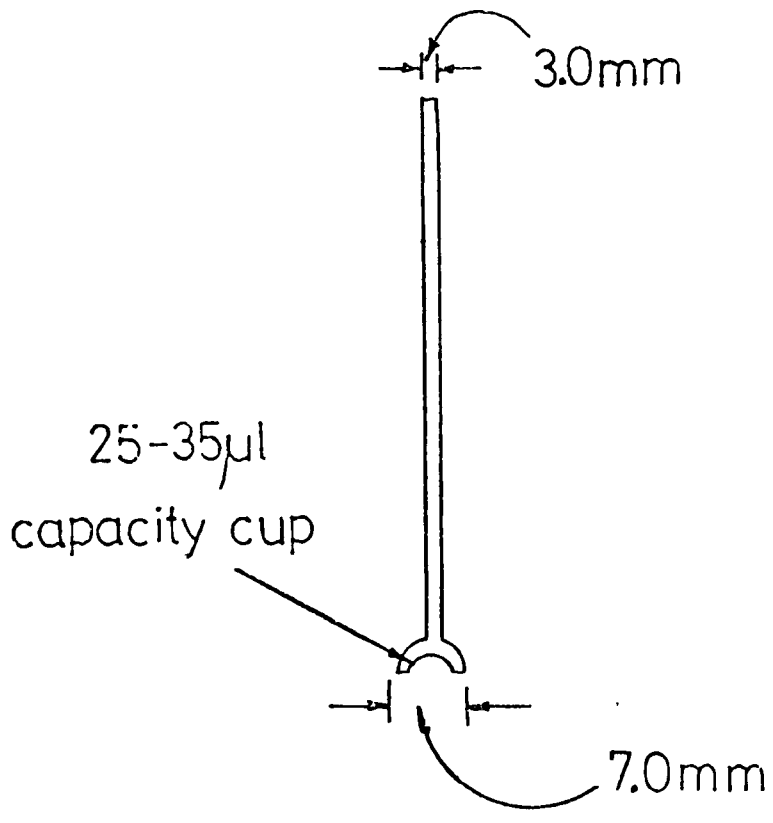


Figure 63. General features of cuvette mixer used in kinetic studies

surfactant solution was sonicated whilst adding the pre-requisite amount of the dioxime in tetrahydrofuran. Samples were then withdrawn at regular intervals, monitoring the 228nm peak in a thermostated (40°C) spectrophotometer cuvette. The rate constants for the equilibration were calculated using the absorbance at infinite time at the monitored wave-length and the integrated first order equation

$$kt = \ln [(A_\infty - A_t)/(A_\infty - A_o)]$$

Kinetic runs involving nickel ions and dioxime-surfactant solutions were all conducted at 30°C in a thermostatically controlled spectrophotometer cell. A solution of the required dioxime in a surfactant solution was equilibrated for 6 hours at 30°C. The required volume (<20μl) of a nickel chloride solution was mixed with the dioxime-surfactant solution using the cuvette mixer shown in Figure 63. The rate constants for these reactions was obtained in a manner previously described above. All kinetic runs were carried out in triplicate, and the value of k_{obs} quoted is an average of these runs. Any pseudo-first order kinetic run which on least squares regression gave a correlation coefficient <0.9990 was rejected. The pH of each kinetic run was checked after reaction and found to be consistent with the pH value prior to reaction.

Variable temperature ^{1}H- and ^{13}C-n.m.r.

studies were recorded after calibration of the respective spectrometers by either a thermocouple or by the induced chemical shift of methanol.[261]

Preparation of 1-octyne

1-Octyne was prepared by adaptation of the method in the literature.[200]

Acetylene (ca. 15mlminute^{-1}), dried by passage through concentrated sulphuric acid and potassium hydroxide pellets, was passed into stirred ammonia (500ml), held under reflux with a dry ice condenser. After 5 minutes sodium (24g, 1.04mol), previously cut into small slivers and washed in 30-40^{o} petrol, was added at such a rate that a totally blue colouration was not attained until addition was complete. After dissolution ofthe sodium the acetylene flow was continued for 30 minutes. To this solution was added n-hexyl bromide (82.5g, 0.5mol) in anhydrous dimethylformamide (25ml) over 1 hour. The resulting solution was kept at reflux for 4.5 hours before quenching by slow addition of aqueous ammonia (1:1 v/v 880 ammonia-water, 120ml), over 45 minutes. The reaction mixture was slowly warmed to room temperature when most of the ammonia evaporated. The residue was partitioned between dichloromethane (300ml) and water (300ml). The aqueous phase was extracted with dichloro-methane (2x100ml) and the combined organic layers washed with 6M aqueous hydrochloric acid (2x50ml), 10%

aqueous sodium bicarbonate (until the aqueous washings were neutral) and finally water (5x100ml). The organic layers were dried and concentrated *in vacuo* to a pale yellow oil, which was flash-distilled collecting the fractions boiling below 150°C (at atmospheric pressure). This crude distillate was shown to contain *ca.* 80% 1-octyne and 20% hexyl bromide by n.m.r. analysis. This oil was dissolved in anhydrous dimethylformamide (50ml) and held at 0°C whilst adding thiourea (10g) over 30 minutes. Upon completion of addition the solution was refluxed for 3 hours, cooled and water added (50ml). The upper organic layer was collected and the aqueous phase extracted with diethyl ether (2x50ml). The combined organic layers were washed with water (5x100ml), dried, filtered through a short alumina column (25g) and concentrated *in vacuo* to afford a pale yellow oil. Distillation gave 20.5g of 1-octyne (37% yield, based on the weight of bromide consumed) as a clear colourless oil, b.p. 124°C (758mm Hg) (lit.[264] 123°C, 760mm Hg). ^{1}H-n.m.r. (60MHz, $CDCl_3$):- δ^{TMS} 0.89(t, 3H, $CH_3(CH_2)_5$, J=6Hz), 1.1-1.85(m, 8H, $CH_3(CH_2)_4$), 1.89(t, 1H, C≡CH, J=2.5Hz), 2.03-2.35(m, 2H, $CH_2C{\equiv}CH$) p.p.m.

Preparation of 7-tetradecyne. General procedure

n-Butyl lithium (155 ml, 1.43M in hexane, 222mmol) was added by syringe over 1 hour to a stirred anhydrous solution of 1-octyne(24g, 218mmol) in tetrahydrofuran (175ml) held at 0°C under nitrogen. When addition was complete, the light tan solution so obtained was stirred at 0°C for 1 hour and hexyl bromide (82g, 497mmol) in anhydrous hexamethylphosphoramide (150ml) was then added over 1.5 hours. The now golden coloured solution obtained was stirred at 0°C for 30 minutes and at room temperature for 12 hours whereupon n.m.r. analysis of a sample indicated that the reaction was complete. Water (150ml) was added and the product extracted with hexane (3x200ml). The combined organic layers were washed with water (5x200ml), brine (200ml), water (200ml), dried and concentrated in vacuo to give an orange oil. Vacuum distillation gave 21g of hexyl bromide, b.p. 60°C (20mm Hg) (lit.[265] 154-158°C, 760mm Hg), as a clear colourless liquid, identical by n.m.r. and i.r. with an authentic sample. Vacuum distillation of the residue gave 17.5g of 7-tetradecyne (41% yield, based on the weight of acetylene consumed), as a clear, colourless liquid, b.p. 124-130°C (1mm Hg), (lit.[266] 68°C, 0.05mm Hg) (≥96% pure g.l.c. on column A, R_t=1.58 minutes at 250°C)

Found:- C=86.1%, H=13.3% ($C_{14}H_{26}$ requires C=86.5%, H=13.5%)

^{1}H-n.m.r.(60MHz,CCl_4):- δ^{TMS}0.89(crude t, 3H, $\underline{CH_3}(CH_2)_5$, J=6Hz), 1.05-1.7(m,8H, $CH_3(\underline{CH_2})_4CH_2C{\equiv}C$) 1.8-2.3 (m, 2H, $\underline{CH_2}C{\equiv}C$) p.p.m.

I.r.($CHCl_3$):- 2960vs, 2930vs, 2860vs, 1680w, 1460-1440 br m, 1380 cm^{-1}

Mass spectrum:- 194(M,1), 110(14), 109(49), 96(39), 95(65), 91(11), 83(17), 82(30), 81(97), 79(28), 77(16), 69(29), 68(33), 67(100), 65(13), 55(49), 54(41), 53(25), 52(13), 51(10), 43(61), 42(14), 41(65), 39(33), 32(35), 29(37), 28(63), 27(29) m/e (%)

Preparation of 1-tetradecyne. General procedure

1-Tetradecyne was prepared by adaptation of the method of Beckmann et al.[206]

Acetylene (ca. 15ml $minute^{-1}$), dried by passage through concentrated sulphuric acid, was passed into stirred, anhydrous tetrahydrofuran (200ml), under nitrogen, held at 0°C, whilst n-butyl lithium (240ml, 1.5M in hexane, 360mmol) was added dropwise by syringe over 1 hour. The resulting grey slurry was stirred at 0°C for a further hour under a reduced acetylene flow (ca. 10ml $minute^{-1}$) in order to ensure formation of monolithium acetylide. n-Dodecyl bromide (50g, 200mmol) in anhydrous hexamethylphosphoramide (200ml), was added dropwise, by syringe over 30 minutes, maintaining a temperature of 0°C. On complete addition, the solution was stirred at 0°C for 4 hours and at room temperature for 12 hours,

after which time there was found to be no n-dodecyl bromide present (n.m.r. analysis of a quenched aliquot). Water (250ml) was added to the reaction mixture which was extracted with hexane (5x250ml), the organic phases were combined and washed with water (10x500ml), brine (500ml) and water (500ml). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to give 38.9g of a dark yellow oil, which on vacuum distillation gave 36.7g (92% yield, based on the bromide consumed) of 1-tetradecyne, b.p. 65-68°C (0.2mm Hg) (lit.[264] 70-78°C, 0.7mm Hg) as a clear colourless liquid (>97% pure, g.l.c. on column A, R_t=2.35minutes at 225°C).

Found:- C=86.4%, H=13.6% ($C_{14}H_{26}$ requires C=86.6%, H=13.4%) (distilled bulb-to-bulb sample).

^{1}H-n.m.r.(100MHz, CCl_4):- δ^{TMS}0.89 (t, 3H, $CH_3(CH_2)_{11}$, J=5Hz), 1.25 (s, 20H, $-(CH_2)_{10}-$, $w_{\frac{1}{2}}$=4Hz), 1.74(t, 1H, H-C≡C, J=2.6Hz), 1.85-2.3(m, 2H, $CH_2C{\equiv}C$) p.p.m.

I.r.($CHCl_3$):- 3318vs (C≡CH), 2960m, 2930s, 2860vs, 2120w(C C), 1470m, 1460m, 1435w, 625 br s cm^{-1}

Mass spectrum:- 123($M^+-C_5H_{11}$,1), 95(21), 82(26), 81(57), 79(13), 69(17), 68(14), 67(52), 57(21), 56(13), 55(63), 54(16), 53(22), 43(52), 42(18), 41(100), 40(10), 39(31), 29(35), 27(33). m/e (%)

Spectroscopic examination of the distillation residue (1.8g), which solidified on cooling indicated a dialkylated alkyne. Extraction of the solid with

95% ethanol, filtration through a celite pad and decolourisation with charcoal, gave, upon slow evaporation, 1.45g of 13-hexacosyne as fluffy, white plates, m.p. 36-36.5°C (lit.[267] 36-36.5°C)

Found:- An analytical sample was prepared by two recrystallisations from 95% ethanol, C=85.9%, H=13.8% ($C_{26}H_{50}$ requires C=86.1%, H=13.9%)

^{1}H-n.m.r.(60MHz, CCl_4):- δ^{TMS}0.89(t, 3H, $CH_3(CH_2)_{11}$, J=5Hz), 1.28(s, 20H, $-(CH_2)_{10}-$, $w_{\frac{1}{2}}$=3Hz), 1.7-2.3(m, 2H, $CH_2-C\equiv C$) p.p.m.

I.r.($CHCl_3$):- 3010m, 2960s, 2930vs, 1860vs, 1468m, 1460m, 1445w, 1380w. cm^{-1}

Mass spectrum:- 362(M^+,5), 193(13), 180(11), 137(12), 124(10), 123(24), 111(15), 110(16), 109(39), 97(34), 96(61), 95(66), 93(10), 83(44), 82(63), 81(72), 80(10), 79(16), 71(11), 69(37), 68(26), 67(54), 57(37), 55(51), 43(100), 42(19), 41(51), 39(13), 29(24), m/e (%)

Preparation of 2-pentadecyne. General procedure

To a stirred solution of 1-tetradecyne (19.4g, 100mmol) in anhydrous tetrahydrofuran (80ml), held at 0°C under nitrogen, was added n-butyl lithium (61ml, 1.65M in hexane, 101mmol) by syringe over 30 minutes. Upon complete addition anhydrous hexamethylphosphoramide (20ml) was added and the solution stirred at 0°C for 1 hour. The solution was cooled to -70°C, stirred for a further 30 minutes and then methyl iodide

(8.5ml, 136mmol) in anhydrous hexamethylphosphoramide (25ml) was rapidly added over 1 minute with vigorous stirring. The solution was stirred at -70°C for 4 hours, 0°C for 2 hours and room temperature for 6 hours. N.m.r. analysis of an aliquot taken from the reaction mixture indicated complete reaction. Water (100ml) was added and the product extracted with hexane (5x250ml), followed by washing of the organic layer with water (5x250ml) and brine (250ml), drying ($MgSO_4$) and concentration in vacuo. Vacuum distillation of the residue gave a single fraction of 20.1g (96% yield, based on acetylene consumed) of 2-pentadecyne, b.p. 80-83°C (0.15mm Hg) as a clear colourless oil (97% pure, g.l.c. on column A, R_t=10.9 minutes at 100°C)

Found:- C=86.5%, H=13.6% ($C_{15}H_{28}$ requires C=86.5%, H=13.5%) (bulb-to-bulb distilled sample)

^{1}H-n.m.r.(90MHz, $CDCl_3$):- δ^{TMS} 0.89(t, 3H, $CH_3(CH_2)_{11}$, J=6Hz), 1.27(s, 20H, $-(CH_2)_{\overline{10}}$, $w_{\frac{1}{2}}$=3Hz), 1.76(t, 3H, $CH_3C\equiv C$, J=2.7Hz), 1.96-2.2(m, 2H, $CH_2C\equiv C$) p.p.m.

I.r.($CHCl_3$):- 3008m, 2960s, 2930s, 2860s, 1470m, 1460m, 1380w, 790m, 765m cm^{-1}

Mass spectrum:- 208(M^+,1), 119(12), 117(13), 110(18), 109(39), 97(12), 96(48), 95(100), 83(15), 82(25), 81(60), 79(10), 69(23), 68(48), 67(44), 57(18), 55(38), 54(23), 53(19), 43(36), 41(46), 39(14), 29(18), 28(11) m/e (%)

Preparation of tetradecan-7,8-dione. General procedure

Ozone in oxygen (4% v/v, $18lh^{-1}$) was passed into a stirred solution of 7-tetradecyne (1g, 5.2mmol), carbon tetrachloride (20ml) and glacial acetic acid (5ml), held at $-25^{o}C$, until a permanent blue colouration was achieved. The reaction was quenched, at $-25^{o}C$, by addition of sodium iodide in glacial acetic acid (10ml, 10% solution) and the resulting red-brown solution warmed to room temperature. Carbon tetrachloride (25ml) was added and the solution washed with aqueous 5% sodium thiosulphate (2x50ml) and then aqueous 10% sodium bicarbonate until the aqueous washings were neutral to litmus. The lower organic layer was run off, dried and concentrated in vacuo to give a yellow oil, which solidified on standing (0.89g). Recrystallisation from methanol, at $-40^{o}C$, afforded 0.564g of tetradecan-7,8-dione (48% yield) as lustrous yellow plates, m.p. $40.5-41^{o}C$ (lit.[268] $38-39^{o}C$)

Found:- C=74.2%, H=11.5% ($C_{14}H_{26}O_2$ requires C=74.3%, H=11.6%)

^{1}H-n.m.r. (60MHz, $CDCl_3$):- δ^{TMS} 0.86(t, 3H, $CH_3(CH_2)_5$, J=7Hz), 1.05-1.65(m, 8H, $CH_3(CH_2)_4$), 2.71(t, 2H, CH_2CO, J=7Hz) p.p.m.

I.r. ($CHCl_3$):- 3030w, 2960m, 2940s, 2860m, 1714vs (C=O), 1710s (C=O), 1470m cm^{-1}

Mass spectrum:- 226(M^+,1), 113($C_6H_{13}CO^+$,100) 85(38), 57(17), 43(92), 41(22) m/e (%)

Preparation of pentadecan-2,3-dione. General procedure.

Ozone in oxygen (4% $^{v}/_{v}$, $181h^{-1}$) was passed into a stirred solution of 2-pentadecyne (5, 24mmol), carbon tetrachloride (100ml) and glacial acetic acid (25ml), held at $-25^{o}C$, until a permanent blue colouration was achieved. The reaction was quenched at $-25^{o}C$ by addition of sodium iodide in glacial acetic acid (10ml, 10% solution). The resulting red-brown solution was warmed to room temperature slowly and diluted with dichloromethane (75ml). The organic layer was washed with aqueous 5% sodium thiosulphate (2x100ml) and aqueous 10% sodium bicarbonate until the aqueous washings were neutral to litmus. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to a yellow oil, which solidified on standing at room temperature (5.3g). Infra-red analysis of the solid indicated the presence of an anhydride ($1820cm^{-1}$) and a ketone ($1715cm^{-1}$). The solid was dissolved in CH_2Cl_2 and held at $0^{o}C$ for 2 hours.Filtration of the solution afforded 1.42g of tridecanoic anhydride (14% yield) as white plates, m.p. 49-50°C (lit.[269] 50°C)

Found:- C=75.7%, H=12.4% ($C_{26}H_{50}O_3$ requires C=76.0%, H=12.3%)

^{1}H-n.m.r. (100MHz, $CDCl_3$): δ^{TMS} 0.88(t, 3H, $CH_3(CH_2)_{11}$, J=5.5Hz), 1.25-1.42(s,16H, $-(CH_2)_8-$, $w_{\frac{1}{2}}$=3.5Hz), 1.45-1.8 (m, 4H), 2.45(t, 2H, CH_2CO, J=7Hz) p.p.m.

Infra-red($CHCl_3$):- 3030w, 2960m, 2930vs. 2860s, 1820vs (C=O), 1750m, 1710m, 1470m, 1080--1040 br cm^{-1}

Mass spectrum:- 480(M^+ 1), 198(15), 197(100), 112(10), 98(39), 85(18), 84(19), 83(14), 73(25), 71(26), 69(21), 60(24), 57(49), 56(12), 55(44), 43(55), 41(41), 29(18) m/e (%)

The filtrate was evaporated, redissolved in methanol and cooled to -30°C for 6 hours to afford 3.47g of pentadecan-2,3-dione (60% yield) as a yellow micro-crystalline material, m.p. 39-41.5°C

Found:- C=69.7%, H=11.7% ($C_{15}H_{28}O_2.H_2O$ requires C=69.7%, H=11.7%)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS}0.9(t, 3H, $CH_3(CH_2)_{11}$, J=6Hz), 1.3(s, 16H, $-(CH_2)_8$, $w_{\frac{1}{2}}$=3Hz), 1.4-1.8(m, 4H, $(CH_2)_2$), 2.33(s, 3H, CH_3CO), 2.74(t, 2H, CH_2CO, J=7Hz) p.p.m.

I.r. ($CHCl_3$):- 3040w, 2960m, 2930s, 2860s, 1715vs(C=O), 1470m, 1360m(CH_2CO), 1265m, 1150--1000 br m. cm^{-1}

Mass spectrum:- 240(M^+, 1%), 198(13), 197(90), 109(10), 97(12), 95(18), 87(13), 85(32), 83(11), 81(10), 74(16), 71(54), 69(16), 57(100), 55(36), 43(100), 42(13), 41(50), 29(24) m/e (%)

Ultra-violet(CH_3OH):- 219(2.24), 280(1.77) nm(logε)

Preparation of 2,3-bis(oximino)pentadecane. General procedure

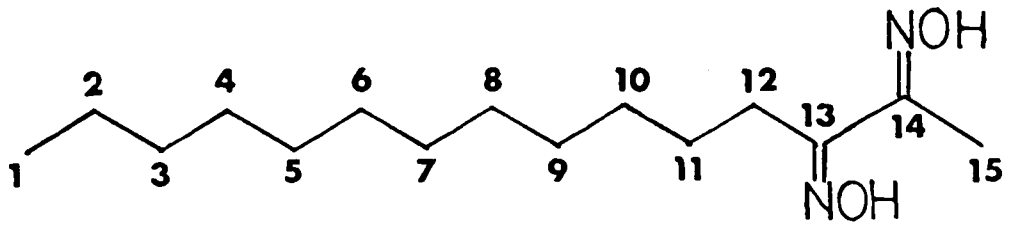
To a stirred solution of pentadecan-2,3-dione (1.329g, 5.5mmol), hydroxylamine hydrochloride (0.8g,

11.5mmol) and anhydrous methanol (25ml), held at 0°C, was added sodium methoxide in methanol (8ml, 1.4M, 11.2mmol) over 10 minutes. The initial yellow colour was discharged after 5 minutes. The solution was stirred at 0°C for 30 minutes and at room temperature for 12 hours. The solvent was removed *in vacuo* to give a white crystalline material, which on recrystallisation from methanol gave 1.23g of *2,3-bis(oximino)pentadecane* (83% yield) as small white crystals, m.p. 158-160°C (dec.).

Found:- C=64.6%, H=10.7%, N=10.0% ($C_{15}H_{30}N_2O_2 \cdot \frac{1}{2}H_2O$ requires C=64.5%, 11.1%, N=10.0%)

^{1}H-n.m.r. (100MHz, d^6-DMSO):- δ^{TMS} 0.87 (t, 3H, $\underline{CH_3}(CH_2)_{11}$, J=5Hz), 1.25 (s, 20H, $CH_3(\underline{CH_2})_{10}$, $w_{\frac{1}{2}}$=3.5Hz), 1.92 (s, 3H, $\underline{CH_3}C(NOH)$), 2.53 (m, 2H, $CH_2\underline{CH_2}C(NOH)$), 10.16 (s, 1H, $\underline{CH_2}C(NOH)$), 10.23 (s, 1H, $C(\underline{NOH})CH_3$ p.p.m.

^{13}C-n.m.r. (22.63MHz, d^6-DMSO):- δ^{TMS} 9.1 (C_{15}), 13.6 (C_1), 21.9 (C_2), 23.0 (C_{12}), 26.8 (C_{11}), 28,5, 28.7, 29.2, 31.1 (C_3), 152.2 (C_{14}), 156.5 (C_{13}) p.p.m.



I.r. (KBr disc):- 3600-3300 br m, 2920m, 2850s, 1470m, 1450m, 1430s, 1375m, 1360m, 1155w, 1080w, 1010m, 980s, 910s cm^{-1}

Mass spectrum:- 270(M,3), 254(10), 253(M-OH,100), 239(15), 126(15), 112(32), 99(18), 85(10), 69(14), 58(17), 57(15), 55(26), 43(37), 42(29), 41(36) m/e (%)

Ultra-violet (THF):- 228(3.96) nm(logε)

Preparation of 7,8-bis(oximino)tetradecane. General procedure.

To a stirred solution of tetradecan-7,8-dione (0.5g, 2.2mmol), hydroxylamine hydrochloride (0.3g, 4.3mmol) and anhydrous methanol (15ml), held at 0°C, was added sodium methoxide in methanol (3.1ml, 1.4M, 4.34mmol) over 5 minutes. On addition of the methoxide solution the initial yellow colouration was discharged after 10 minutes and a colourless solution was obtained. The solution was stirred at 0°C for 3 hours and at room temperature overnight. The solvent was removed *in vacuo* to give a white crystalline slurry. Two recrystallisations from anhydrous methanol afforded 0.423g of 7,8-bis(oximino)-tetradecane (79% yield) as off-white crystals, m.p. 178-181°C (dec.), which decomposed on standing in air.

Found:- C=65.7%, H=10.8%, N=10.8% ($C_{14}H_{28}N_2O_2$ requires C=65.6%, H=11.0%, N=10.9%

^{1}H-n.m.r. (90MHz, d^6-DMSO):- δ^{TMS} 0.86(t, 3H, $CH_3(CH_2)_5$, J=6Hz, 1.28(s, 6H, $CH_3(CH_2)_3(CH_2)_2C(NOH)$, $w_{\frac{1}{2}}$=9Hz) 1.35-1.8(m, 2H, $C_4H_9CH_2CH_2C(NOH)$), 2.54(m, 2H, $CH_2CH_2C(NOH)$), 11.18(s, 1H, NOH) p.p.m.

I.r. (KBr disc):- 3610-3300 br m, 2930m, 2850s, 1460m, 1430m, 1380m, 1150w, 1055w, 990m, 975m, 965m,

915vs, 770-720 br m, 695 cm^{-1}

Mass spectrum:- 256(M, 1), 239(30), 110(13), 83(33), 82(58), 69(22), 68(20), 55(46), 54(43), 43(70), 41(100) m/e (%)

Ultra-violet (THF): 228(3.97) nm(logε)

Preparation of 1-N,N-dimethylamino-3-chloropropane.

General procedure.

A solution of 1-N,N-dimethylamino-3-chloropropane hydrochloride (200g, 1.267mol) in water (200ml) was added over 45 minutes to an aqueous potassium hydroxide solution (200g in 250ml of water) held at 0°C, with vigorous stirring. Upon complete addition the solution was then stirred at 0°C for 30 minutes and the upper amine layer separated. The aqueous phase was adjusted to pH 6 with 6M aqueous hydrochloric acid and extracted with diethyl ether (4x100ml). The combined organic layers were washed with water (5x400ml), dried and concentrated *in vacuo* at 0°C to afford a pale yellow liquid. Vacuum distillation afforded 115g of 1-N,N-dimethylamine-3-chloropropane (75% yield) as a clear, colourless liquid b.p. (30-32°C (12 mm Hg) (lit.[270] 29-32°C 12 mm Hg).

^{1}H-n.m.r. (60MHz, CCl_4): δ^{TMS} 1.6-2.15(m, 2H, $CH_2\underline{CH_2}CH_2N$), 2.12(s, 6H, $-N(\underline{CH_3})_2$), 2.15-2.55(m, 2H, $CH_2\underline{CH_2}NMe_2$), 3.5(t, 2H, $CH_2\underline{CH_2}Cl$, J=6Hz) p.p.m.

This product was stored under nitrogen and at -30°C.

Preparation of heptadec-4-ynyl-1-tri-methylammonium iodide.

To a stirred anhydrous solution of 1-tetradecyne (16g, 80mmol), in tetrahydrofuran (100ml), held at 0°C under nitrogen, was added n-butyl lithium (30ml, 2.12M in hexane, 81mmol) by syringe over 15 minutes. On complete addition the solution was then stirred at 0°C for 1 hour and then 1-N,N-dimethylamino-3-chloropropane (12.5g, 103mmol) in anhydrous hexamethylphosphoramide (60ml) was added over 15 minutes with vigorous stirring. The solution was stirred at 0°C for 4 hours and room temperature for 3 days. The reaction was quenched by addition of water (100ml) and extracted with hexane (3x150ml). The combined organic layers were washed with water (6x500ml), dried and concentrated in vacuo to give 19.5g of a pale yellow oil. N.m.r. analysis of this oil indicated ca. 40% of the desired product. The oil was dissolved in distilled acetone (50ml) and the solution held at 0°C, whilst adding methyl iodide (10ml) in acetone (20ml) over 30 minutes with vigorous stirring. The turbid solution was stirred at 0°C for 1 hour then refluxed for 18 hours. The hot solution was diluted with hexane until the solution became slightly cloudy (ca. 25ml) and allowed to cool to room temperature. Suction filtration gave 7.1g of heptadec-4-ynyl-1-trimethylammonium iodide

(21% yield, based on the weight of acetylene consumed) as small, white platelets m.p. 184-187°C (dec.)

Found:- C=56.5%, H=9.8%, N=3.4%, I=29.7% ($C_{20}H_{40}NI$ requires C=57.0%, H=9.6%, N=3.3%, I=30.1%)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 0.9(t, 3H, $\underline{CH_3}(CH_2)_{10}$, J=6Hz), 1.28(s, 22H, $CH_3(\underline{CH_2})_{10}$, $CH_2\underline{CH_2}CH_2NMe_3$, $w_{\frac{1}{2}}$=4Hz), 1.76-2.5(br m, 4H, $CH_2\underline{CH_2}C{\equiv}C\underline{CH_2}CH_2$), 3.5(s, 9H, $-\overset{+}{N}(\underline{CH_3})_3$), 3.6-3.9(m, 2H, $CH_2\underline{CH_2}NMe_3$) p.p.m.

I.r. ($CHCl_3$):- 2980s, 2950s, 2900s, 1450m, 1390m, 1240m, 1085s, 1050s, 880vs, 705s cm^{-1}

The tetrafluoroborate salt was prepared by ion-exchange, using methanol as the elutant. Recrystallisation from methanol gave the tetrafluoroborate, m.p. 154-159°C.

Found:- C=61.1%, H=10.5%, N=3.7%, ($C_{20}H_{40}NBF_4.\frac{1}{2}H_2O$ requires C=61.4%, H=10.5%, N=3.6%)

Reaction of ozone with hexadecyltrimethylammonium tetrafluoroborate in the presence of tetracyanoethylene.

The tetrafluoroborate salt was prepared by ion-exchange of hexadecyl trimethylammonium chloride, using methanol-acetone (1:1 v/v) as elutate and concentration in vacuo to give a white solid, with < 1% chlorine (by analysis).

Ozone in oxygen (4%, v/v, 18 l hour^{-1}) was passed into a stirred solution of the fluoroborate salt (0.160g, 0.44mmol), tetracyanoethylene (0.056g, 0,44mmol) and dry dichloromethane held at -70°C until

a blue colouration was obtained. The ozone stream was stopped and the reaction mixture warmed to room temperature, with passage of nitrogen through the solution. Concentration *in vacuo* afforded a light-brown solid which on sublimation gave 0.048g of tetracyanoethylene epoxide and 0.1715g of a residue which was shown by n.m.r. to be 95% starting material.

A similar experiment, conducted at -25°C, using 4:1 v/v carbon tetrachloride-glacial acetic acid as solvent with iodide in acetic acid as a quenching agent gave *ca*. 90% recovery of starting material.

Reaction of ozone with heptadec-4-ynyl-1-trimethylammonium tetrafluoroborate in the presence of tetracyanoethylene.

Ozone in oxygen (4%, v/v, 181 h^{-1}) was passed into a stirred solution of heptadec-4-ynyl-1-trimethylammonium tetrafluoroborate (0.18g, 0.47mmol), tetracyanoethylene (0.257g, 2mmol), ethylacetate (20ml) and dichloromethane (5ml), held at -70°C, until a permanent blue colouration was obtained. The mixture was slowly warmed to room temperature whilst flushing with a slow stream of oxygen. The solution was concentrated *in vacuo*, triturated with dichloromethane, filtered and the filtrate concentrated *in vacuo* to give a white solid. Sublimation of this white solid afforded 0.15g of tetracyanoethylene epoxide, identical by i.r. to an authentic sample. N.m.r. analysis of the residue

indicated a mixture of products, showing the absence of a $-\overset{+}{N}(CH_3)_3$ functionality. No further purification was attempted.

Reaction of ozone with heptadec-4-ynyl-1-trimethylammonium tetrafluoroborate.

Ozone in oxygen (4%, v/v, 181 $hour^{-1}$) was passed into a stirred solution of heptadec-4-ynyl-1-trimethylammonium tetrafluoroborate (116mg, 0.3mmol), carbon tetrachloride (20ml) and glacial acetic acid (5ml), held at -25°C, until a permanent blue colouration was obtained. The reaction was quenched at -25°C by addition of sodium iodide in glacial acetic acid (5ml, 10% solution) and the solution warmed slowly to room temperature. On warming a two-phase system became apparent with an upper brown-red layer and a lower orange layer. Ground solid sodium thiosulphate was added, with shaking, until no further colour change occurred. Examination of both layers (t.l.c., n.m.r., i.r.) indicated a complex mixture of what appeared to be fragmentation products. An isolation procedure was not attempted.

Preparation of heptadec-4-enyl-1-trimethyl-ammonium tetrafluoroborate.

A solution of heptadec-4-ynyl-1-trimethylammonium tetrafluoroborate (1.99g, 5.2mmol) in anhydrous methanol (50ml) was hydrogenated at 50 p.s.i. for 6 hours at

room temperature, in the presence of Lindlar's catalyst (0.2g). The solution was filtered through a celite pad, washing the filter pad with methanol (50ml) and the filtrate was concentrated *in vacuo* to give a white solid. Recrystallisation from water-methanol gave 1.045g of *heptadec-4-eny-1-trimethylammonium tetrafluoroborate* (52% yield) as small white crystals, m.p. 183-185°C.

Found:- C=63.3%, H=11.0%, N=3.7% ($C_{20}H_{42}NBF_4$ requires C=62.7%, H=11.0%, N=3.7%)

^{1}H-n.m.r. (90MHz, d^6-DMSO):- δ^{TMS} 0.85(t, 3H, $\underline{CH_3}(CH_2)_{11}$, J=6Hz, 1.23(s, 20H, $CH_3(\underline{CH_2})_{10}$, $w_{\frac{1}{2}}$=3Hz), 1.55-2.2(m, 6H, $\underline{CH_2}CH{=}CH(\underline{CH_2})_2CH_2N$), 3.05(s, 9H, $N(\underline{CH_3})_3$), 3.15-3.3(m, 2H, CH_2NMe_3), 5.2-5.6(m, 2H, $\underline{CH}{=}\underline{CH}$) p.p.m.

I.r. ($CHCl_3$):- 3040w, 2960m, 2930s, 2860s, 1490m, 1480m, 1470m, 1150-100 br s cm^{-1}

Preparation of 1-N,N-dimethylaminoheptadec-4-yne.

n-Butyl lithium (5ml, 1.8M in hexane, 9mmol) was added by syringe over 5 minutes to a stirred anhydrous solution of 1-tetradecyne (1.6g, 8.2mmol) in tetrahydrofuran (10ml), held at 0°C under nitrogen. The solution obtained was then stirred at 0°C for 30 minutes and the solvent gently removed *in vacuo* at 0°C to *ca*. 5 ml. The residue was redissolved in anhydrous tetrahydrofuran-hexamethylphosphoramide (1:1 v/v, 15ml), cooled to -30°C and stirred for 30 minutes. 1-*N*,*N*-Dimethylamino-3-chloropropane (2.5g, 20mmol) in anhydrous

tetrahydrofuran-hexamethylphosphoramide (1:1, v/v, 5ml) was added to the solution over 30 minutes at -30°C with vigorous stirring. On complete addition, the solution was then stirred at -30°C for 45 minutes, 0°C for 1 hour and allowed to warm to room temperature overnight. The reaction was quenched with water (50ml) and extracted with hexane (3x50ml). The organic layers were combined, washed with water (10x300ml), dried and concentrated *in vacuo* to give a pale orange oil.

This oil was chromatographed on a neutral alumina column (100g), prepared as a slurry with 30-40° petrol/dichloromethane (95:5 v/v). The column was eluted with a solvent system of increasing polarity from 5% dichloromethane-95% petrol to dichloromethane with a 5% increase in dichloromethane for every 50ml of elutate. Fractions of 50ml were collected; combination of fractions 4-7 and concentration *in vacuo* afforded 0.56g of 1-*N*,*N*-dimethylaminoheptadec-4-yne (27% yield) as an air sensitive oil, homogeneous by t.l.c. (alumina, petrol/dichloromethane, 1:1(v/v), R_f=0.54).

^{1}H-n.m.r.(60MHz, $CDCl_3$):- δ^{TMS} 0.89(t, 3H, $\underline{CH_3}(CH_2)_{10}$, J=6Hz), 1.26(s, 20H, $CH_3(\underline{CH_2})_{10}$, $w_{\frac{1}{2}}$=3Hz), 1.4-1.85(m, 2H, $-CH_2\underline{CH_2}CH_2N$), 2.05-2.45(m,6H, $CH_2\underline{CH_2}C{\equiv}C\underline{CH_2}CH_2$, $\underline{CH_2}NR_2$), 219(s, 6H, $N(\underline{CH_3})_2$) p.p.m.

Mass spectrum:- 279(M, 1), 265(14), 264(61), 110(17), 58(100), 43(12), m/e (%)

Reaction of ozone with 1-N,N-dimethyl-aminoheptadec-4-yne

Ozone in oxygen (4%, v/v, 18 l hours^{-1}) was passed into a stirred solution of 1-N,N-dimethylamino-heptadec-4-yne (283mg, 1mmol), carbon tetrachloride (20ml) and glacial acetic acid (5ml), held at -25°C, until a permanent blue colouration was obtained. The reaction was quenched at -25°C, by addition of sodium iodide in glacial acetic acid (5ml, 10% solution) and the resulting brown-violet solution warmed slowly to room temperature and left to stand overnight. Finely ground sodium thiosulphate was then added, with shaking, until a yellow colour was obtained, which did not change on further addition of small amounts of sodium thiosulphate. Examination of the two-phase system thus obtained showed that a complex mixture of products was present in both layers, with none of the products containing a tertiary amine functionality.

Preparation of 1-bromo- and 1-chloro-heptadec-4-yne.

General procedure

n-Butyl lithium (31ml, 1.66M in hexane, 51mmol) was slowly added by syringe over 30 minutes to a stirred anhydrous solution of 1-tetradecyne (10g, 51mmol) in tetrahydrofuran (25ml), held at 0°C under nitrogen. Upon complete addition the resulting pale

yellow solution was stirred at 0°C for 30 minutes before gently removing the bulk of the solvent, *in vacuo* at 0°C, to afford a grey slurry. This material was redissolved at 0°C by addition of anhydrous tetrahydrofuran-hexamethylphosphoramide (1:1 (v/v), 50ml). The homogeneous solution obtained being cooled to -70°C and stirred for 15 minutes. 1-Bromo-3-chloropropane (12g, 76mmol) was then added by syringe over 15 minutes with vigorous stirring. On complete addition the solution was stirred at -70°C for 2 hours and room temperature for 24 hours, when the reaction was quenched by addition of water (150ml) and extracted with hexane (4x100ml). The combined organic layers were washed with water (10x500ml), dried and concentrated *in vacuo* to afford 12g of a pale yellow oil. N.m.r. analysis of this oil indicated *ca.* 25% of the desired product, as a *ca.* 4:1 mixture of the 1-chloro- and bromo-derivatives.

This crude material was combined with 20.5g of similar material obtained in two subsequent runs and distilled *in vacuo* to give 18.88g of 1-tetradecyne (63% recovery from 30g used in three preparative runs) as a colourless oil b.p. 75-78°C (0.05mm Hg), identical in all respects (n.m.r., i.r. g.l.c.) to an authentic sample.

Bulb-to-bulb distillation of the residue gave 4.34g of a *ca.* 4:1 mixture of 1-chloro- and

1-bromoheptadec-4-yne (25% yield, based on the weight of acetylene consumed) as a pale yellow oil, b.p. 135°C 0.05mm Hg.

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 0.91(t, 3H, $\underline{CH_3}(CH_2)_{10}$, J=5Hz), 1.29(s, 20H, $CH_3(\underline{CH_2})_{10}$, $w_{\frac{1}{2}}$=4Hz), 1.8-2.5(m, 6H, $\underline{CH_2}C{\equiv}C(\underline{CH_2})_2CH_2X$, 3.52 and 3.65(t,t, 2H together, $CH_2\underline{CH_2}X$ X=Br Cl respectively, J=7Hz) p.p.m.

I.r. (film):- 2960vs, 2860s, 1470s, 1440s, 1380m, 1340m, 1330m, 1290m, 1250m, 860m, 720s(Cl), 655m(Br) cm^{-1}

Preparation of 1-choro- and 1-bromoheptadec-4,5-dione.

General procedure.

Ozone in oxygen (4%, v/v, 181 $hour^{-1}$) was passed into a stirred solution of 1-chloro- and 1-bromo-heptadec-4-yne (1.5g), carbon tetrachloride (20ml) and glacial acetic acid (5ml), held at -25°C, until a permanent blue colouration was obtained (ca. 1.25 hours). The reaction was quenched at -25°C, by addition of sodium iodide in glacial acetic acid (10ml, 10% solution) and the resulting red-brown solution warmed to room temperature. Carbon tetrachloride (25ml) was added and the solution washed with aqueous 5% sodium thiosulphate (2x50ml) and then aqueous 10% sodium hydroxide (5x100ml) until the aqueous washings were at ca. pH 11. The lower organic layer was run off, dried and concentrated in vacuo to afford a lemon yellow oil, which solidified on standing. Recrystallisation from methanol afforded

1.21g of a mixture of 1-chloro- and 1-bromoheptadec-4,5-dione as lustrous yellow plates, m.p. 41-46°C as a ca. 3:1 mixture by n.m.r. analysis.

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 0.9(crude t, 3H, $\underline{CH_3}(CH_2)_{11}$, J=6Hz), 1.29(s, 18H, $CH_3(\underline{CH_2})_9$, $w_{1/2}$=4Hz) 1.45-1.8(m, 2H, $CH_3(CH_2)_9\underline{CH_2}CH_2CO$), 1.9-2.25(m, 2H, $COCH_2\underline{CH_2}CH_2X$), 2.73(t, 2H, $C_{11}H_{23}\underline{CH_2}COCO$, J=7Hz), 2.94(t, 2H, $COCO\underline{CH_2}(CH_2)_2X$), 3.52 and 3.64(tt, 2H together, $CH_2\underline{CH_2}X$ X=Br, Cl respectively, J=7Hz) p.p.m.

I.r. ($CHCl_3$):- 2960s, 2930vs, 2860vs, 1715vs (CO), 1470m, 1460m, 1405m, 1265m cm^{-1}

Mass spectrum:- 348(M^+ ^{81}Br,<1) 346(M^+ ^{79}Br,<1), 304(M^+ ^{37}Cl, 1), 302(M^+ ^{35}Cl, 1), 266(M^+-HX, 5) m/e (%)

Preparation of 2-ethoxy-1,3-dioxolane

This compound was prepared by adaptation of the method of Banganz and Domaschke.[221]

To a stirred solution of anhydrous ethan-1,2-diol (15.5g, 250mmol) and concentrated sulphuric acid (0.5 ml), was added triethyl orthoformate (49g, 250mmol) dropwise over 30 minutes. On complete addition, the solution was stirred for 2 hours and then heated to 100°C, whereupon the ethanol formed was removed by fractionation (30.5ml, b.p. 78-81°C). The residue upon distillation gave 25.5g of 2-ethoxy-1,3-dioxolane (86% yield), as a clear, colourless oil, b.p. 139-143°C (760mm Hg) (lit.[221] 145°C).

Found:- C=50.6%, H=8.6 ($C_5H_{10}O_3$ requires C=50.8%, H=8.53%)

^{1}H-n.m.r.(60MHz, CCl_4):- δ^{TMS}1.18(t, 3H, $\underline{CH_3}CH_2O$, J=7Hz), 3.52(q, 2H, $CH_3\underline{CH_2}O$, J=7Hz), 3.72-4.10(AA^1BB^1m 4H, $w_{1/2}$=6Hz), 5.65(s, 1H, $\underline{CH}$(OEt)) p.p.m.

I.r.($CHCl_3$):- 3010m, 2990m, 2910m, 1490w, 1480w, 1380m, 1370m, 1220vs, 1145vs, 1120vs(CH-O-C_2H_5) 1070s, 950s(CH-O) cm^{-1}

Mass spectrum:- 117(M-1, 2), 73(100), 60(13), 45(28) m/e (%)

Preparation of N,N-dimethyl-2-amino-1,3-dioxolane.

1,1-Dimethoxytrimethylamine (3g, 25mmol) and ethane-1,2-diol (1.55g, 25mmol) and anhydrous ether(5ml) were refluxed under nitrogen for 24 hours. The solution was cooled and the solvent removed in vacuo at 0°C. Vacuum distillation of the residue gave 1.81g of N,N-dimethyl-2-amino-1,3-dioxolane (62% yield) as a clear colourless oil, b.p. 29-31°C (0.5mm Hg) (lit.[222] 142-144°, 760mm Hg).

H-n.m.r. (60MHz, $CDCl_3$):- δ^{TMS}2.23(s, 6H, $N(\underline{CH_3})_2$ 3.75-4.08(A^1BB^1m, 4H, $-O\underline{CH_2CH_2}O-$, $w_{1/2}$= 4Hz), 5.19(s, 1H, O$\underline{CH}$(NMe_2)O) p.p.m.

Reaction of 1-bromo- and 1-chloroheptadec-4,5 dione with 2-ethoxy-1,3-dioxolane

The procedure described is representative of a number of experiments conducted to protect a α-diketone moiety, with either 2-ethoxy-1,3-dioxolane or N,N-dimethyl-2-amino-1,3-dioxolane.

A solution of dione (100mg, 0.3mmol) 2-ethoxy-1.3-dioxolane (1.55g, 13mmol) and p-toluene sulphonic acid hydrate (2mg) was stirred at room temperature, whilst monitoring the reaction by t.l.c. A complex mixture of products was generated even after a short reaction time. Examination of the reaction mixture by n.m.r. indicated a mixture of starting material and degeneration products.

Similar results were obtained using N,N-dimethyl-2-amino-1,3-dioxolane with or without solvent.

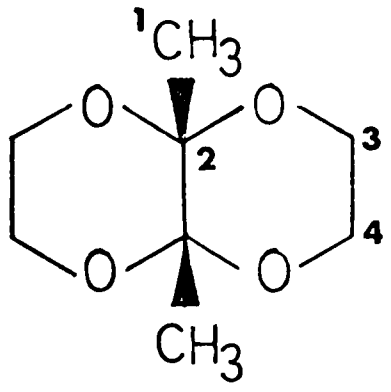
Preparation of cis-4a,8a-dimethylhexahydro-p-dioxino [2,3-b]-p-dioxin.

To a stirred solution of 2-ethoxy-1,3-dioxolane (6.5g, 55mmol), butan-2,3-dione (4.3g, 50mmol) and ethanol (5mol), held at room temperature, was added concentrated sulphuric acid (3 drops). The solution was stirred for 20 minutes and further 2-ethoxy-1,3-dioxolane (6.5g, 55mmol) was added over 5 minutes. On complete addition the solution was then stirred for 48 hours, when n.m.r. analysis of an aliquot indicated the reaction was complete. On removal of the solvent in vacuo a pale yellow crystalline material was obtained, which on slow recrystallisation from hexane gave 6.5g of cis-4a,8a-dimethylhexahydro-p-dioxino[2,3-b]-p-dioxin (92% yield), based on the weight of dione consumed, as lustrous, white platelets m.p. 91°C (lit.[271] m.p. 90-92°C).

Found:- C=54.9%, H=7.7% ($C_8H_{14}O_4$ requires C=55.2%, H=8.0%)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS}1.41(s, 6H, $\underline{CH_3}C$) 3.54-4.2(AA^1BB^1m, 8H), p.p.m.

^{13}C-n.m.r. (22.63MHz, d^8- CH_3):- δ^{TMS}20.2(C_1) 61.2 (C_3,C_4) 95.9(C_2)



I.r. ($CHCl_3$):- 3010s, 2980s, 2960s, 288vs, 1455s, 1380vs, 1300vs, 1285vs, 1265s, 1200s, 1150-1100 br s, 930vs, 920vs, 870vs, 840vs cm^{-1}

Mass spectrum:- 174(M,2), 87(42), 43(100 m/e (%)

Preparation of N-methyl-5-aminopentanoic acid hydrochloride hydrate. General procedure

N-Methyl-5-aminopentanoic acid hydrochloride hydrate was prepared by adaptation of the method of Christman et al.[225]

A stirred solution of N-methyl-2-piperidone (25g, 221mmol) in hydrochloric acid (6M, 50ml) was heated, under nitrogen, at 90°C for 24 hours, when n.m.r. analysis demonstrated the reaction to be complete. The solution was cooled and the water removed in vacuo to give a pale yellow oil, which solidified to

a crystalline mass on standing. Two recrystallisations from dry ethanol/diethyl ether afforded 36.8g of N-methyl-5-aminopentanoic acid hydrochloride hydrate (90% yield) as white needles, m.p. 93-94°C (dec.) lit.[225] 134-135°C)

Found:- C=38.9%, H=9.1%, N=7.7% ($C_6H_{13}NO_2.HCl.H_2O$ requires C=38.8%, H=8.7% N=7.7%)

^{1}H-n.m.r.(90MHz, D_2O):- δ^{DSS} 1.7(m, 4H, $COCH_2(\underline{CH_2})_2CH_2N$) 2.42(t, 2H, $CH_2\underline{CH_2}CO_2H$, J=7Hz), 2.69(s, 3H, $NH(\underline{CH_3})$) 3.02(m, 2H, $CH_2\underline{CH_2}NHCH_3$) p.p.m.

I.r. (KBr disc):- 3600-3200 m br(NH, OH) 2950 m br, 2790m, 2450m, 1725s (C=O), 1465m, 1320m, 1225s (C-O), 1040w, 940(OH) cm^{-1}.

Mass spectrum:- 131(M^+,3), 113(51), 112(19), 57(19), 55(13), 44(100), 42(22), 41(11), 36(HCl, 26), 28(36) m/e (%)

Preparation of 5-Carboxy-1-pentyltrimethylammonium chloride hydrate. General procedure

To a stirred suspension of N-methyl-5-aminopentanoic acid hydrochloride hydrate (36.7g, 198mmol), anhydrous sodium carbonate (30g, 283mmol) and anhydrous ethanol (350ml), held at room temperature, was added methyl iodide (75ml, 1.2mol) over 1 hour. On complete addition, the mixture was refluxed for 15 hours when n.m.r. analysis demonstrated the reaction to be complete. The solution was cooled and the solvent removed in vacuo. The residue was dissolved in 6M hydrochloric acid (100ml) and the solution heated at 60°C for 2.5 hours.

On cooling, the resulting red-brown solution was filtered and the filtrate evaporated *in vacuo* to afford a red-brown paste, which was dissolved in warm water and decolourised twice with charcoal. Removal of the water *in vacuo* afforded a yellow-orange solid which was triturated with hot ethanol (200ml) and filtered. The filtrate was applied to an anion exchange column, previously charged with chloride anion, and eluted with anhydrous methanol. Fractions were collected, with a slow flow rate (*ca.* 5ml $minute^{-1}$) until negative for chloride ion (by the silver nitrate test). The solvent was removed to afford a white solid, which on recrystallisation from anhydrous ethanol-diethyl ether gave 26.1g of

5-carboxy-1-pentyltrimethylammonium chloride hydrate

(62% yield) as small white crystals, m.p. 228.5-230.5°C(dec) (lit.[225] 225°C).

Found:- C=45.2%, H=9.1%, N=6.5% ($C_8H_{18}ClNO_2.H_2O$ requires C=44.9%, H=9.4%, N=6.6%)

^{1}H-n.m.r. (90MHz, D_2O):- δ^{DSS} 1.55-1.9(m, 4H, $CH_2(CH_2)_2CO_2H$), 2.45(t, 2H, CH_2CO_2H, J=7Hz) 3.10(s, 9H, $N(CH_3)_3$) 3.2-3.5(m, 2H, CH_2NMe_3) p.p.m.

I.r. (Nujol mull):- 3600-3200 br m (OH), 3150-3050 br m, 3020m, 2950m, 2920s, 2850s, 2700-2400 br m, 1710s(C=O) 1490m, 1470-1440 br m, 1405m, 1290w, 1265w, 1245w, 1230w, 1210m, 1185 br m, 1040w, 970vs (OH), 915s, 900m cm^{-1}

Preparation of 5-carbomethoxy-1-pentyltrimethylammonium iodide. General procedure.

A mixture of pure 5-carboxyl-1-pentyltrimethyl-ammonium chloride (5g, 25,5mmol) in anhydrous methanol (35ml) and diethyl ether (10ml, saturated with hydrogen chloride) was refluxed for 6 hours, when n.m.r. analysis indicated that esterification was complete. The solvents were removed in vacuo and the off-white solid thus obtained was dissolved in methanol and applied to an ion-exchange column (150g), previously washed with saturated aqueous sodium iodide solution. The column was eluted with methanol, monitoring the fractions collected (125 ml each) with 10% aqueous silver nitrate solution. Concentration in vacuo of the fractions obtained gave a white solid which was recrystallised from anhydrous methanol/ diethyl ether to afford 5.1g of 5-carbomethoxy-1-pentyltrimethylammonium iodide (66% yield) as small white microcrystals, m.p. 125-127°C (dec.)

Found:- C=35.9%, H=6.6%, N=4.7% I=42.2% ($C_9H_{20}INO_2$ requires C=36.0%, H=6.6%, N=4.7%, I=41.4)

^{1}H-n.m.r. (90MHz, D_2O):- δ^{DSS} 1.55-1.9(m, 4H, $CO_2CH_2(CH_2)_2$), 2.45(t, 2H, $CH_2CO_2CH_3$, J=7Hz), 3.04(s, 9H, $-\overset{+}{N}(CH_3)_3$), 3.3-3.65(m, 2H, $CH_2\overset{+}{N}Me_3$), 3.65(s, 3H, CO_2CH_3) p.p.m.

I.r. (Nujol mull):- 2950s, 2920s, 2850s, 1730vs, 1490s, 1465m, 1435vs, 1380m, 1255 br s, 1010vs, 975vs, 925vs, 850m cm^{-1}

Preparation of 1-ethoxy-1,2-dibromoethane. General procedure.

To a stirred anhydrous solution of diethyl ether (100ml) and freshly distilled ethyl vinyl ether (48g, 666mmol), held at -70°C, was added bromine (16ml, 620mmol) in anhydrous diethyl ether (50ml) over 30 minutes. The initially clear solution was stirred at -70°C for 45 minutes to give a white suspension. After stirring for 1 hour at this temperature the solution was slowly warmed to room temperature over a further 3 hours. The solvent and excess vinyl ether were removed in vacuo to afford 132g of 1-ethoxy-1,2-dibromoethane (92% yield, based on the weight of bromine consumed) as a lachromatory, pale yellow liquid. G.l.c. analysis (column A, isothermal at 125°C) indicated that the oil was >95% pure. ^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 1.29(t, 3H, $\underline{CH_3}CH_2O$, J=7Hz), 3.3-4.15(m, 2H, $CHBr\underline{CH_2}Br$), 3.0-4.1(q, 2H, $CH_3\underline{CH_2}O$), 5.97 and 6.03(d,d, 1H, $\underline{CH}BrCH_2Br$, J=7Hz) p.p.m.

This liquid was used immediately, without further purification, to prepare 2-bromo-1-ethyl vinyl ether.

Preparation of 1-bromo-2-ethoxyethylene. General procedure.

To a vigorously stirred solution of anhydrous triethylamine (250ml, 1800mmol), held at room temperature, was slowly added 1-ethoxyl-1,2-dibromoethane (50g, 216mmol) over 30 minutes. Precipitation occurred

immediately and on complete addition the suspension was stirred for 30 minutes, rapidly filtered and the solid collected was washed with triethylamine (50ml) and 30-40° petrol (150ml). The combined filtrates were refluxed for 1 hour, poured into water (250ml), acidified to pH 5 with 5% aqueous hydrochloric acid and extracted with 30-40° petrol (3x150ml). The combined organic layers were washed with water (5x500ml), 10% aqueous cupric sulphate (2x500ml) and brine (2x250ml), dried and concentrated in vacuo to a pale yellow oil. Vacuum distillation gave 23g of 1-bromo-2-ethoxy-ethylene (70% yield) as a clear colourless liquid, b.p. 60-62°C (40mm Hg). (lit.[228] b.p. 62-64°C, 46mm). Analysis by g.l.c. (column A and B) indicated that this liquid was ⩾98% pure and n.m.r. indicated ⩾95% of the Z-isomer. Careful analysis by g.l.c. after further distillation (bulb-to-bulb from potassium carbonate) indicated a 96:4 ratio of isomers.

^{1}H-n.m.r. (100MHz, $CDCl_3$):- δ^{TMS} 1.31(t, 3H, $\underline{CH_3}CH_2O$, J=7Hz), 3.97(q, 2H, $CH_3\underline{CH_2}O$, J=7Hz), 5.10(d, 1H, J=7Hz), 6.60(d, 1H, J=7Hz) p.p.m.

I.r. (film):- 3105vs, 2980s, 2930m, 2880m, 1645vs, 1480m, 1445m, 1390vs, 1320vs, 1305s, 1270-1210 br s, 1170 m, 1110 br s, 690s cm^{-1}

Reaction of lithium phenylthio(n-butyl)cuprate with ethyl bromoacetate

n-Butyl lithium (6.1ml, 1.65M in hexane, 10mmol) was added over 5 minutes to a stirred, anhydrous solution

of thiophenol (1ml, 1.07g, 10mmol) in tetrahydrofuran (10ml), held at 0°C under argon. After stirring for 15 minutes the light tan solution was added, over 15 minutes *via* steel cannula, to a stirred suspension of cuprous iodide (1.9g, 10mmol) in anhydrous tetrahydrofuran (10ml), held at 0°C under argon. The green-yellow solution obtained was stirred at 0°C for 15 minutes before cooling to -70°C. After stirring at -70°C for 15 minutes, *n*-butyl lithium (6.1ml, 1.65M in hexane, 10mmol) was added over 5 minutes, with vigorous stirring. The solution was stirred at -70°C for 30 minutes before adding ethyl bromoacetate (1.5g, 9mmol) in anhydrous tetrahydrofuran (5ml) over 15 minutes. On completion of addition the solution was stirred at -70°C for 2 hours, -30°C for 1 hour, and then quenched by injection of absolute methanol (5ml, 125mmol). The mixture was then poured into saturated aqueous ammonium chloride solution (50ml), with the yellow precipitate formed being removed by filtration through a celite pad. The aqueous phase was extracted with diethyl ether (2x25ml) and the combined organic layers were washed with 0.1M aqueous sodium hydroxide solution (4x50ml) and water (4x50ml), dried and concentrated *in vacuo* to a pale yellow oil. Vacuum distillation gave 0.153g of octane (13% yield), b.p. 50-53°C (48mm Hg) and 0.65g of ethyl caproate (50% yield), b.p. 70-74°C (48mm Hg), both identical with authentic samples (g.l.c., n.m.r., i.r.).

Preparation of the dimethyl sulphide complex of cuprous bromide.

The dimethyl sulphide complex was prepared by adaptation of the method of House et al.[229]

To a stirred dimethyl sulphide solution (75ml), held at 0°C, was added pulverised cuprous bromide (20g) in small portions. The resulting red mixture, which warmed during dissolution, was vigorously stirred for 15 minutes after completion of addition and filtered. The residual solid was stirred with additional dimethyl sulphide (25ml) (to dissolve the bulk of the remaining solid) and filtered. The combined filtrates were evaporated to ca. half volume with a slow stream of nitrogen and diluted with hexane (150ml). The crystalline material that separated was recrystallised from dimethyl sulphide-hexane to afford 16g of the desired complex as white prisms m.p. 127-130°C(dec.) (lit.[229] m.p. 124-129(dec)) H-n.m.r. (60MHz,d^6-DMSO):- δ^{TMS}2.16(s, CH_3S) p.p.m.

Reaction of lithium phenylthio(t-butyl)cuprate with benzoyl chloride

This reaction was carried out by adaptation of the method of Posner et al.[227b]

n-Butyl lithium (9.5ml, 1.65M in hexane, 15.5mmol) was added over 5 minutes to a stirred, anhydrous solution of thiophenol (1.5ml, 1.65, 15mmol) in tetrahydrofuran (15ml), held at 0°C under argon. After stirring for 5 minutes the light tan solution was added via a steel cannula to a stirred suspension of cuprous bromide-dimethyl sulphide complex (3g, 14.5mmol) in anhydrous

tetrahydrofuran (10ml), held at 25°C under argon over 15 minutes. A clear, bright yellow solution was thus obtained, being stirred for 15 minutes before cooling to -70°C. After 15 minutes at -70°C, t-butyl lithium (8ml, 1.86M in pentane, 15mmol) was slowly added by syringe, with vigorous stirring, over 15 minutes. The cuprate solution obtained was stirred at -70°C for 30 minutes and room temperature for 15 minutes before quenching by injection of absolute methanol (5ml, 125mmol). The mixture was poured into saturated aqueous ammonium chloride solution (50ml), and the yellow precipitate thus formed was removed by filtration through a celite pad. The aqueous phase was extracted with diethyl ether (4x25ml) and the combined organic layers were washed with 0.1M aqueous sodium hydroxide solution (2x50ml) and water (4x50ml), dried and concentrated *in vacuo* to give a pale yellow oil. Vacuum distillation gave 1.91g of pivalophenone (91% yield, based on the weight of benzoyl chloride taken), as a colourless oil, b.p. 92-96°C (12mm Hg) (lit.[227b] b.p. 105-106°C, 15mm Hg), which was found to be >95% pure by g.l.c. (column A).

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 1.3(s, 9H, $C(\underline{CH_3})_3$) 7.2-7.45(m, 3H, Ar<u>H</u>), 7.6-7.75(m, 2H, Ar<u>H</u>) p.p.m.

I.r. (film):- 3040m, 2960s, 2920m, 2970m, 1675vs, 1600vs, 1480s, 1460m, 1445m, 1395m, 1365m, 1275vs, 1190vs, 1175s, 960s, 720s, 705s cm^{-1}

Reaction of lithium phenylthio(n-butyl)cuprate with 1-bromo-2-ethoxyethylene.

The experiment described is representative of a number of attempts to alkylate 1-bromo-2-ethoxyethylene.

n-Butyl lithium (3ml, 1.65M in hexane, 5mmol) was added over 5 minutes to a stirred anhydrous solution of thiophenol (0.5ml, 0.54g, 5mmol) in tetrahydrofuran (5ml) held at 0°C under argon. After stirring at 0°C for 5 minutes the light tan solution was added *via* a steel cannula over 15 minutes to a stirred suspension of cuprous bromide-dimethyl sulphide complex (1g, 4.8mmol) in anhydrous tetrahydrofuran (5ml), held at 0°C under argon. A clear, bright yellow solution was stirred at 0°C for 15 minutes and adding n-butyl lithium (3ml, 1.65M in hexane, 5mmol) over 5 minutes. The cuprate solution thus obtained was stirred at -70°C for 15 minutes before addition over 15 minutes, *via* a steel cannula, to a stirred solution of 1-bromo-2-ethoxyethylene (0.65g, 4.3mmol) in anhydrous tetrahydrofuran (5ml) held at -70°C. The solution was stirred at -70°C for 2 hours and -25°C for 3 hours, before quenching by injection of absolute methanol (2ml, 125mmol). The solution was warmed to room temperature and poured into saturated aqueous ammonium chloride solution (50ml), and the yellow precipitate formed removed by filtration through a celite pad. The aqueous phase was extracted

with diethyl ether (2x25ml) and the combined organic layers were washed with 0.1M aqueous sodium hydroxide solution (2x50ml) and water (4x50ml). Drying and concentration *in vacuo* at 0°C gave 0.71g of a pale yellow oil. N.m.r. analysis of this oil indicated >95% recovery of starting material. Vacuum distillation gave 0.6g of 1.bromo-2-ethoxyethylene (92% recovery) b.p. 30-32°C (12mm Hg).

Reaction of ethyl vinyl lithium with ethyl acetate

t-Butyl lithium (10ml, 1.8M in pentane, 18mmol) was slowly added by syringe to an anhydrous solution of ethyl vinyl ether (2.5ml, 26mmol) in tetrahydrofuran (10ml), held at -70°C, with vigorous stirring. The solution, now a canary yellow colour, was warmed to *ca.* -5°C over 15 minutes until the yellow colour was discharged (*ca.* 5 minutes) and a clear solution was obtained. The solution was then cooled to -70°C and stirred for 30 minutes before adding ethyl acetate (2ml, 20mmol) in tetrahydrofuran (2.5ml), *via* a steel cannula over 5 minutes. The solution was stirred at -70°C for 30 minutes, -30°C for 30 minutes and room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride solution (25ml) and extracted with diethyl ether (2x15ml). The organic layers were combined, washed with water (4x25ml), dried and concentrated *in vacuo* to half volume (*ca.* 15ml). 1M Aqueous hydrochloric acid (5 drops) was added to the solution which was then stirred overnight at room temperature.

Hydroxylamine hydrochloride (1.5g, 21mmol) and sodium acetate (2g) in ethanol (5ml) were added. After 2 hours the precipitate formed was filtered off and recrystallised from methanol, to give 1.54g of dimethylgloxime, (72% yield) m.p. 237-238(dec), identical, by mixed m.p., n.m.r. and i.r., with an authentic sample.

Reaction of ethyl vinyl lithium with benzoic acid.

t-Butyl lithium (15ml, 1.86M in pentane, 28mmol) was slowly added by syringe to a stirred anhydrous solution of ethyl vinyl ether (2.5ml, 2.6mmol) in tetrahydrofuran (10ml), held at -70°C, over 5 minutes. The resulting canary yellow solution obtained was then stirred at -5°C until a clear, colourless solution formed (ca. 5 minutes). The solution was then immediately cooled to -70°C, stirred for 15 minutes and then added, via a steel cannula over 30 minutes to a vigorously stirred solution of benzoic acid (1.586g, 13mmol) in dry tetrahydrofuran (10ml), held at -70°C. The solution was stirred, on completion of addition, at -70°C for 30 minutes, 0°C for 2 hours and room temperature for 1 hour before quenching the reaction with saturated aqueous ammonium chloride solution and extracting with diethyl ether (4x25ml). The combined organic layers were washed with saturated aqueous ammonium chloride solution (2x50ml) and water (2x50ml), dried and concentrated in vacuo to afford a pale yellow oil, which contained

>95% of α-benzoyl ethyl vinyl ether, by n.m.r. analysis.
^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 1.3 (t, 3H, $\underline{CH_3}CH_2O$, J=7Hz), 3.83 (q, 2H, $CH_3\underline{CH_2}O$, J=7Hz), 4.67 and 4.93 (ABq, $\rangle C=\underline{CH_2}$, J=2.7Hz), 7.25-7.6 (m, 3H, aromatic H) 7.75-7.95 (m, 2H, aromatic H) p.p.m.

The oil was dissolved immediately in anhydrous methanol (15ml), and 1M aqueous hydrochloric acid (2 drops) was added. The solution was stirred at room temperature for 2 hours, and then o-phenylene diamine (2g, 19mmol) was added. After stirring for a further 3 hours, the solvent was removed in vacuo to afford a yellow solid, which on recrystallisation from methanol gave 2-methyl-3-phenylquinoxaline, 0.099g, m.p. 63.5-64°C (lit.[272] 63-64°C)

^{1}H-n.m.r. (60MHz, $CDCl_3$):- δ^{TMS} 2.76 (s, 3H, $\underline{CH_3}$-C) 7.0-8.2 (m, 9H, aromatic H) p.p.m.

Preparation of 1,1-diethoxytridecane. General procedure.

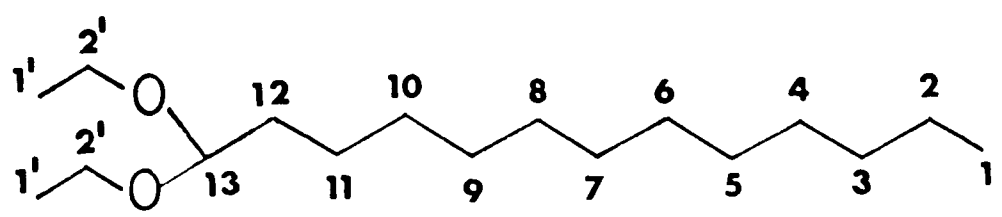
To a stirred suspension of magnesium turnings (5.1g, 205mmol) in anhydrous diethyl ether (100ml), under nitrogen, was added n-dodecyl bromide (50g, 200mmol) in anhydrous diethyl ether (100ml) at a rate sufficient to ensure gentle refluxing of the mixture. Addition was complete after 1 hour and the solution was refluxed for 4 hours and cooled to 0°C. Triethyl orthoformate (30g, 202mmol) in anhydrous diethyl ether (100ml) was added dropwise to the Grignard reagent over 2 hours

with vigorous stirring, at 0°C. On complete addition the solution was refluxed for 8 hours, cooled to 0°C and quenched by addition to a stirred solution of 5% aqueous hydrochloric acid (400ml), over 30 minutes at 0°C. The organic layer was collected and the aqueous phases extracted with 30-40° petrol (5x100ml). The combined organic phases were washed with water (5x100ml), 10% aqueous sodium bicarbonate (5x200ml), brine (2x100ml) and water (2x100ml), dried ($MgSO_4$) and concentrated *in vacuo*. Vacuum distillation of the residue afforded 31.5g of 1,1-diethoxytridecane (58% yield) as a clear, colourless oil, b.p. 115-120°C (0.2mm Hg)

Found:- C=75.2%, H=13.1% ($C_{17}H_{36}O_2$ requires C=73.9% H=13.3%)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 0.9(t, 3H, $CH_3(CH_2)_{11}$, J=7Hz), 1.22(t, 6H, CH_3CH_2O, J=7Hz), 1.29(s, 20H, $CH_3(CH_2)_{10}$, $w_{\frac{1}{2}}$=3Hz), 1.5-1.75(m, 2H, $CH_2CH(OR)_2$), 3.3-3.85(AA^1BB^1m, 4H, OCH_2CH_3), 4.48(t, 1H, $CH(OR)_2CH_2$, J=5Hz) p.p.m.

^{13}C-n.m.r. (22.63MHz, $CDCl_3$):- δ^{TMS} 13.8(C_1), 15.1(C_1), 22.5(C_2), 24.6(C_{12}), 29.2, 29.5, 31.8(C_3), 33.4(C_{11}), 60.6(C_2), 102.8(C_{13}) p.p.m.



I.r. (film):- 3010m, 2930vs, 2860vs, 1470m, 1460m, 1380m, 1120s (C-O), 1060s (C-O), 1060s (C-O) 720m cm^{-1}

Mass spectrum:- 227(M^+-OEt, 16), 103(100), 97(11), 85(10, 83(15), 75(25), 69(18), 57(20), 55(22), 47(23), 43(26), 41(24), 29(15), 28(18) m/e (%)

Preparation of 1-ethoxy-1-dodecene. General procedure

1-Ethoxy-1-dodecene was prepared by adaptation of the method of Wohl.[230]

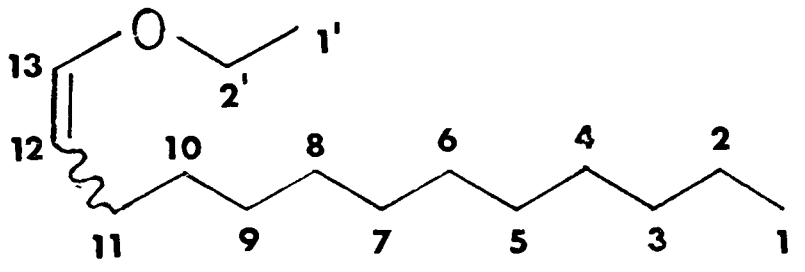
A stirred solution of 1,1-diethoxytridecane (12.5g, 46mmol) and anhydrous p-toluenesulphonic acid (0.35g, 3% by weight) was heated at 150°C and 50mm Hg for 5 hours, whereupon the ethanol formed was removed by fractionation (2.032g, 96% conversion). The residue was vacuum distilled to afford 7.41g of 1-ethoxy-1-dodecene (71% yield) as a clear colourless oil, b.p. 140-145°C (0.1mm Hg). N.m.r. analysis showed that this oil was a 1:1 mixture of the E- and Z-isomers respectively.

Found:- C=79.6%, H=13.4% ($C_{15}H_{30}O$ requires C=79.6%, H=13.4%)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 0.86(t, 6H, 2x$CH_3(CH_2)_9$, J=6Hz), 1.21(t, 6H, 2xCH_3CH_2O, J=7Hz), 1.25(s, 36H, 2x$CH_3(CH_2)_9$, $w_{\frac{1}{2}}$=4Hz), 1.75-2.25(m, 4H, $CH_2CH=CH$) 3.65(q, 2H, OCH_2CH_3, Z-isomer, J=7Hz), 3.73(q, 2H, OCH_2CH_3, E-isomer, J=7Hz), 4.3(t, t. 1H, $CH=CHOC_2H_5$, Z-isomer, J=6.3 and 7Hz), 4.73(t, t, 1H, $CH=CHOC_2H_5$, E-isomer, J=7 and 12.3Hz), 5.87(t, t, 1H, $CH=CHOC_2H_5$,

Z-isomer, J=1.3 and 6.3Hz), 6.17(t, t, 1H, CH=CHOC$_2$H$_5$, E-isomer, J=1.0 and 12.3Hz) p.p.m.

^{13}C-n.m.r. (22.63MHz, $CDCl_3$):- δ^{TMS}14.0(C_1), 14.6(Z-$C_{1'}$) 15.2(E-$C_{1'}$), 22.7(C_2), 23.9(E-C_{11}), 24.8(Z-C_{11}), 27.8(C_9), 28.8, 29.1, 29.4, 29.7, 30.8 (C_{10}), 31.9(C_3), 64.1(E-$C_{2'}$), 67.2(Z-$C_{2'}$), 103.8(E-C_{12}), 107.0(Z-C_{12}), 144(Z-C_{13}), 146(E-C_{13}) p.p.m.



I.r. (film):- 2950m, 2930s, 2860s, 1665m, 1655m, 1460m, 1445m, 1380m, 1175m, 1105 br s cm^{-1}

Mass spectrum:- 227(M+1,4), 226(M,3), 103(29), 99(10), 96(11), 85(100), 83(10), 82(24), 81(11), 69(10), 68(13), 67(12), 57(85), 55(19), 43(25), 41(30), 32(11), 29(25), 28(32) m/e (%)

Attempted deuteration of 1-ethoxy-1-dodecene with deuterium oxide

The experiment described below is representative of an extensive series carried out with the enol ether under a variety of conditions, using both deuterium oxide and methyl iodide as quenching agents.

A solution of 1-ethoxy-1-dodecene (0.2g, 0.9mmol) in anhydrous tetrahydrofuran (50ml), cooled to -70°C, was added, *via* a steel cannula, to an anhydrous stirred solution of *t*-butyl lithium (0.5ml, 1.86M in pentane, 0.9mmol) tetrahydrofuran (5ml) and tetramethyl-ethylenediamine (5ml), held at -70°C, over 2 minutes. The solution was warmed to 0°C over 15 minutes and held there for 10 minutes, before cooling to -30°C for 10 minutes and cooling to -70°C for 10 minutes whereupon deuterium oxide (0.5ml) was added over 1 minute. The solution was stirred at -70°C for 5 minutes and then slowly warmed to room temperature. The reaction was quenched by addition of saturated aqueous ammonium chloride and extracted with diethyl ether (3x10ml). The combined organic layers were washed with water (3x25ml), dried and concentrated *in vacuo* to give 0.18g of a pale yellow oil. N.m.r. analysis indicated only the presence of starting enol ether with no change in the isomer distribution and no incorporation of deuterium.

Preparation of 2-dodecyl-1,3-dithiane. General procedure.

2-Dodecyl-1,3-dithiane was prepared by adaptation of the method of Eliel.[234]

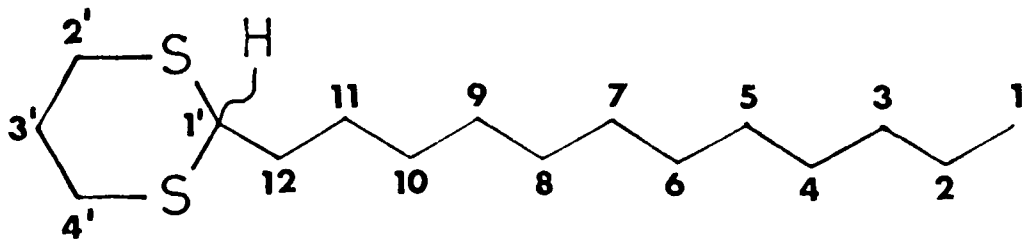
To a refluxing solution of 1,1-diethoxy-tridecane (13.5g, 50mmol), propane-1,3-dithiol (5.4ml, 54mmol) and dry chloroform (50ml) was added boron trifluoride etherate (13ml) in dry chloroform over

30 minutes. On complete addition the solution was refluxed for 2.5hours, cooled to room temperature and quenched by addition of water (50ml) over 30 minutes. The organic layer was separated and the aqueous phase extracted with chloroform (2x100ml). The combined organic layers were washed with 10% aqueous potassium hydroxide (4x50ml) and water until the aqueous washings were neutral, dried and concentrated *in vacuo* to afford an oil which solidified on standing. Recrystallisation from hexane at -30°C gave 13.67g of 2-dodecyl-1,3-dithiane (95% yield) as small white needles, m.p. 22.5-24.5°C. A microanalytical sample, m.p. 23.5-25°C, was prepared by short path distillation at 0.01mm.

Found:- C=66.9%, H=11.2%, S=21.8%, ($C_{16}H_{32}S_2$ requires C=66.6%, H=11.2%, S=22.2%)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 0.89(t, 3H, $\underline{CH_3}(CH_2)_{11}$, J=7Hz, 1.27(s, 20H, $CH_3(\underline{CH_2})_{10}$, $w_{\frac{1}{2}}$=4Hz), 1.65-2.15 (m, 4H, $SCH_2\underline{CH_2}CH_2S$, CH_2CH), 2.75-2.95(m, 4H, $\underline{SCH_2}CH_2\underline{CH_2}S$) 4.04(t, 1H, $CH_2\underline{CH}<$, J=6.7Hz) p.p.m.

^{13}C-n.m.r. (22.63MHz, $CDCl_3$):- δ^{TMS} 13.9(C_1), 22.3(C_2), 26.0(C_{12}), 26.5($C_{2'}$,$C_{4'}$), 29.3, 29.6, 30.4(C_3), 31.9(C_3), 35.4(C_{11}), 47.6 ($C_{1'}$) p.p.m.



I.r. ($CHCl_3$):- 2960m, 2930s, 2860vs, 1470m, 1460m, 1430m, 1280w, 910w cm^{-1}

Mass spectrum:- 290(M+2.2), 289(M+1,4), 288(M,22), 213(20), 121(11), 119(100), 85(100), 71(12), 57(21), 55(14), 43(20), 41(17) m/e (%)

Attempted deuteration of 2-dodecyl-1,3-dithiane with deuterium oxide.

The experiment described is representative of an extensive series of attempts to prepare and quench 2-lithio-2-dodecyl-1,3-dithiane with high efficiency.

n-Butyl lithium (0.7ml, 1.5M in hexane, 1mmol) was added by syringe over 5 minutes to a stirred, anhydrous solution of 2-dodecyl-1,3-dithiane (0.2g, 0.7mmol) in tetrahydrofuran (6ml), held at -20°C under argon. The solution was stirred at -20°C for 30 minutes and -70°C for 30 minutes before addition of deuterium oxide (3ml) over 2 minutes, by syringe. The solution was slowly warmed to room temperature over 1 hour, extracted with hexane (2 x 10ml), with the organic layers being washed with water (2x15ml), dried and concentrated *in vacuo* to afford 0.175g of a pale yellow oil, which solidified on standing. N.m.r. analysis (at 4.04 p.p.m.) of this oil indicated that 38% deuteration had been achieved.

Preparation of bis(ethylthio)methane. General procedure

To a vigorously stirred suspension of para-formaldehyde (15g, 500mmol), boron trifluoride etherate (50ml) and anhydrous diethyl ether (150ml), held at 0°C, was added ethanethiol (75ml, 62g, 1mol) in anhydrous diethyl ether (50ml) over 1 hour. When addition was finished the solution was then refluxed for 2.5 hours, after which time n.m.r. analysis of an aliquot demonstrated that the reaction was complete. The solution was cooled to 0°C, poured onto crushed ice (500g) and neutralised with 10% aqueous sodium carbonate. The organic layer was separated and the aqueous phase extracted with diethyl ether (3x150ml). The combined organic layers were washed with 5% aqueous potassium hydroxide (2x250ml) and water (4x250ml), dried and concentrated *in vacuo*. Vacuum distillation of the residue afforded 66.6g of bis(ethylthio)ethane (98% yield) as a clear, colourless liquid b.p. 93-95°C (18mm Hg) (lit.[273] 74-76°C, 11mm Hg) (>99% pure, g.l.c. on column A, R_t=7.3 minutes at 125°C).

^{1}H-n.m.r. (60MHz, $CDCl_3$):- δ^{TMS} 1.25(t, 6H, $\underline{CH_3}CH_2S$, J=7Hz), 2.65(q, 4H, $CH_3\underline{CH_2}S$, J=7Hz), 3.63(s, 2H, $S\underline{CH_2}S$) p.p.m.

Preparation of (±)-[(ethanesulphinyl)methyl]thioethane.

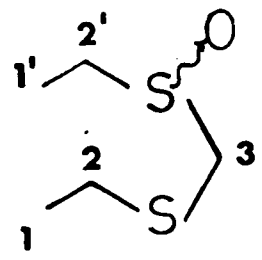
General procedure

To a stirred solution of bis(ethylthio)methane (50g, 368mmol) in glacial acetic acid (200ml), held at 15°C, was added 100 volume hydrogen peroxide (50ml) over 1 hour. On complete addition the solution was vigorously stirred at room temperature for 2.5 hours

whereupon n.m.r. analysis of an aliquot showed the reaction to be finished. The solution was diluted with dichloromethane (300ml) and poured onto crushed ice (1kg). The organic layer was separated and the aqueous phase neutralised by slowly adding sodium carbonate with vigorous stirring and then extracted with dichloromethane (4x150ml). The combined organic layers were washed with 10% aqueous sodium carbonate (2x250ml) and water (4x250ml), dried and concentrated <u>in vacuo</u>. Vacuum distillation of the residue afforded 29.4g of (±)-[(ethylsulphinyl)methyl]-thioethane (52% yield) as a pale yellow, clear oil b.p. 91-93°C ($5x10^{-3}$mm Hg), (lit.[235] 90°C, $5x10^{-3}$mm Hg) (≥95% pure, g.l.c. on column B, R_t=25 minutes at 130°C)

<u>^{1}H-n.m.r.</u> (90MHz, $CDCl_3$):- δ^{TMS}1.3(t, 3H, <u>CH_3</u>CH_2S, J=7Hz), 1.34(t, 3H, <u>CH_3</u>CH_2S(O), J=7Hz), 2.51-3.2(m, 4H, CH_3<u>CH_2</u>S(O), CH_3<u>CH_2</u>S), 3.71(s, 2H, S(O)<u>CH_2</u>S) p.p.m.

<u>^{13}C-n.m.r.</u> (22.63MHz, $CDCl_3$):- δ^{TMS}5.2($C_{1'}$), 13.5(C_1), 26.2($C_{2'}$), 42.8(C_2), 50.1(C_3) p.p.m.



<u>I.r.</u> (film):- 2980s, 2930m, 2870m, 1455s, 1380m, 1265m, 1240-1210 br m, 1180m, 1040vs(S-O), 1015vs, 970m, 835m cm^{-1}

Preparation of bis(1-propylthio)methane. General procedure

To a vigorously stirred suspension of paraformaldehyde (15g, 500mmol), 1-propanethiol (90ml, 1mol) and anhydrous diethyl ether (150ml), held at 0°C, was slowly added boron trifluoride etherate (65ml), so that a slow reflux ensued. On completion of addition, the slightly cloudy solution was refluxed for 30 minutes, cooled, quenched by pouring onto crushed ice (500g) and extracted with diethyl ether(3x150ml). The combined organic layers were washed with 10% aqueous sodium hydroxide (100ml), water (2x200ml), dried and concentrated *in vacuo* to give a pale yellow oil. Vacuum distillation afforded 62.6g of bis(1-propylthio)-methane (76% yield) as a clear, colourless liquid, b.p. 105°C (1.5mm Hg) (lit.[274] 216°C, 760mm Hg) (>99% pure, g.l.c. on column A, R_t=8.3 minutes at 125°C).

Found:- C=50.9%, H=9.6%, S=38.8% ($C_7H_{16}S_2$ requires C=51.2%, H=9.8%, S=39.0%) (bulb-to-bulb distilled sample)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 0.98(t, 6H, $\underline{CH_3}(CH_2)_2$, J=7Hz), 1.39-1.85(m, 4H, $CH_3\underline{CH_2}CH_2$), 2.70 (t, 4H, $C_2H_5\underline{CH_2}S$, J=7Hz), 3.63(s, 2H, $S\underline{CH_2}S$) p.p.m.

I.r. ($CHCl_3$):- 2960s, 2930s, 1870s, 1455m, 1375s, 1290m, 1195s, 740-710 br m (C-S) cm^{-1}

Mass spectrum:- 166(M+2,3), 165(M+1,3), 164(M,49), 89(100), 88(18), 61(22), 47(27), 43(63), 41(21), 27(10) m/e (%)

Preparation of Z- and E-bis(1-propylsulphinyl)methane

To a vigorously stirred suspension of t-butyl alcohol (20ml), water(5ml), vanadium pentoxide (10mg), and bis(1-propylthio)methane (5g, 30mmol), held at 0°C, there was added hydrogen peroxide (7.5ml, 8.5M in water, 64mmol) dropwise over 15 minutes. On completion of addition the orange solution became cloudy and turned yellow after ca. 5 minutes. The solution was stirred at 0°C for 30 minutes and at room temperature for 2.5 hours, whereupon a clear solution was obtained. N.m.r. analysis of an aliquot indicated a single product and the reaction was quenched with water (50ml). The aqueous phase was extracted with chloroform (3x50ml). The combined organic layers were washed with water (5x100ml), dried and concentrated in vacuo to give a white solid. Recrystallisation of this solid from 60-80° petrol/carbon tetrachloride gave 3.42g of a 1:1 mixture of E- and Z-bis(1-propyl-sulphinyl)methane (57% yield) as white, crystalline needles, m.p. 76-77°C.

Found:- C=42.6%, H=8.0%, S=32.4% ($C_7H_{16}O_2S_2$ requires C=42.9%, H=8.2%, S=32.7%)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 1.11(t, 12H, $CH_3(CH_2)_2$, J=7Hz), 1.6-2.2(m, 8H, $CH_3CH_2CH_2$), 2.8-3.4(m, 8H, $C_2H_5CH_2SO$), 4.0(s, 2H, $SOCH_2SO$, E-isomer), 3.75 and 4.1 (ABq, 2H, $SOCH_2SO$, Z-isomer, J_{AB}=13Hz) p.p.m.

I.r. ($CHCl_3$):- 3000s, 2940s, 2880s, 2850s, 1460s, 1400m, 1384m, 1320m, 1240-1200br m, 1060-1000 br s (SO) cm^{-1}

Mass spectrum:- 196(M,1), 106(19), 92(39), 91(13), 89(12). 64(21), 63(100), 43(88), 41(43), 39(12), 27(22) m/e (%).

Preparation of 1-(propylsulphinyl)-1-(propylsulphonyl)methane

To a stirred suspension of vanadium pentoxide (2mg) in t-butyl alcohol (10ml), held at 0°C, was slowly added hydrogen peroxide (0.5ml, 8.5M in water, 6mmol) over 5 minutes. After ca. 5 minutes a bright orange-red solution was obtained and bis(1-propylthio)methane (1g, 6mmol) in t-butyl alcohol (5ml) was then added over 5 minutes. The orange-red colour persisted for 15 minutes before changing to yellow. Further hydrogen peroxide (0.5ml) was added, whereupon the orange-red colouration was regenerated. After 15 minutes the colour was discharged and a yellow solution obtained again. Water (50ml) was added and the solution extracted with dichloromethane (3x30ml). The combined organic layers were washed with water (3x50ml), dried and concentrated in vacuo to give a yellow-green oil, which solidified on standing. Recrystallisation from diethyl ether gave 0.56g of 1-(propylsulphinyl)-1-(propylsulphonyl)methane (43% yield) as beautiful, small white crystals, m.p. 53-57°C.

Found:- C=39.6%, H=7.7%, S=30.3% ($C_7H_{16}O_3S_2$ requires C=39.6%, H=7.6%, S=30.2%)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 1.1(t, 3H, $\underline{CH_3}(CH_2)_2SO$, J=7Hz), 1.12(t, 3H, $\underline{CH_3}(CH_2)_2SO_2$, J=7Hz), 1.16-2.15 (m, 4H, $CH_3\underline{CH_2}CH_2SO$ and $CH_3\underline{CH_2}CH_2SO_2$), 2.98(ddd, 2H, $CH_2\underline{CH_2}SO$, J=7Hz and 3Hz), 3.13-3.4(m, 2H, $CH_2\underline{CH_2}SO_2$), 4.14(s, 2H, $SO\underline{CH_2}SO_2$) p.p.m.

I.r. ($CHCl_3$):- 3000w, 2970m, 2930w, 1460m, 1320s (SO_2), 1135m(SO_2), 1040s(SO), 830m cm^{-1}.

Mass spectrum:- 212(M, 1), 196(1), 170(11), 127(14), 89(12), 64(17), 63(100), 43(60), 41(28), 28(12), 27(13) m/e (%)

Preparation of bis(1-propylsulphonyl)methane

To a vigorously stirred suspension of t-butyl alcohol (20ml), water (5ml), vanadium pentoxide (10mg) and bis(1-propylthio)methane (5g, 30mmol), held at 0°C, was added hydrogen peroxide (17.5ml, 8.5M in water, 150mmol) dropwise over a period of 4 hours. On complete addition the solution obtained was stirred at 0°C for 1 hour and at room temperature for 12 hours, when n.m.r. analysis indicated the reaction to be complete. Water (50ml) was added and the mixture extracted with chloroform (3x50ml). The combined organic layers were washed with water (5x100ml), dried and concentrated in vacuo to give a fluffy white solid. Recrystallisation from 60-80° petrol/carbon tetrachloride gave 2.8g of bis(1-propylsulphonyl)methane (41% yield) as fluffy, white needles m.p. 89.5-90.5°C.

Found:- C=37.0%, H=7.0%, S=28.2% ($C_7H_{16}O_4S_2$ requires C=36.8%, H=7.1%, S=28.1%)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 1.10(t, 3H, $\underline{CH_3}(CH_2)_2SO_2$, J=7Hz), 1.68-2.15(m, 2H, $CH_3\underline{CH_2}CH_2$), 3.25-3.5(m, 2H, $C_2H_5\underline{CH_2}SO_2$), 4.43(s, 2H, $SO_2\underline{CH_2}SO_2$) p.p.m.

I.r. ($CHCl_3$):- 3020w, 2990w, 2930w, 1460w, 1330s (SO_2), 1130vs (SO_2), 840 cm^{-1}

Mass spectrum:- 228(M,1), 123(12), 122(28), 94(18), 81(44), 80(25), 63(13), 43(100), 41(27) m/e (%)

Preparation of 1-(ethylsulphinyl)-1(ethythio)tridecane.

General procedure.

To a stirred, anhydrous solution of diisopropylamine (20ml, 13.8g, 138mmol) and tetrahydrofuran (50ml), held at -30°C under argon, was added n-butyl lithium (69ml, 1.48M in hexane, 102mmol) by syringe over 15 minutes. On complete addition the solution obtained was stirred at -30°C for 15 minutes and 0°C for 30 minutes. To this anion solution was added [(ethylsulphinyl)methyl] thioethane (15.5g, 101mmol) in anhydrous hexamethylphosphoramide (15ml), at 0°C over 10 minutes and the solution stirred at 0°C for 30 minutes. n-Dodecyl bromide (25g, 100mmol) in anhydrous hexamethylphosphoramide (40ml) was then added over 5 minutes, with vigorous stirring. The solution was stirred at 0°C for 30 minutes and at room temperature for 12 hours. The reaction was quenched

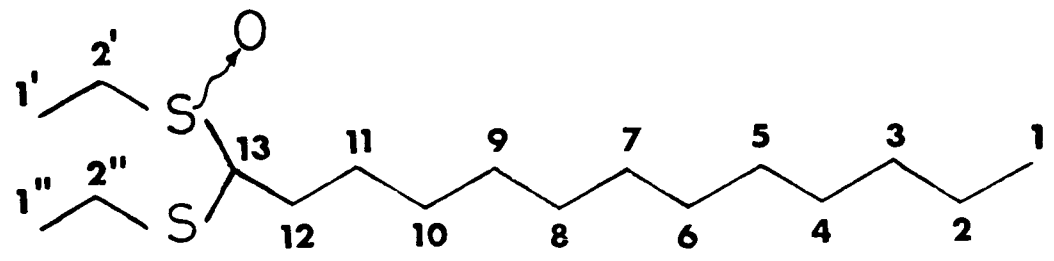
by addition of water (250ml) and the organic material extracted with ethyl acetate (4x200ml). The combined organic layers were washed with water (4x250ml), brine (2x250ml) and water (2x250ml), dried and concentrated *in vacuo* to afford 27.3g of a pale orange oil. T.l.c. (Al_2O_3, ether elution) showed the presence of two components with R_f=0.97 and 0.61. The oil was dissolved in methanol and centrifuged at -30°C for 4 hours. The liquid was decanted and the pale yellow solid obtained recrystallised from methanol at -30°C. T.l.c. analysis showed the presence of two components, R_f=0.97 (faint) and 0.61, in this low melting solid (<30°C). Chromatography on activated alumina (500g) with careful elution using diethyl ether/ethyl acetate afforded 20.2g (62% yield) of *E* - and *Z* -1-(ethylsulphinyl)-1-(ethylthio)tridecane m.p. 31-34°C, homogeneous by t.l.c. in several solvent systems.

Found:- C=63.9%, H=11.4%, S=20.1%, ($C_{17}H_{36}OS_2$ requires C=63.7%, H=11.3%, S=20.0%)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 0.88(t, 3H, $CH_3(CH_2)_{11}$, J=6Hz), 1.27(s, 20H, $CH_3(CH_2)_{10}$ $w_{\frac{1}{2}}$=4Hz), 1.23(t, 3H, CH_3CH_2S, J=7Hz), 1.37(t, 3H, CH_3CH_2SO, J=7Hz), 1.95-2.35 (m, 2H, $CH_2CH(SO)(S)$), 2.45-3.15(m, 4H, CH_3CH_2SO and CH_3CH_2S), 3.3-3.7(m, 1H, $CH_2CH(SO)(S)$) p.p.m.

^{13}C-n.m.r. (22.63MHz, $CDCl_3$):- δ^{TMS} 6.5 and 7.7 ($C_{1'}$), 13.7(C_1), 14.5($C_{1''}$), 22.3(C_2), 24.4, 25.2, 26.2, and

26.4 ($C_{2'}$), 27.0 and 27.4 (C_{12}), 28.8, 29.0, 29.3, 31.5 (C_3), 39.3, 42.6, 65.4 and 66.2 (C_{13}) p.p.m.



I.r. ($CHCl_3$):- 2990m, 2930s, 2860vs, 1455m, 1380m, 1260-1210 br m, 1040s (S-O), 1015s cm^{-1}

Mass spectrum:- M^+ unobserved, 244(19), 243(100), 97(24), 83(35), 76(60, 69(39), 67(11), 54(24), 55(36), 43(22), 41(20, 32(14), 29(15), 28(55), 18(10) m/e (%)

Preparation of 1-ethylthio-1-tridecene

A solution of 1-ethylsulphinyl-1-ethylthio-tridecane (1.6g, 5mmol) in hydrogen chloride saturated toluene (25ml) was refluxed under argon for 6 days, whereupon n.m.r. analysis indicated that the required elimination to the vinyl sulphide was complete. The solution was cooled, water (50ml) was added and the organic material extracted with toluene (2x25ml). The combined organic layers were washed with 10% aqueous sodium bicarbonate (5x50ml), brine (2x50ml) and water (2x50ml), dried and concentrated in vacuo to afford 1.1g of a pale yellow oil. G.l.c. - m.s. of this oil (column C)

indicated that this oil was a mixture of 1-ethylthio-1-tridecene (90%), tridecanal (5%) and 1-tridecyne (5%). This oil was chromatographed on neutral alumina (50g) and on careful elution with 2:1 v/v diethyl ether/ethyl acetate afforded 0.79g of 1-ethylthio-1-tridecene as a pale yellow liquid (R_f 0.9, Al_2O_3, 2:1 diethyl-ethyl acetate). Analysis by g.l.c. (column C) and n.m.r. indicated that this liquid was ca. 95% pure and a 1:1 mixture of the E- and Z-isomers. A number of attempts to prepare a microanalytical sample were unsuccessful.

H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 0.88(t, H, $CH_3(CH_2)_{10}$, J=6Hz), 1.18-1.5(s, 21H, CH_3CH_2S, $CH_3(CH_2)_9$, $w_{\frac{1}{2}}$=12Hz), 1.85-2.3(m, 2H, $CH_2CH=CH=S$), 2.65(q, 2H, $-SCH_2CH_3$, J=7Hz), 5.39.6.00(m, 2H, E- and Z-CH=CH-SR) p.p.m.

I.r. (film):- 2980m, 2965s, 2930vs, 1460m, 1260m, 1180-1050 br m, 1020m, 800m, 725m cm^{-1}

Mass spectrum:- 242($\overset{+}{M}$,16), 213($M-C_2H_5$,20), 180($M-C_2H_5SH$,3), 123(5), 109(7), 101(100), 97(25), 96(25), 95(25), 83(30), 82(35), 81(35), 73(18), 69(20), 68(18), 67(80), 59(40), 57(35), 55(70). m/e (%)

Reaction of 1-lithio-1-ethylsulphinyl-1-ethyl-thio-tridecane with 5-carbomethoxy-1-pentyltrimethylammonium iodide.

The procedure described is representative of numerous experiments conducted with both the ester and acid chloride.

n-Butyl lithium (7.2ml, 1.4M in hexane, 10mmol) was added to a stirred anhydrous solution of 1-ethylsulphinyl-1-ethylthiotridecane (3.2g, 10mmol) in tetrahydrofuran (10ml), held at 0°C over 5 minutes. The solution was stirred at 0°C for 15 minutes and then added at room temperature, via a steel cannula, to a stirred anhydrous solution of the ester (1g, 3mmol) in hexamethylphosphoramide (7.5ml) over 5 minutes. The brown-tan solution obtained was stirred at room temperature for 12 hours, before addition of absolute methanol (1ml). The resulting solution was diluted with diethyl ether and then centrifuged. Precipitated material (0.8g) was demonstrated to be the initial quaternary ammonium ester by n.m.r. spectroscopy. The filtrate from hexane extraction (2x15ml) was washed with water, dried and concentrated in vacuo to give 2.8g of a pale yellow oil, which was found by n.m.r. to be initial sulphoxide by comparison with an authentic sample.

Preparation of (±)-3-tetradecyl-2(3H)-dihydrofuranone.

General procedure.

n-Butyl lithium (80ml, 1.44M in hexane, 115mmol) was added by syringe to a stirred anhydrous solution of diisopropylamine (20ml, 14.4g, 143mmol) and tetrahydrofuran (75ml), held at 30°C under argon, over 30 minutes. The solution was stirred at -30°C for 30 minutes and -80°C for 30 minutes before adding 2(3H)-dihydrofuranone

(8ml, 8.96g, 105mmol) in anhydrous tetrahydrofuran (30ml) dropwise, very slowly over 1 hour with vigorous stirring at -80°C. On completion of addition anhydrous hexamethylphosphoramide (5ml) was then added and the reaction stirred at -80°C for 1 hour, before warming to -40°C over 15 minutes. n-Tetradecyl bromide (15ml, 15.15g, 55mmol) in anhydrous hexamethylphosphoramide (30ml) was added over 45 minutes with vigorous stirring, ensuring that the temperature was held between -40° and -45°C. The solution was stirred at -40°C for 30 minutes and warmed slowly to room temperature overnight with continued stirring. The reaction was quenched by addition of water (250ml) and extracted with diethyl ether (4x150ml). The combined organic layers were washed with water (4x500ml), brine (2x500ml) and water (500ml), dried and concentrated *in vacuo*. There was thus obtained 12.32g of a pale yellow oil which solidified on standing. T.l.c. (silica, 2:1, v/v ether/60-80° petrol) indicated the presence of three components with R_f= 0.91 (tetradecyl bromide), 0.49 and 0.31.

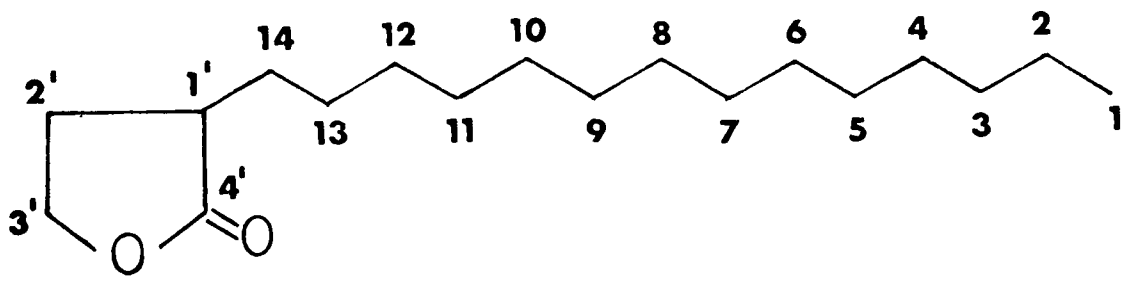
This crude material was combined with 22.58g of material obtained in two subsequent runs, dissolved in pentane and cooled to -30°C for 3 hours. The liquid was decanted and the waxy solid left was recrystallised four times from pentane at -30°C to afford a solid, m.p. 49-53°C, showing two components by t.l.c., R_f=0.49

and 0.31. This material was chromatographed on a silica gel column (450g), prepared as a slurry with diethyl ether/60-80° petrol (1:1 v/v). The column was eluted with a solvent gradient system of increasing polarity from 1:1 v/v diethyl ether/petrol to diethyl ether with a 10% increase in ether (v/v) for every 500ml of elutate. Fractions of 250ml were collected; concentration *in vacuo* of fractions 3-5 afforded 9.876g of (±)-3-tetradecyl-2(3H)-dihydrofuranone as small white crystals (21% yield), m.p. 55.5-56.5°C, R_f=0.49 on silica t.l.c. (2:1(v/v) diethyl ether/60-80° petrol)

Found:- C=76.3%, H=12.0% ($C_{18}H_{34}O_2$ requires C=76.5%, H=12.1%)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 0.88(t, 3H, $\underline{CH_3}(CH_2)_{13}$, J=6Hz), 1.25(s, 26H, $CH_3(\underline{CH_2})_{13}$, $w_{\frac{1}{2}}$=3Hz), 1.65-2.2 (m, 1H, $OCH_2\underline{CH_2}CHR$), 2.25-2.6(m, 1H, $CH_2\underline{CH}RCO$), 4.05-4.45(m, 2H, $\underline{OCH_2}CH_2CHR$) p.p.m.

^{13}C-n.m.r. (22.63MHz, $CDCl_3$):- δ^{TMS} 13.9(C_1), 22.6(C_2), 27.4(C_{13}), 28.7($C_{2'}$), 29.5, 29.7, 30.4(C_{14}), 32.0(C_3), 39.3($C_{1'}$), 66.6($C_{3'}$), 179.7($C_{4'}$) p.p.m.



I.r. ($CHCl_3$):- 2930vs, 2850vs, 1765vs (C=O), 1465m, 1455m, 1375vs, 1190-1150 br m, 1025vs, cm^{-1}

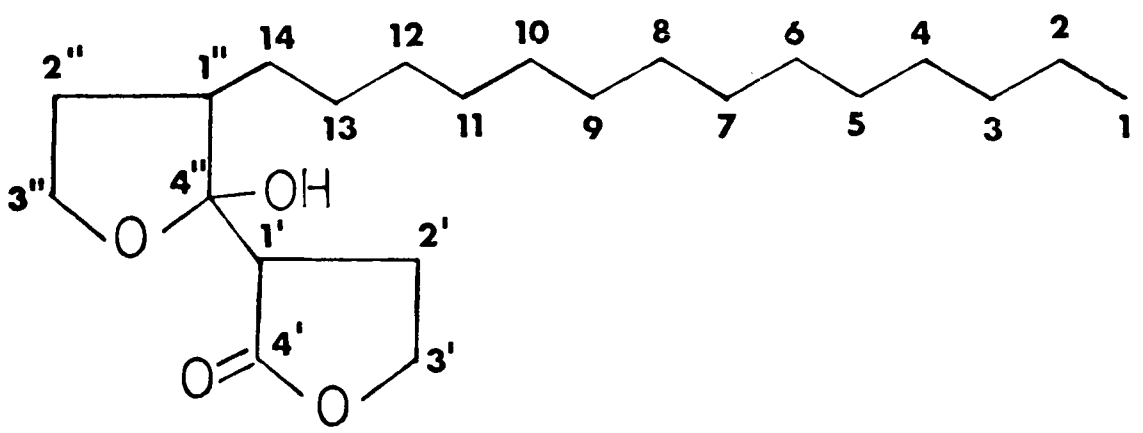
Mass spectrum:- 283(M+1,3), 282(M+1,11), 99(100), 86(83), 55(18), 43(16), 41(17), 28(19) m/e (%)

Fractions 6-10, on concentration in vacuo afforded a pale yellow solid which, when recrystallised from pentane at -30°C, gave 1.367g of 3-[2-(2-hydroxy-3-tetradecyl-tetrahydrofuranyl)]-2(3H)-dihydrofuranone (2.25% yield) as small white microcrystals, m.p. 53.5-55°C, R_f=0.31 by t.l.c. (silica, 2:1 (v/v), diethyl ether/60-80° petrol).

Found:- C=71.9%, H=11.1% ($C_{22}H_{40}O_4$ requires C=71.7% H=10.9%)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS} 0.88(t, 3H, $CH_3(CH_2)_{13}$, J=6Hz), 1.25(s, 26H, $CH_3(CH_2)_{13}$, $w_{1/2}$=4Hz), 1.7-2.2(m,5H), 2.9(dd, 1H, J=10 and 11Hz), 3.5-4.4(m, 5H, OH and 2xOCH_2CH_2) p.p.m.

^{13}C-n.m.r. (22.63MHz, $CDCl_3$):- δ^{TMS} 13.9(C_1), 22.6(C_2), 24.5(C_{13}), 28.4($C_{2'}$), 28.6($C_{2''}$), 28.9, 29.2, 29.6, 29.8, 30.5, 31.5(C_{14}), 31.8(C_3), 44.3($C_{1''}$), 45.8($C_{1'}$), 66.6($C_{3'}$), 66.8($C_{3''}$), 104.5($C_{4''}$), 179.1($C_{4'}$) p.p.m.



I.r.($CHCl_3$):- 3600-3400 br m (OH), 2930vs, 2340vs, 1755 br s (C=O), 1470m, 1455m, 1380s, 1180m, 1140m, 1025s, 1000m cm^{-1}

Mass spectrum:- M^+ unobserved, 350(18), 283(19), 265(6), 167(79), 154(100), 125(17), 123(21), 111(27), 109(21), 97(39), 95(27), 86(24), 85(27), 83(36), 81(29), 71(35), 69(48), 57(55), 55(52), 43(45), 41(35), m/e (%)

A further quantity of 3-tetradecyl-2(3H)-dihydrofuranone (5.6g) was obtained by repeated chromatography of the filtrates retained from the first pentane recrystallisation. Likewise, n-tetradecyl bromide (11.85g, 26% recovery) was obtained in 97% purity (g.l.c.).

Preparation of 3-(ethoxycarbonyl)-2(3H)-dihydrofuranone

Pieces of sodium (25g, 1.09mol) were added to a stirred solution of diethyl malonate (160g, 1mol) in anhydrous ethanol (150ml), held at room temperature over 1.5 hours. On complete addition the solution obtained was then refluxed under nitrogen for 1 hour. The resulting yellow solution was cooled to room temperature and, diluted with anhydrous diethyl ether (50ml). On cooling to 0^oC a dispersion of sodium diethylmalonate was obtained. An isopropanol-dry ice-condenser was fitted and ethylene oxide (66g, 1.5mol) in anhydrous diethyl ether (50ml) added to the anion solution, with vigorous stirring, over 1 hour down

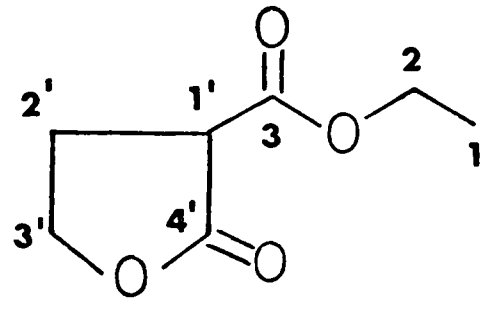
the inside of the condenser. After 15 minutes the dispersion cleared and gentle refluxing ensued. On complete addition, precipitation occurred and the reaction mixture became increasingly difficult to stir. Although anhydrous diethyl ether (50ml) was added, efficient stirring was difficult and the reaction was quenched, 1 hour after complete addition, by pouring into a stirred, saturated aqueous ammonium chloride (500ml) held at $0^{o}C$. The organic layer was separated and the aqueous phase extracted with diethyl ether (2x200ml). The combined organic layers were washed with water (2x200ml), brine (2x200ml) and water (2x200ml), dried and concentrated in vacuo to an oil, which partially solidified on standing. The solid was redissolved in hot chloroform and filtered through a celite pad, and the filtrate concentrated in vacuo to give 97.5g of a yellow oil. Fractional distillation in vacuo afforded 33.62g of 3-(ethoxycarbonyl)-2(3H)-dihydrofuranone (21% yield) as a clear, colourless oil b.p. 105-108^{o}C (1mm Hg) (lit.[275] 155^{o}C, 20mm Hg) (98%, g.l.c. on column B, R_t=8 min at 150^{o}C).

Found:- C=52.9%, H=6.4%, ($C_7H_{10}O_4$ requires C=53.2%, H=6.4%)

^{1}H-n.m.r. (90MHz, $CDCl_3$):- δ^{TMS}1.27(t, 3H, $\underline{CH_3}CH_2O$, J=7Hz), 2.56(pseudo q, 2H, $OCH_2\underline{CH_2}CHCO_2C_2H_5$), 3.59 (dd, 1H, $\underline{CH}(CO_2C_2H_5)$, J=7.5 and 9Hz), 4.2-4.62(m, 2H,

$CO_2\underline{CH_2}CH_2$), 4.27(q, 2H, $O\underline{CH_2}CH_3$, J=7Hz), p.p.m.

<u>^{13}C-n.m.r.</u> (22.63MHz, $CDCl_3$):- δ^{TMS} 14.1(C_1), 26.9($C_{2'}$) 46.3($C_{1'}$), 62.0(C_2), 67.8($C_{3'}$), 168.6(C_3), 173.2($C_{4'}$) p.p.m.



<u>I.r.</u> ($CHCl_3$):- 3015m, 2990w, 2910w, 1780vs(CO. lactone), 1735vs(CO ester), 1375s, 1300m, 1260m, 1160s, 1030s, 1010m cm^{-1}

<u>Mass spectrum</u>:- 159(M+1,3), 158(M,5), 131(18), 130(12), 115(11), 113(47), 101(13), 87(12), 86(100, 85(15), 73(10), 69(100), 68(22), 55(43), 45(15), 44(13), 42(16), 41(60) m/e (%)

<u>Preparation of hexadecyltrimethylammonium chloride</u>.

<u>General procedure</u>.

Hexadecyltrimethylammonium bromide (5g, recrystallised twice from acetone/diethyl ether) in methanol (25ml) was applied to an ion-exchange column previously washed with aqueous saturated sodium chloride solution. The column was eluted with methanol monitoring the fractions (50ml) until no chloride was observed on treatment with aqueous silver nitrate

solution. Concentration in vacuo of the fractions gave a white solid which on recrystallisation from methanol-diethyl ether gave, routinely, 3.2-3.6g of hexadecyl-trimethylammonium chloride m.p. 235-237(dec.). This material gave no minimum in a surface tension-concentration plot and a cmc value of 1.0×10^{-3}M.

Preparation of {bis-[pentadecan-2,3-bis(oximato)]}-nickel (II).

To a stirred solution of nickel chloride hexahydrate (0.05g, 0.2mmol) in water (15ml), acidified to pH3 with 1M hydrochloric acid and held at 70°C, was added a hot solution (70°C) of 2,3-bis(oximino)pentadecane (0.1g, 0.4mmol) in methanol (15ml) over 5 minutes. 10% aqueous ammonia (9ml) was slowly added to the hot solution whereupon an orange-yellow precipitate was formed. The solution was gently refluxed for 15 minutes filtered and the solid collected, washed with 10% aqueous ammonia (3x15ml), water (2x10ml), and dried in vacuo. The orange solid was ground, dissolved in hot methanol, filtered and left to cool to room temperature to afford 0.23g of {bis-[pentadecan-2,3-bis(oximato)]} nickel (II), (100% yield) as a yellow orange microcrystalline powder, m.p. 87-91°C.

Found:- C=60.4%, H=9.8%, N=9.3% ($C_{30}H_{58}N_4O_4Ni$ requires C=60.3%, H=9.7%, N=9.4%)

I.r. (KBr disc):- 3600-3300 br w, 2950s, 2930s, 2870s,

1560 br s, 1470vs, 1460vs, 1370m, 1240s, 1220m, 1125s, 1090m, 1055m, 985m, 880 br m, 850 br m, 820 br m, 750-720 br m cm^{-1}

Mass spectrum:- 598($M+1^{+}$, 4), 597(M^{+}, 5), 596($M-H^{+}$, 10), 579($M-OH^{+}$, 3), 548(5), 442(5), 360(80), 358(80), 253(90%), 237(100%), m/e (%)

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