ABSTRACT

Carbon Nuclear Magnetic Resonance Studies of Conformational Equilibria

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One bond coupling constants were measured as a function of temperature for bonds between carbon and carbon ($^1J_{CC}$) and, less commonly, hydrogen ($^1J_{CH}$) or fluorine ($^1J_{CF}$). Precisions of ± 0.01 Hz were achieved using double isotopic substitution (for $^1J_{CC}$) and least squares curve fitting. Temperatures were measured to ± 0.5 K using carbon chemical shift thermometers.

Molecules having no conformational equilibria showed substituent, temperature and solvent effects on the couplings, throwing doubt on some conformational uses of higher order couplings.

Comparison of $^1J_{CC}$ values and their temperature dependences ($\Delta J/\Delta T$) for some amines and appropriate models allowed determination of conformational free energies (ΔG^o). ΔG^o was estimated for some ethylamines (*trans* and *gauche* conformers) and for piperidine (axial and equatorial N-H). The method depends on the differences in $^1J_{CC}$ for a bond in an ethyl group (ethylamines) or ring (piperidines) according to whether it is *cis*, *gauche*, or *trans* to a nitrogen lone pair. Conformational information was generally obtained from comparison of absolute $^1J_{CC}$ values, not from $\Delta J/\Delta T$.

A hindered internal rotation of the ethyl in *r*-2,*c*-4,*c*-6-trimethyl-*N*-ethylpiperidine was discovered; $^1J_{CC}$ was observed for separate conformers at low temperature and ΔG^o was estimated at room temperature. The result was compared with ΔG^os obtained using other carbon n.m.r. methods, i.e., measurement of line broadening, integrated resonances at low temperature and averaged chemical shifts. Axial/equatorial equilibr were studied by known n.m.r. methods for *N*-ethyl- and analogous *N*-methyl-piperidines.

$^1J_{CC}$ is dependent on conformation in [($^{13}C_2$)ethyl]benzene and its mesityl analogue; mathematical treatment should provide an estimate of the barrier to rotation in ethylbenzene. $^1J_{CC}$ is dependent on conformation in ketones (e.g. diethylketone) and on the configuration (*syn/anti*) of their derivatives.

Hyperconjugation with unsaturated centres explains the conformational dependences of $^1J_{CC}$, analogous to those known for $^1J_{CH}$.

CARBON NUCLEAR MAGNETIC RESONANCE

STUDIES OF CONFORMATIONAL EQUILIBRIA

A Thesis submitted for the Degree

of Doctor of Philosophy

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To all those who have made this work possible

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INTRODUCTION

The field of conformational analysis encompasses the study of the properties of the conformations of a wide range of molecules. The requirements that more than one conformation of a molecule may exist are only that rotation about one or more bonds or inversion at one or more atoms may take place within that molecule. Hence the molecules which may be studied range from ethane to the macromolecules.

The origins and recent history of conformational analysis have been described and discussed in such works as those of Eliel *et al.*[1] and Hanack.[2] The latter author points out that conformational analysis was first used successfully on systems having fused cyclohexane rings such as steroids or triterpenoids. These compounds were relatively easy to deal with because their rigid structures usually allow only one conformation. By contrast, ethane and its derivatives present more problems, despite their small size.

Many methods have been used to investigate the conformational behaviour of molecules. A useful, brief review of some of the most important methods for studying small molecules has been given, as a prelude to an article on the microwave method, by Wilson.[3] Work using molecular orbital theory, vibrational and rotational spectroscopy has been compared by Truax and Wieser.[4] Methods for studying rotational isomerism have been reviewed by Parr and Schaefer, to provide a comparison with a method using nuclear magnetic resonance spectroscopy.[5] These review articles are a useful supplement to the books mentioned earlier.

In this introduction some comments will be made on the various methods used in conformational analysis, particularly on those methods which have been used to study molecules of the types encountered in the work described in this thesis. The methods may be broadly divided into the physical, chemical and theoretical. The information thereby gained may be one or more of the following:-

(1) The number of different conformations which a molecule adopts.

(2) The arrangement in space of all or some of the contained atoms in any given conformation (i.e. the shape of a conformer).

(3) The relative energies of the conformers (sometimes their total energies).

(4) The height of the barrier to interconversion between two conformers.

(5) The rate of such an interconversion.

(6) The physical and chemical properties of the conformers.

Taking the three groups of methods mentioned above in reverse order, it may be said that theoretical calculations and predictions are best used in conjunction with results obtained experimentally. The mutual interdependence of molecular orbital theory and spectroscopy is stressed by Truax and Wieser.[4]

Many of the methods used make use of the relation:-

$$P_{obs} = \sum_i n_i P_i$$

where P_{obs} = an observed parameter,

P_i = the value of that parameter for each conformer

and $\Sigma n_i = 1$

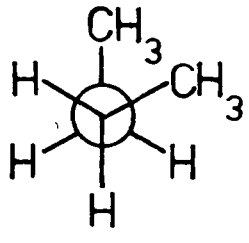
Use of such a relation usually requires that model compounds be available to estimate P_i for each conformer in order that P_{obs} may be used to determine conformer populations, that is, the values of n_i. This is particularly easy when the conformers are cyclohexane derivatives, having axial or equatorial substituents. Methods used to study such compounds, including many chemical methods, have been discussed and criticized by Eliel *et al.*[1a]. These methods, which include kinetic and equilibrium studies, give no information on shape; the possible conformers must be known from other evidence.

Equilibrium studies may be included under the heading of thermodynamic methods which overlap with the purely physical. Besides the free energy differences obtained from equilibration methods (for cyclohexane derivatives) enthalpies and entropies may also be determined thermodynamically. By measurements of heats of combustion and heat capacities some precise conformational information has been obtained, particularly for hydrocarbons, but the methods are very tedious. Examples have been given by Eliel *et al.*[1b]. Of particular interest is the fact that hindered rotation is revealed by comparison of thermodynamic and spectroscopic entropies, the first and most fundamental example having been the rotation in ethane. Of especial relevance to the present work was early work on *n*-butane, which showed the energy difference between the *trans* and *gauche* forms[1c] (see Figure 1).

Diffraction methods give very detailed information about the total structure of molecules (including bond lengths and angles) but are not generally applicable. X-ray diffraction, though capable of dealing with even very large molecules, requires a crystalline

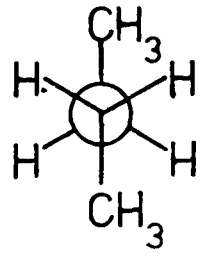
Figure 1

n-Butane



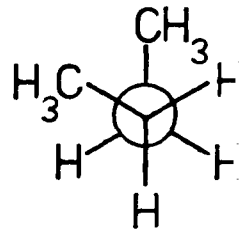
gauche

τ 60°



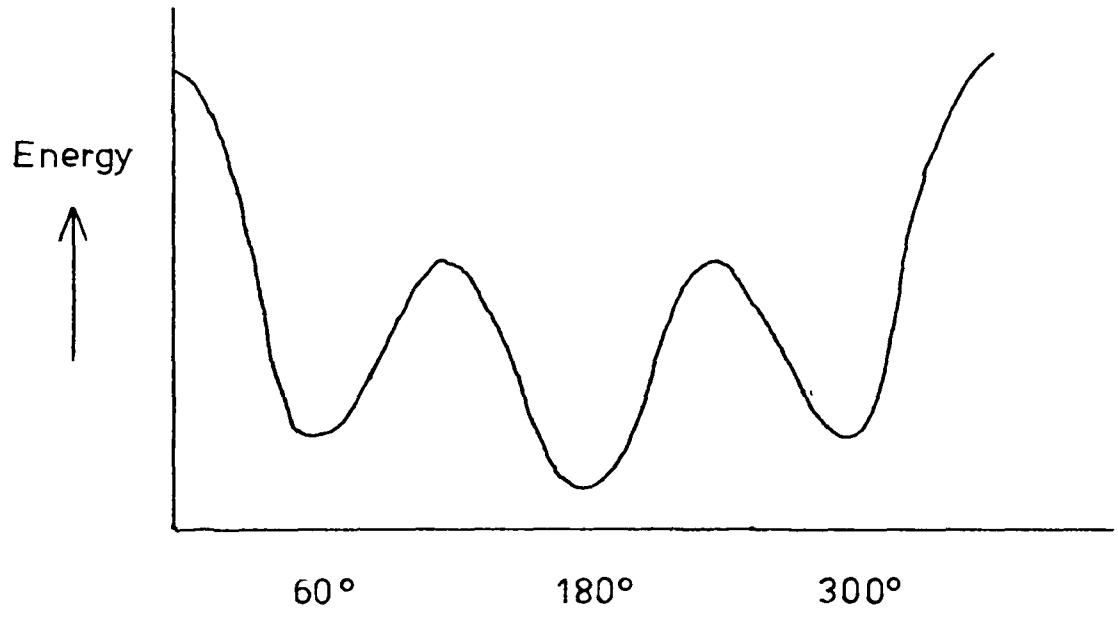
trans

180°



gauche

300°



sample of the compound under study. Often, moreover, only one conformer exists in the solid while in solution there is usually more than one. The conformer in the solid may not even be the same as any of those found in solution (the latter being of more immediate interest to the chemist, biologist, pharmacologist *et al.*). Electron diffraction is best used, by contrast, with gaseous samples but can give misleading results if attempts are made to analyse data obtained for even moderately large molecules (e.g. cyclooctatetraene[1d]).

Microwave spectroscopy is one of the most valuable methods for small molecules; a clear account of its uses has been given by Wilson.[3] Since moments of inertia are obtained from analysis of the rotational spectrum, very accurate bond lengths and angles may be determined. Moreover, unlike analyses using electron diffraction or vibrational spectroscopy, those using rotational (microwave) spectroscopy do not require one to work backwards from possible, assumed structures.

Vibrational spectra (infra-red and Raman) give information on symmetry from which conformations may be inferred. No bond lengths or bond angles are determined so shapes are not found in the way that they are by the microwave method. Some of the most well known work using vibrational spectroscopy was on ethane and its halogenated derivatives.[6]

Infra-red (and less commonly ultra-violet) spectra may also be used in a simpler way, particularly for derivatives of cyclohexane, because the group frequencies for chlorine, hydroxyl etc. vary according as the involved group is axial or equatorial. Errors in the free energy differences based on intensity measurements can, however,

arise out of false assumptions about molar extinction coefficients and Fermi resonance. A criticism of the infra-red method, together with some other methods to be mentioned below, is given by Robinson *et al.*[7] in discussing the preferred conformation of *N*-methylpiperidine.

Infra-red spectra are often obtained for a species in the solid, liquid and gaseous phases. Changes in the number of lines observed are associated with changes in the number of conformers present. For example, it is often assumed that a set of lines for the solid corresponds to one conformer and the appearance of more lines for the liquid means that two or more conformers exist in it. However, unless spectra can be analysed carefully, misleading results can be obtained. The example of fluorocyclohexane has been discussed.[1e] It was assumed that the liquid contained only one conformer because its spectrum was the same as that of the solid, but the solid probably contains both conformers (see Figure 2).

Some physical methods employ measurements of properties that are often harder to relate to conformational behaviour than those already mentioned. The most commonly used have been measurements of dipole moments, chiroptical properties, Kerr constants and acoustic properties. The interpretation of all these involves rather more assumptions than are used in most spectroscopic methods. The misleading results from dipole moments [7] and Kerr constants[1f] for *N*-methylpiperidine have been discussed and illustrate how large the errors can be. In measurements of ultrasonic relaxation there can even be confusion about which process is resulting in the acoustic phenomenon.[1g]

The branch of spectroscopy used in this work is nuclear magnetic resonance (n.m.r.) which Wilson[3] reckoned, even ten years ago, had

Figure 2

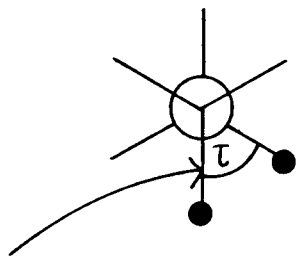
Fluorocyclohexane



F and H are of similar size

Figure 3 (see p.12)

Dihedral angle dependence of $^1J_{CC}$



$^1J_{CC}$ for this bond depends on τ

been the type most used for conformational work in recent years. At that time proton n.m.r. was by far the most commonly used kind. Since then, other nuclei have become increasingly amenable to study. Of particular interest to the organic chemist is carbon-13 n.m.r. which provides a more direct probe of the carbon skeleton than does proton n.m.r. A very useful work on carbon-13 n.m.r. including discussion of all but the most recent publications is the book by Wehrli and Wirthlin[8]. This includes descriptions of the parameters which may be measured and their uses in conformational studies.

A survey of the use of n.m.r. in conformational work has been included, as a matter of course, in the reviews of work in n.m.r. over the past ten years.[9] Of particular value have been the reviews on uses of n.m.r. in conformational analysis in the last two years by Riddell[9a].

N.M.R. is used in conformational work almost exclusively for species in solution. The time-scale of measurements, moreover, is slow so that at room temperature an n.m.r. spectrum contains signals characterised by parameters which are due to the weighted average of all conformers present. Hence the method is particularly attractive to the organic chemist since it relates directly to his intuitive idea of a compound. Conformational work in n.m.r. often involves low temperatures so that rates of interconversion between conformers may be slowed down. Such an interconversion, or exchange, is said to be slow on an n.m.r. time-scale if the nucleus under investigation exchanges between two environments at a rate which is small compared to the difference in resonance frequencies for the given nucleus in the two environments. Thus at low

temperatures, separate signals may sometimes be seen for individual conformers. This is more likely with carbon rather than proton n.m.r. because frequency differences caused by conformational effects are commonly larger for carbon. Moreover, when carbon spectra are obtained with full proton decoupling (the most common method) very simple bandshapes result which make analysis much easier.

A survey of the literature shows that the most commonly used parameters in conformational work employing n.m.r. are the intensity, chemical shift, vicinal coupling constant and relaxation time (T_1). Work may be divided into studies of bond rotation, ring inversion and inversion at an atom, usually nitrogen.

Measurements of relative integrated intensities are made from low temperature spectra. This is analogous to the use of infra-red intensities but does not suffer from the inaccuracies arising from uncertainties in optical extinction coefficients nor, usually, from those caused by overlapping bands. The method can thus be used to determine free energy differences for axial and equatorial groups in various solvents. Moreover, near the point where the two separate signals converge to one (the coalescence temperature) the rate of interconversion and hence activation energy may be obtained. These measurements, it should be noted, are for conformers with relatively high barriers to interconversion. Rotational processes with very low barriers are more easily studied using other forms of spectroscopy. However, for fairly rapidly rotating groups, measurements of averaged chemical shifts and vicinal coupling constants have been used to find conformer populations. The chemical shift is the less well suited parameter as it is more sensitive to solvent, temperature and substituent effects. The

fact that a parameter for an individual conformer (P_i in the previous equation) may vary with temperature always causes uncertainties in the use of temperature dependence studies to infer conformational behaviour. Use of the vicinal coupling constant has mostly involved the Karplus relation for proton-proton coupling constants ($^3J_{HH}$) but more recently couplings involving carbon ($^3J_{CH}$ and $^3J_{CC}$) have been used. These are more sensitive, of course, to the presence of substituents than is $^3J_{HH}$ because one or more of the involved atoms may itself be substituted. Hence deductions about the dihedral angle must be made with more caution from the coupling constants involving carbon. Relaxation rates (T_1 measurements) can be used to study internal rotation of flexible side groups attached to a more rigid part of a molecule. They have been used mainly to study hindered rotation in substituted benzenes, including biphenyls. T_1 values are, however, the most difficult type of parameter to measure of the four mentioned.

The parameter used most often in this work is the one bond carbon-carbon coupling constant, $^1J_{CC}$. In contrast to $^3J_{CC}$ this has received remarkably little attention from a conformational point of view. In his recent, comprehensive compilation of carbon-carbon coupling constants[10], Wray observed that:

> 'orientational effects of substituents are not well documented but appear to be small, except in certain cases.'

The latter qualification one can illustrate by an exhaustive search of the literature. This reveals that although conformational effects on $^1J_{CC}$ have occasionally been observed they are rarely

commented upon, being neglected in favour of those observed for $^{3}J_{CC}$. This course seems unwise as $^{1}J_{CC}$ may more readily be interpreted theoretically than a coupling over more bonds. (Theoretical and experimental work on coupling constants has been reviewed[9b,10,11]). Even recent calculations[12] show that, certainly for bonds between sp^3 carbon atoms, $^{1}J_{CC}$ is closely related to the simple concept of hybridization and hence bond angles.

Most workers have classed any effects they saw on $^{1}J_{CC}$ as insignificant in comparison to the size of the coupling constant (about 34 to 40 Hz for normal acyclic bonds between sp^3 carbon atoms). Their attention has been drawn by the proportionately larger changes seen for $^{3}J_{CC}$ which cause it to vary from 0 to 6 Hz. We have taken the opposite view; that a small change superimposed on a large quantity is more readily observable, particularly under difficult conditions (such as low temperature) when viscosity broadening may completely obscure the splittings caused by $^{3}J_{CC}$.

A search of the literature shows that the one bond carbon-hydrogen coupling constant ($^{1}J_{CH}$) has not been so neglected. Work, some of which has been reviewed[9c] or mentioned in our own preliminary communication on $^{1}J_{CC}$ [13], has shown that $^{1}J_{CH}$ is sensitive to the orientation of other groups, particularly those involving lone pairs or unsaturation. Thus, for example, $^{1}J_{CH}$ varies for equatorial and axial hydrogen in cyclohexane[14], to a larger extent in sugar derivatives[15] and for a wide variety of other systems. $^{1}J_{CH}$ is in fact harder to measure than $^{1}J_{CC}$ since it is measured from a necessarily more complex spectrum, whether by carbon or proton n.m.r.

More recently, significant conformational effects on $^{1}J_{CC}$ in carbohydrates were observed[16] but not discussed (though using this observation other workers have used constancy of $^{1}J_{CC}$ to infer constancy of conformation in an isolated example).[17] There is one example of a comment on orientational effects on $^{1}J_{CC}$ by Berger.[18] Many hidden conformational effects are clearly present in variations seen in $^{1}J_{CC}$ in peptide studies. The latter, which have been reviewed[19], provide a mass of data that cannot readily be interpreted until simpler molecules have been studied.

That the conformation of substituents should affect $^{1}J_{CC}$ was found in calculations by Maciel and co-workers[20] as long ago as 1971 but the idea was neglected. In 1975 Barfield *et al.*[21] calculated and observed a dihedral angle dependence for $^{1}J_{CC}$ (see Figure 3) but, as mentioned above, this was neglected in favour of effects seen for $^{3}J_{CC}$.

In our preliminary communication[13] we reported large (greater than 10%) changes in $^{1}J_{CC}$ according to whether a methyl group was axial or equatorial with respect to an adjacent nitrogen lone pair or carbonyl group. In the work described in this thesis it was hoped to extend the range of molecules studied to those having other, less well known orientations than axial and equatorial. These include many open chain molecules which contain an ethyl group which can rotate. Through this work, not only would conformational information be gained for the simple molecules under study, but a greater understanding of $^{1}J_{CC}$ through examination of experimental results would develop and permit its use as a new conformational tool, perhaps for the study of more complex molecules. To this end, the measurement of $^{1}J_{CC}$ as a function of temperature was made for many molecules. Accurate temperature measurement and curve fitting

techniques, as described in this thesis, allowed very precise measurements to be made. Coupling constants were generally measured with a precision of $\pm$ 0.01 Hz and could be found, via curve fitting, quite precisely even at low temperatures when lines were broad. Temperatures were known to $\pm$ 0.5 K though for most of the work involved such high precision was greater than required.

Studies were made on a group of ethyl amines including *N*-ethylpiperidines. In the course of attempts to provide model compounds, an example of severely hindered rotation in a multiply substituted piperidine was discovered. This was also studied using other, previously known, n.m.r. techniques both to provide confirmatory evidence and to investigate the limits of the techniques. Ethyl amines were especially prepared containing two adjacent atoms (in the ethyl group) substituted with carbon-13 (or only one atom for the other techniques). This double substitution enabled rapid and precise measurement of $^{1}J_{CC}$.

Piperidine and some derivatives were prepared with double isotopic substitution in the ring to study $^{1}J_{CC}$ and provide more evidence for the recently controversial equilibrium at nitrogen in piperidine itself.[22]

Apart from these amines, ethylbenzene and some derivatives were studied. Model compounds were used to investigate the parent compound and the derivatives were examined more briefly.

Lastly, a brief study of diethylketone and some derivatives was made. In the latter, differences between $^{1}J_{CC}$ values for *syn* and *anti* forms were seen. Such effects have been observed by Wray and reported in the review mentioned[10] but do not appear to have been discussed in a full paper to date.

DISCUSSION

Chapter 1

Inherent Temperature Effects: One bond coupling constants in systems having no conformational equilibria or having only equivalent conformers

The main intent of the work described in this thesis was to investigate certain conformational equilibria by the study of the variation of one bond carbon-carbon coupling constants ($^1J_{CC}$) with temperature as well as by examination of differing absolute values of $^1J_{CC}$. Before detailed interpretation of the temperature variation of $^1J_{CC}$ for conformationally mobile systems could be made, it was necessary to investigate what changes in $^1J_{CC}$ occurred in simple, conformationally fixed systems. Systems classed as 'conformationally fixed' included those derivatives of ethane, such as the haloethanes, in which the conformers are all equivalent though internal rotation may take place. In addition, $^1J_{CH}$ was measured as a function of temperature for two halomethanes, in which there is no conformational equilibrium whatsoever. To set in perspective any variations found with temperature, some solvent effects on $^1J_{CH}$ for the readily available (^{13}C)iodomethane were measured.

The solvent effects are demonstrated in Table 1, where some solvent parameters are also given. The temperature effects are given in Table 2 where the absolute values of $^1J_{CX}$ for the different compounds may also be found.

In addition to the discussion of solvent effects on coupling constants given in reviews already mentioned in the Introduction[9b,11] a comprehensive discussion has been given in a separate review by Barfield and Johnson[23]. More recent work is cited in a recent paper

Table 1

Solvent effects on $^{1}J_{CH}$ for iodomethane, ($^{13}CH_3I$)

Solvent[a]	ϵ[b]	D[c]	$^{1}J_{CH}$[d]	Error[e]
A	8.75	1.60	151.33	0.04
B	20	2.88	151.46	0.01
C	33.6	1.70[f]	151.12	0.02
D	2.26	0	151.12	0.003
E	1.91	0	151.21	0.02
F	39.5	low[f]	151.26	0.02
G	2.02	0	150.31[g]	-
H	46	3.82	151.59[g]	-

a Solvents are A: CD_2Cl_2 B: $(CD_3)_2CO$ C: CD_3OD, D: C_6D_6, E: $(CH_3)_4Si$, F: CF_3CO_2H, G: C_6H_{12}, H: $HCONMe_2$

b ϵ = dielectric constant of solvent (protonated not deuteriated) at 35°C[2]

c D = dipole moment of (protonated) gaseous solvent molecule (Debye)[25a]

d $^{1}J_{CH}$ in Hz, measured as described in the Experimental (298 K)

e Error, $\pm$ Hz, obtained as described in Appendix 1.

f Value for methanol is for gas. It is probably in effect much lower in the liquid owing to extensive dimer formation. The value for trifluoroacetic acid, though not recorded, is probably low for similar reasons

g Literature values[26] (for concentrated solutions; values obtained in this work are for 1M solutions).

on the solvent dependence of $^1J_{CH}$ in chlorine-substituted ethanes.[24] It is apparent that solvent effects, even on $^1J_{CH}$ which is relatively simple to treat, are not well understood, although the theoretical framework is on a sounder basis than that for chemical shifts. Work on poly-chlorine-substituted ethanes, which have more than one conformer, indicated that the solvent effect on $^1J_{CH}$ arises mainly from electronic changes in the solute molecules caused by intermolecular solute-solvent interactions, more than from the change in the conformer populations.[24]

In this work it was also found, experimentally and theoretically, that the dielectric constant affected $^1J_{CH}$ more than did the temperature. (Temperature dependence was measured for the neat liquid.)

The data in Table 1 suggest that for iodomethane there is no correlation of $^1J_{CH}$ with the dielectric constant of the solvent but there appears to be a better correlation with the dipole moment of the solvent molecules. High values of $^1J_{CH}$ are associated with high dipole moment, though the fractional changes are very small. Such small changes, have scarcely been recorded by previous workersbut they have been mentioned in a study of hydrogen bonding effects on $^1J_{CH}$ by Evans.[27] The latter worker recorded, for example, a change of + 0.8 Hz in $^1J_{CH}$ for iodomethane on changing the solvent from tetrachloromethane to *N,N*-dimethylformamide which he regarded as showing than non-specific polar effects are not very important. This was by contrast with specific hydrogen bonding effects seen on $^1J_{CH}$ forchloroform (trichloromethane). For this compound $^1J_{CH}$ varied, for the same solvent pair, by + 9 Hz. There is a fair correlation between the changes seen by Evans in $^1J_{CH}$ for chloroform

and the changes seen in this work for iodomethane. A significant exception is methanol, which was clearly bonding quite strongly to chloroform, thus increasing $^1J_{CH}$, but is associated with a low value of $^1J_{CH}$ here. This suggests the following interpretation of the results for iodomethane. "Hydrogen bonding" with iodomethane will be very weak, but still a significant factor at the level of precision encountered here. While, for example, a strong hydrogen bonding base, *N,N*-dimethylformamide, increased $^1J_{CH}$ for chloroform greatly it still has a significant, though small effect on $^1J_{CH}$ for iodomethane. Acetone has a similar but smaller effect. The low value of $^1J_{CH}$ when methanol is the solvent suggests that, unlike chloroform, iodomethane cannot compete with the self-association of the methanol molecules. Thus the iodomethane molecules act as if they were in a less polar solvent, like benzene.

Such ideas are very tentative and it is quite likely that $^1J_{CH}$ can be correlated with no one parameter in a simple way. The solvent effects seen may still act as a *caveat* that there is little purpose in making detailed comparisons of $^1J_{CX}$ values unless solvents are the same. Bearing this in mind, we may turn to Table 2 where temperature effects on $^1J_{CH}$ are given first. Since the solution of bromomethane was more concentrated than that of iodomethane, no significance can be attached to the differing values of $\Delta J/\Delta T$, though the fact that the change for acetonitrile is so small must be significant. $^1J_{CF}$, obtained only for fluoroethane, showed a large temperature dependence. The variation of $\Delta J/\Delta T$ for $^1J_{CC}$ amongst the haloethanes appears significant, particularly the large difference for fluoroethane. Acetonitrile shows that concentration may affect the absolute value of $^1J_{CC}$ as well as $\Delta J/\Delta T$. $\Delta J/\Delta T$ for sodium acetate is barely significant at the level of precision for

Table 2

$^{1}J_{CX}$ and $\Delta J/\Delta T$ for some simple compounds[i]

Compound	Solvent,[a]	Molarity	$^{1}J_{CX}$[b]	$\Delta J/\Delta T$[c]
			$^{1}J_{CH}$	
$^{13}CH_3I$	A	1	151.29	-0.4
$^{13}CH_3Br$[d]	A	4	151.70	-0.5
$^{13}CH_3{}^{13}CN$	A	2.5	136.10	-0.1[e]
			$^{1}J_{CF}$	
$^{13}CH_3{}^{13}CH_2F$	A	1.6	-160.2	-1.88
			$^{1}J_{CC}$[f]	
$^{13}CH_3{}^{13}CH_2I$	A	1	35.814	+0.12
$^{13}CH_3{}^{13}CH_2I$	neat		35.866	+0.11
$^{13}CH_3{}^{13}CH_2Br$	A	1.5	35.972	+0.12
$^{13}CH_3{}^{13}CH_2Cl$	A	1.5	35.166	+0.11
$^{13}CH_3{}^{13}CH_2F$	A	1.6	38.161	+0.08
$^{13}CH_3{}^{13}CN$	A	2.5	56.839	+0.28
$^{13}CH_3{}^{13}CN$	A	0.5	57.625	+0.25
$^{13}CH_3{}^{13}CO_2Me$[g]	C	0.5	59.332	+0.18
$^{13}CH_3{}^{13}CO_2Na$	C	0.5	52.30[h]	-0.03

a See footnotes to Table 1

b Value at 298 K, in Hz

c Hz/K x 10^2 (change in $^{1}J_{CX}$ with temperature). Range usually 200-300 K.

Footnotes to Table 2 (continued)

d Supplied by BOC Prochem (only 60 atom % of ^{13}C)

e Change showed slight curvature, see Appendix 1

f Precision $\pm$ 0.01 Hz, see Appendix 1

g Prepared *in situ* from $^{13}CH_3{}^{13}CO_2H$ i.e. it is $^{13}CH_3{}^{13}CO_2CD_3$

h Less precise, see Appendix 1

i After due allowance for solvent effects and imprecision of previous work, there is agreement with literature values for $^1J_{CH}$ [31] and $^1J_{CC}$ [32] (methyl acetate not previously recorded).

this compound (worse than $\pm$ 0.01 Hz).

The fact that a coupling constant might have an inherent temperature dependence was pointed out long ago by several groups of workers, particularly those attempting to use three bond couplings for conformational work. Govil and Bernstein[28], using $^3J_{HH}$ for 1,1,2,2-tetrabromoethane to study the internal rotation, pointed out that the method might be limited by the temperature dependence of the separate ^3J_g and ^3J_t (for the *gauche* and *trans* forms). They cited work by several other groups including Gutowsky *et al.*[29]. The latter suggested that $^3J_{FF}$ might be affected by inherent factors such as torsion, vibrational motions and solvent or temperature dependent intermolecular interactions.

It appears that couplings involving fluorine may be exceptionally sensitive, more so than these ($^1J_{CC}$) used in the bulk of the work in this thesis. The temperature dependence seen here for $^1J_{CF}$ is fractionally much larger than that seen for $^1J_{CC}$ or $^1J_{CH}$. Work cited in the review of fluorine couplings by Emsley *et al.*[30] shows that $^1J_{CF}$ is very solvent dependent (a range of 4.46 Hz is recorded for difluoromethane). No temperature dependences for $^1J_{CF}$ appear to have been recorded by other workers but couplings over more bonds (eg. $^2J_{FF}$, $^3J_{FF}$) have shown large temperature coefficients. Possible mechanisms for inherent temperature dependence were discussed in the review just cited but most workers using three bond couplings such as $^3J_{FF}$ seem to have ignored the possibility of such dependence.

Certainly, the possibility that $^1J_{CF}$, for the C-F bonds making up the three bonded pathway for $^3J_{FF}$, may vary with temperature has been overlooked. This would appear to be a serious omission. At the time of writing, doubts have been raised in a new paper on

the reliability of using $^{3}J_{CF}$ values as probes for intramolecular substituent interactions. It is suggested that $^{1}J_{CF}$ would be more reliable.[33] Although the couplings involving hydrogen and carbon are less sensitive than those involving fluorine, the same reservations about work involving $^{3}J_{HH}$, $^{3}J_{CH}$ and $^{3}J_{CC}$ hold, since these couplings will surely have some temperature dependence, for whatever reason.

In the light of the results which have been obtained, it is instructive to consider what might cause the inherent temperature dependences which have been observed. We may consider the suggestions of Gutowsky *et al.*[29], namely that changes in coupling constants are due to changes in:-

(1) torsional motion

(2) vibrational motion

(3) intermolecular interactions

These factors may, of course, interact. This matter has been neglected theoretically. The only theoretical study of temperature dependence appears to be one of $^{1}J_{HX}$ in dihydrogen and its isotopomers.[34] This predicts that $^{1}J_{HX}$ will increase with temperature, apparently as a result of increased rotational motion. Clearly this simple idea cannot be carried over to the results seen here, since $^{1}J_{CH}$ and $^{1}J_{CC}$ change in opposite senses. Table 3 shows some parameters which may be of relevance to the changes seen here for $^{1}J_{CC}$.

Torsion was the first possible reason mentioned for temperature dependence of couplings. A theoretical study of ethane showed that $^{1}J_{CC}$ should be greater for the eclipsed than for the staggered form.[35]

Table 3

Some physical parameters related to Table 2

Compound	D[a]	k_b[b]	ν[c]	V_3[d]
CH_3CH_2F	1.94	1.22	415?	13.83
CH_3CH_2Cl	2.05	0.96	-	15.42
CH_3CH_2Br	2.03	0.90	-	15.41
CH_3CH_2I	1.91	0.82	-	13.47
CH_3CN	3.92	-	380[39]	0[e]
CH_3CO_2Me	1.72	-	429[40]	1.25
CH_3CO_2Na	-	-	471[41]	0[e]

a D = dipole moment, gas phase, in Debye[25a]

b k_B = force constant for CCX bend in mdyn$\text{Å}^{o}\text{rad}^{-2}$ [36]

c ν = low frequency deformation frequency (in plane bending) in cm^{-1}. The value for fluoroethane was tentatively assigned from the literature[37] cited by Meyer and Allinger[36] but values for the other haloalkanes were not identified from the literature similary cited (e.g. chloroethane[38]). The value for sodium acetate was obtained from a solution in water. (The others are gas phase).

d V_3 = V_3 torsion barrier in kJ[42]

e There is no such barrier for CH_3CN and for $CH_3CO_2^-$ the barrier will be a very low, V_6 type.

Table 4

Variation of dielectric constant with temperature[25b]

$CHCl_3$		CH_3OH		C_7H_8	
T(°C)	ε	T(°C)	ε	T(°C)	ε
20	4.806	25	32.63	20	2.38
-60	6.76	-80	54	181	2.04

This might, at a first approximation, rationalize the fact that $^1J_{CC}$ is greater at high temperatures and even that the change is small or negligible for sodium acetate. (The acetate anion is expected to have a very low, V_6 barrier to torsion). This idea, however, does not bear close examination because the V_3 barrier in fluoroethane is very similar to that of iodoethane but $\Delta J/\Delta T$ for fluoroethane is 33% less. For the haloethanes the second factor, i.e. vibrations, seems more plausible because there is a fair correlation between $\Delta J/\Delta T$ and the ease of deformation of the CCX bond angle. One can conceive some motion that might transfer electron density into the C-C bond, thus increasing $^1J_{CC}$ while removing it from the C-H bond, thus decreasing $^1J_{CH}$. A vibrational change might account for the changes seen in $^1J_{CH}$ for the halomethanes, though not quantitatively. The bending motion may also explain the change in $^1J_{CF}$ which is concomitant with but in the opposite sense to the change in $^1J_{CC}$ for fluoroethane.

It is not clear whether such arguments can account for the negligible change observed for sodium acetate. Although literature values were not found for bending force constants in acetonitrile, methyl acetate and sodium acetate, values for bending vibration frequencies were located. The lowest frequency vibrations in sodium acetate are somewhat higher than those in the other compounds but the difference is probably not large enough to account for the unique behaviour of $^1J_{CC}$ for this compound.

There are indications that the third factor, intermolecular interactions, may be of importance. Firstly, from the solvent studies on $^1J_{CH}$ for iodomethane, we know that a solvent dependence of $^1J_{CX}$, possibly mediated *via* dipolar type interactions, exists. Secondly, methyl acetate exhibits a larger $\Delta J/\Delta T$ than do the haloethanes,

although having a closely comparable tendency to deformation. Thirdly, acetonitrile, though having no torsion barrier and having a similar bending vibration frequency to fluoroethane shows a large, concentration dependent $\Delta J/\Delta T$.

The fact that methyl acetate shows a large $\Delta J/\Delta T$ is probably because it was studied in methanol. Using Table 4, we can see that in effect, a large change in temperature for methanol is like a change in solvent because the fractional change in dielectric constant is large. By contrast, the changes for chloroform and toluene are small and we may assume that the change for dichloromethane would be similarly low. Thus, the large $\Delta J/\Delta T$ for methyl acetate may be, at least in part, mediated by changing intermolecular interactions, either solute-solute, or more probably, solute-solvent.

The even larger $\Delta J/\Delta T$ for acetonitrile was however, observed when the solvent was dichloromethane. Here, the argument about a gross change in dielectric constant with temperature does not apply. It is very probable that the large change in coupling is due to the fact that the dipole moment of acetonitrile is approximately double that of the other species (the haloethanes and methyl acetate). Thus, dipolar intermolecular interactions must be larger. It would appear that these interactions must be in part solute-solute type because in the more dilute solution $\Delta J/\Delta T$ was smaller and $^{1}J_{CC}$ itself was larger. This suggests that the interaction is withdrawing s-electron density from the C-C bonding region, thus reducing $^{1}J_{CC}$. Hence dilution or a temperature rise increase $^{1}J_{CC}$ by reducing the interactions. If this argument is correct then it implies that the change in s-electron density takes place in the -CN region

since $^{1}J_{CH}$ changed very little with temperature for acetonitrile. A similar argument applied to the haloethanes would suggest that for them, the intermolecular interactions were such that they increased s-electron density, so that $^{1}J_{CH}$ is higher at low temperatures.

Since there is no correlation of $\Delta J/\Delta T$ with dipole moment for the haloethanes, it seems likely that the true picture is that a combination of factors exists. Thus, for the haloethanes which are of only moderate polarity the correlation with ease of deformation dominates, while for acetonitrile the dipolar effect is overlaid on the deformation effect. That even the haloethanes may show effects due to differing solvent-solute interactions was shown by the different values of $^{1}J_{CC}$ and $\Delta J/\Delta T$ obtained for iodoethane when they were measured for the neat compound. Sodium acetate remains problematic.

Whatever the correct interpretation of the results obtained, the results themselves must be borne in mind when observing the solvent or temperature dependence of $^{1}J_{CC}$ in systems having conformational equilibria. A change should not be assumed to be conformational in origin when it may be due to slight vibrational changes or changes in solvent interaction.

Further experimental evidence on inherent effects on $^{1}J_{XX}$ is desirable, so that it may be used to test the many theories on solvent effects and provide tests of future theories of temperature effects. The theoretical work itself is of value to the understanding of bonded and non-bonded interactions, of which $^{1}J_{XX}$ is a very direct and useful measure.

Chapter 2

The Conformation of Ethylamine and its Derivatives

Knowledge of the equilibria in small ethylamines is of interest *per se* and because ethylamine-like fragments are found in larger molecules whose conformations are also of interest. It is often assumed that in amines, factors determining conformation are very similar to those in hydrocarbons, which will not be true because certain bond lengths and angles differ. For example, in work on aminocyclohexane and its *N*-methylated derivatives, Booth compared the amino groups with their hydrocarbon analogues (methyl, ethyl and isopropyl) without reference to such possible differences.[43]

Values of $^{1}J_{CC}$ have been obtained in the present work for ethylamine and some of its derivatives, at room temperature and as a function of temperature in some cases. $^{1}J_{CC}$ (^{1}J) was measured for the amine hydrochlorides only at room temperature for reasons given in Appendix 1. For this reason, to enable the proper comparisons, all absolute values of ^{1}J are quoted for 298K (25°C) which is the normal, approximate, ambient operating temperature of the Bruker WH90 spectrometer. Values of ^{1}J and $\Delta J/\Delta T$ (the change that occurs in ^{1}J when the sample temperature is raised by 1K) are given in Table 5. None of the couplings has been measured before except that for ethylamine[20] for which there is the expected agreement with the literature value. (That is, agreement within 0.2 Hz, the discrepancy being caused by differences in solvent and temperature).

The first group of compounds to be examined included ethylamine and its mono- and di-methylated derivatives. These exhibit ^{1}J values of approximately 36, 37 and 38 Hz. The simple interpretation of these values involves the differing conformational equilibria

Table 5

$^{1}J_{CC}$ and $\Delta J/\Delta T$ for ethylamine and derivatives

Compound	Solvent[a]	$^{1}J_{CC}$[b]	$\Delta J/\Delta T$[c]
$^{13}CH_3{}^{13}CH_2NH_2$	I	36.01	+ 0.12
$^{13}CH_3{}^{13}CH_2NH_3Cl$	F	35.2[d]	-
$^{13}CH_3{}^{13}CH_2NH_3Cl$	J	35.50[e]	-
$^{13}CH_3{}^{13}CH_2N(H)Me$	I	36.92	0
$^{13}CH_3{}^{13}CH_2N(H_2)MeCl$	F	35.1[d]	-
$^{13}CH_3{}^{13}CH_2NMe_2$	I	38.14	0[f]
$^{13}CH_3{}^{13}CH_2N(H)Me_2Cl$	F	35.10[e]	-
$^{13}CH_3{}^{13}CH_2N(H)Me_2Cl$	J	35.45[g]	-
N-($^{13}CH_3{}^{13}CH_2$)piperidine	I	38.24	- 0.09
N-($^{13}CH_3{}^{13}CH_2$)piperidine	K	38.07	- 0.04[h]
N-($^{13}CH_3{}^{13}CH_2$)piperidine HCl	J	35.4[d]	-
N-($^{13}CH_3{}^{13}CH_2$)pyrrolidine	I	38.18	+ 0.06
N-($^{13}CH_3{}^{13}CH_2$)pyrrolidine HCl	J	35.32[i]	-
$^{13}CH_3{}^{13}CH_2NEt_2$	I	37.91	+ 0.15
$^{13}CH_3{}^{13}CH_2N(H)Et_2Cl$	J	35.63[g]	-
$^{13}CH_3{}^{13}CH_2N(H)t$-Bu	I	37.26	+ 0.03
$^{13}CH_3{}^{13}CH_2(NH_2)t$-BuCl	J	34.89[e]	-
$^{13}CH_3{}^{13}CH_2N(Me)t$-Bu	I	39.12	-
$^{13}CH_3{}^{13}CH_2N(Me)t$-BuHCl	J	35.27[i]	-
$^{13}CH_3{}^{13}CH_2NMe_3I$	J	35.58	-

a Solvents: F = CF_3CO_2H, I = C_7D_8, J = D_2O, K = $(CD_3)_2SO$

b Value at 298 K in Hz c Hz/K x 10^2

d Not subjected to curve fitting; value from "peak picker" subroutine of Bruker program FT73EM

e Precision $\pm$ 0.02 Hz, see Appendix 1

(Footnotes to Table 5, continued)

f Change was within the precision (it showed curvature, see Appendix 1). Temperature range was 300-340 K

g Precision $\pm$ 0.04 Hz, see Appendix 1

h 300-400 K range (Usual range 200-300 K)

i Precision $\pm$ 0.03 Hz, see Appendix 1

in these molecules. These are depicted in Figure 4, using Newman projection formulae which show the interactions of interest in the clearest possible way. The projections are along the N-C bond. The bond for which $^{1}J_{CC}$ was measured is from the rear carbon to the methyl carbon shown at the top. The lone pair is shown as a directed orbital (n-type).

It is assumed that the equilibria are between staggered, *trans* and *gauche* forms with eclipsed forms as high energy intermediates. In this work *'gauche'* and *'trans'* as descriptions of conformers always refer to the relative orientation of the bond for which $^{1}J_{CC}$ is measured and the lone pair. Unfavourable *gauche* methyl-methyl steric interactions are indicated on the formulae. It is of importance to notice that all the equilibria are statistically weighted in favour of the *gauche* forms by a factor of two. One is interested in determining a value of k, the equilibrium constant for the conformational equilibrium, that takes this factor into account. One can thus estimate the real energy difference between a *trans* and a single *gauche* form. In *N*-methylethylamine ((2) in Figure 4) there will also be a considerable energy difference between the two pairs of *gauche* conformers for which the difference in numbers of *gauche* methyl-methyl interactions is very similar to the overall difference in such steric interactions between *trans* and *gauche* forms. It should be noted that one of the forms called *'gauche'* for this compound is called *'s-trans'* using another nomenclature system.

Our preliminary communication reported that a carbon-carbon bond *trans* to a lone pair exhibited a value of $^{1}J_{CC}$ approximately 4 Hz less than did a bond *gauche* to a lone pair.[13] Hence the interpretation

Figure 4

The conformations of (1) ethylamine, (2) N-methylethylamine and (3) N,N-dimethylethylamine

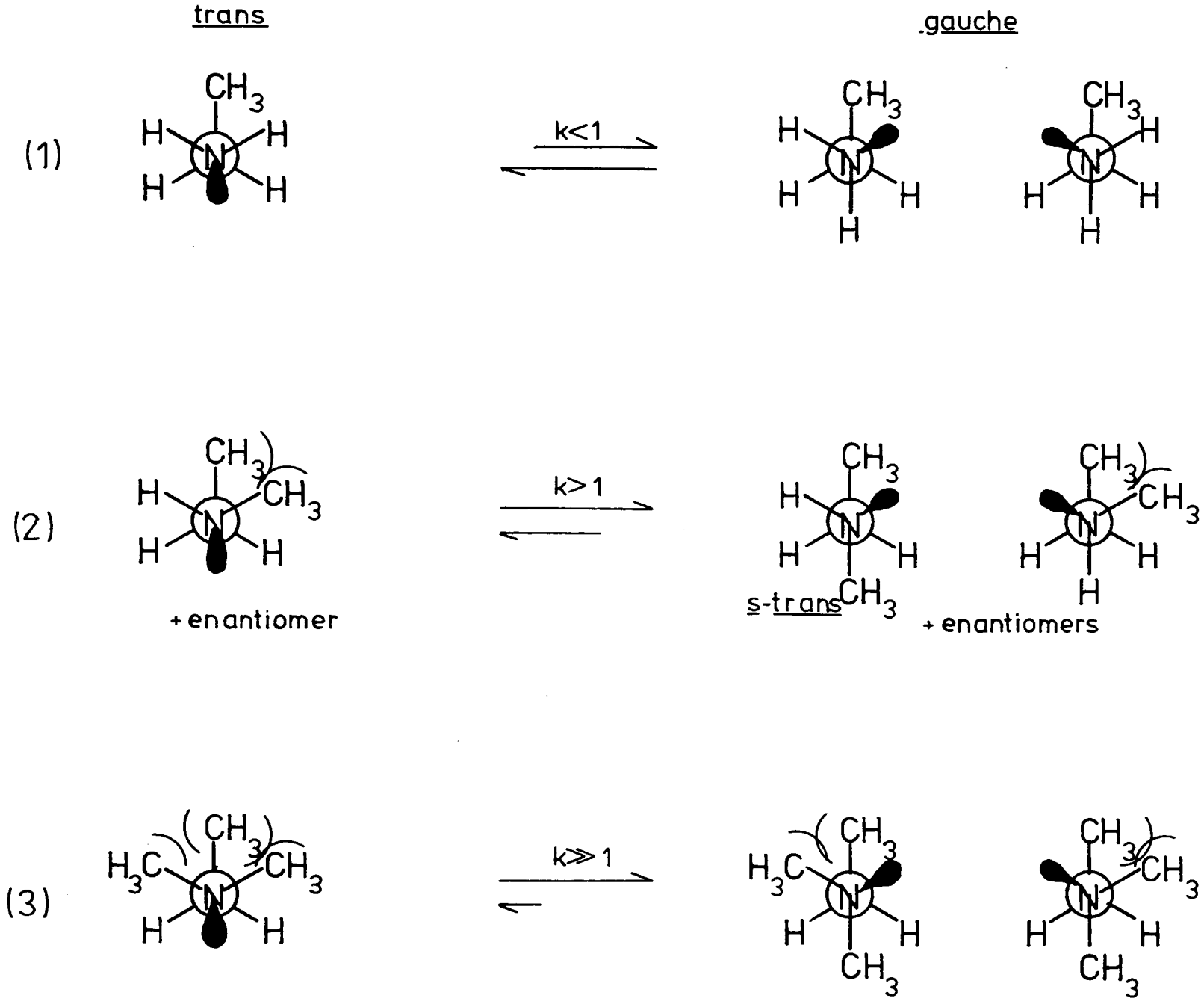
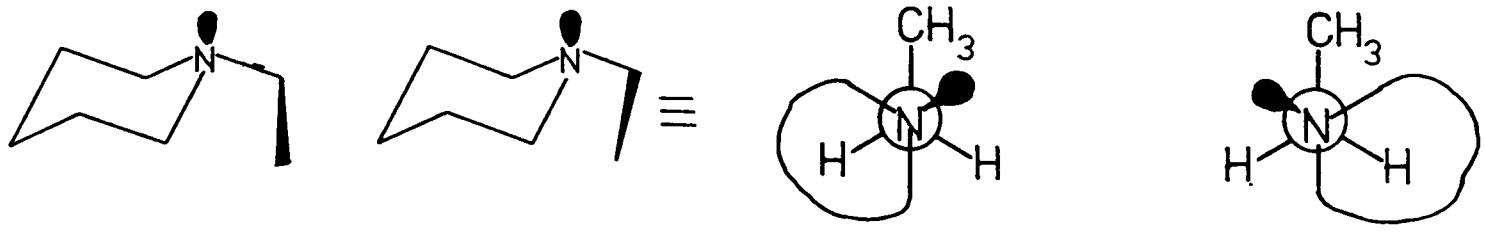


Figure 5

The conformation of N-ethylpiperidine



of the present results is that the observed coupling constants reflect the differing natures of the averaged bond/lone pair interactions in these molecules. As the equilibria are forced increasingly towards the *gauche* forms by increased *gauche* methyl-methyl interactions caused by increased methylation, so ^{1}J increases. That is, ^{1}J is raised by having increasing proportions of conformers with the C-C bond and lone pair in a *gauche* orientation.

A difference in $^{1}J_{CH}$ according as the involved C-H bond was *cis* or *trans* to a lone pair was predicted by Gil and Teixeira-Dias.[44] (Experimental results showing this effect on $^{1}J_{CH}$ were cited in the Introduction[9c,15]). Their arguments may be extended to $^{1}J_{CC}$ since they involved the concept of hyperconjugation of an n-type lone pair with a σ^{*} orbital. A more qualitative but similar theory was used by Hamlow to account for differences in proton (n.m.r) chemical shifts for axial and equatorial protons in amines[45]. This phenomenon was related to one already known in infra-red spectroscopy, that is the existence of Bohlmann bands (for C-H bonds *trans* to lone pairs). Methyl tilt in amines and the anomeric effect (and generalisations thereof[≠]) are related phenomena. The anomeric effect has also been explained in terms of n-type lone pair interactions.[46] Theories for methyl tilt and Bohlmann bands in methylamine invoking p-type lone pair interactions with methyl π and π^{*} orbitals[47,48] cannot be so readily extended to the phenomenon seen here for $^{1}J_{CC}$ for an ethyl group.

That the effect seen for $^{1}J_{CC}$ is due primarily to the lone pair orientation is shown by the fact that ^{1}J values for the amine salts

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≠ the general effect is known as the *'gauche'* effect but I wish to avoid using this term yet again. The same effect is also called the *'trans'* effect!

are very similar to one another. The origin of the solvent effect on ^{1}J for the salts is unknown though presumably is related to differing ion - solvent interactions. ^{1}J for all the salts is lower than for the free amines because all the free amines have a preponderance of conformers containing a *gauche* lone pair/C-C bond orientation. Removal of the lone pair interaction by protonation removes the raising effect that the *gauche* lone pair has on ^{1}J.

A more detailed interpretation of the ^{1}J values for the free amines may be given, in an attempt to deduce the conformational behaviour more precisely. From results found in our previous work[13] (not discussed in that publication) and results to be described later (see the chapter on piperidines) it would appear that an *N*-methyl group also has an effect on ^{1}J relative to an *N*-H. A *trans N*-methyl has an effect of the same type as a *trans* lone pair but of much smaller magnitude. Thus it lowers ^{1}J by approximately 0.45 to 0.55 Hz relative to the effect of a proton. A *gauche* methyl group appears to raise ^{1}J by about 0.3 to 0.6 Hz; the size of the effect is probably affected by the exact torsional angle involved. That is, the dihedral angle between the bond for which ^{1}J is measured and the N-methyl bond affects the amount by which the methyl group raises ^{1}J. Theories to explain conformational and substituent effects on $^{3}J_{CC}$[49] may have some relation to these effects.

The small effects of methyl groups must be taken into account, as well as the large effects of lone pairs, in order to give a detailed account of the conformations of the ethylamines. This

account requires one to have models for the *gauche* and *trans* forms. *N*-Methyl substituent effects can then be added to the ^1J values of the models when necessary. We shall have to make the assumption that the effects are additive and that, in this case at least, the *gauche* and *trans* methyl effects are equal though of opposite sign. Later it will be shown what happens if the latter assumption is varied.

Our model for a *gauche* ethylamine is dimethylethylamine, which has one *gauche* and one *trans* *N*-methyl group. There are several pieces of evidence in favour of this choice. Firstly, $\Delta J/\Delta T$ for this compound is effectively zero which indicates that its conformational preference is held to rigidly. Secondly, the *gauche* form was shown to dominate by vibrational spectroscopy.[50] Thirdly, *N*-ethylpiperidine has a similar value of ^1J and a small and negative $\Delta J/\Delta T$. The conformation of the latter compound is shown in Figure 5 where it can be seen to be very similar to that of dimethylethylamine, except that the methyls are replaced by ring methylenes. Evidence that *N*-ethylpiperidine exists in the *gauche* form was obtained by comparison of its ^1J value with that for model compounds (see Chapter 4). The slight decrease in ^1J with temperature rise for *N*-ethylpiperidine may be due to a slight amount of *trans* form but it may also be due to the kinds of effects discussed in Chapter 1. That similar conformation gives rise to a similar ^1J for these two ethylamines is very encouraging. Since we are assuming, for the moment, that the *gauche* and *trans* *N*-methyl effects on ^1J cancel, ^1J will be the same as for the model for both *gauche* methylethylamine and *gauche* ethylamine itself, i.e. 38.14 Hz.

The model for the *trans* ethylamines is described later (see Chapters 3 and 4). The model has a ^{1}J of 34.0 Hz and has two *gauche N*-methyl interactions. If we assume, for example, that for the ethylamines the *N*-methyl effect is $\pm$ 0.5 Hz, then *trans* ethylamine will have a ^{1}J of 33.0 Hz and *trans* methylethylamine a ^{1}J of 33.5 Hz.

We are now in a position to interpret the observed ^{1}J values for these two compounds, using the equations:

$$38.14n_g + 33.0n_t = 36.01$$

where $n_g + n_t = 1$

for ethylamine

and $38.14n_g + 33.5n_t = 36.92$

for methylethylamine.

n_g/n_t will be the actual ratio of *gauche* and *trans* forms. The ratio required to find the energy difference (allowing for the multiplicity of the *gauche* forms) is:

$2n_t/n_g = k$, the equilibrium constant desired

in both cases.

This will give $\Delta G^{o} = -RT\ln k$ where T= 298 K. For ethylamine one obtains:

$k = 1.39$, $\Delta G^{o} = 0.82$ kJ and for methylethylamine:

$k = 0.71$, $\Delta G^{o} = -0.84$ kJ

Thus for ethylamine the *trans* form is more stable and for methylethylamine the *gauche*. These energy differences seem unexpectedly similar in magnitude if steric factors are dominant in determining the equilibria, because in ethylamine the differences in steric interactions between *trans* and *gauche* forms seem slighter than in methylethylamine. It is necessary to discuss how accurate our assumptions

were. The assumption that the *trans* and *gauche N*-methyl effects cancel must be true for the amine salts for otherwise ^{1}J would have varied amongst them. However, this may not be true in the free amines where bond lengths and angles may differ. In the light of results obtained for different systems, e.g. piperidines, it is extremely unlikely that the estimates of the *trans* and *gauche N*-methyl effects are very inaccurate. The likely range of true free energy difference for the two compounds above may be found by allowing the *gauche N*-methyl effect to vary from 0.3 to 0.6 Hz

(a) <u>If the effect is + 0.3 Hz</u>

we have for ethylamine:

$$38.34n_g + 33.4n_t = 36.01$$

and for methylethylamine:

$$38.14n_g + 33.7n_t = 36.92$$

giving for ethylamine:

$$k = 1.5 \text{ and } \Delta G^{o} = 1.0 \text{ kJ}$$

and for methylethylamine:

$$k = 0.76 \text{ and } \Delta G^{o} = -0.69 \text{ kJ}$$

These relative results look less plausible.

(b) <u>If the effect is + 0.6 Hz</u>

we have for ethylamine

$$38.04n_g + 32.8n_t = 36.01$$

and for methylethylamine:

$$38.14n_g + 33.4n_t = 36.92$$

giving for ethylamine:

$$k = 1.26 \text{ and } \Delta G^{o} = 0.58 \text{ kJ}$$

and for methylethylamine:

$$k = 0.69 \text{ and } \Delta G^{o} = -0.91 \text{ kJ}.$$

The latter set of results looks more likely. In order to use $^{1}J_{CC}$ values for more quantitative work it is necessary to provide very exact models. At present the *N*-methyl effects have had to be obtained from salts (see Chapter 3). However, it is very encouraging that even on altering our assumptions quite drastically, we do not change the sign or order of magnitude of the conformational free energy differences obtained for nearly all the species encountered in our work.

No previous work has indicated even the range of ΔG^{o} values for methylethylamine. Vibrational spectroscopy showed that there were two conformers,[51] microwave showed the presence of the *s-trans* form[52] and infra-red/Raman work showed that the latter was of lower energy[53], as one would expect.

Ethylamine has been the subject of much more study, leading to conflicting results. At the time of the review by Truax and Wieser[4] most work had indicated the *gauche* form to be the more stable but now the opposite is the case. An early Raman study[54] showed the *trans* form to be more stable and a more recent Raman study suggested that the *trans/gauche* energy difference was 2.47 kJ[55]. This value seems high. An infra-red study was at first interpreted to indicate that the *gauche* form was more stable[56] but this interpretation was later reversed.[57] The *trans* form was then estimated to be more stable by 2.74(5) kJ. These two values are in good agreement and are two to four times the size of the present estimate.

If the *trans* form is the more stable then this might either be because methyl-hydrogen interactions are less unfavourable than methyl-lone pair interactions or because forms having the lone

pair *trans* to a hydrogen are less stable than those having it *trans* to a methyl. This is the very opposite situation to the one discussed by Truax and Wieser[4] and McKean.[58] In the former review, the now out-dated evidence for dominance of the *gauche* conformer of ethylamine was linked with a general phenomenon, that favoured conformers have the maximum possible number of *trans* lone pair/hydrogen interactions. McKean even suggested[58] that this "*trans* lone pair effect" would tend to favour the conformer of piperidine having N-H axial. This is contrary to what is found by experiment (see reference 22 and Chapter 3).

The other ethylamines will now be discussed more briefly, starting with *N*-ethylpyrrolidine. This compound has a similar ^{1}J to *N*-ethylpiperidine, suggesting that the ethyl has a similar *gauche* orientation. There is no obvious explanation for the fact that $\Delta J/\Delta T$ for this compound and all the others except *N*-ethylpiperidine is positive. One could interpret, for example, the sign of $\Delta J/\Delta T$ for ethylamine as further evidence that the *trans* form is more stable were it not that $\Delta J/\Delta T$ for most of the compounds having the *gauche* form more stable is of the same sign. It is possible, though, that one could classify small changes (0.08 Hz or less) as due only to vibrational changes etc., while the larger changes are of conformational significance. This can only be tentative, however, since even the "large" changes for these amines are similar to those seen for iodoethane.

$\Delta J/\Delta T$ is largest, for this group of compounds, for triethylamine which shows a ^{1}J value of a little less than the "pure *gauche*" model. Earlier work using vibrational spectroscopy has shown that, of the conformers likely to be present on steric grounds, the *tgg* and *ggg*

forms can be detected[59,60] and that the *tgg* form is the more stable in the vapour.[59] Rayleigh light scattering results suggested that the energy difference between the two major conformers (not specified) was 5.0 kJ[61]. The *tgg* form is like one *trans* and two *gauche* ethylamines "fused" so that the nitrogen atoms coincide. The unfavourable steric interactions are analogous to those in dimethylethylamine and *N*-ethylpiperidine but will be more severe. Although $N-CH_2-CH_2-$ in a ring had the same effect on ^1J as $N-CH_3$, $N-CH_2-CH_3$ is not "held back" like the ring methylenes. Thus our *N*-methyl substituent effects on ^1J are probably not applicable. There is a need to provide special "*N*-ethyl effect" models. The differing sizes of steric interactions probably explain why ^1J for triethylammonium chloride is higher than that for the dimethylethylammonium salt. If our previous models were applicable we should have ^1J of 38.14 Hz for the *gauche* fragments in triethylamine and 34 Hz for the *trans*. Thus the *tgg* conformer should have a ^1J of 36.76 Hz. On statistical grounds the *tgg* forms are favoured by a factor of three over the *ggg* form. Allowing for the possibility of *g*+ and *g*- the final inherent weighting of the *tgg* form is 9/2. The conformers we are considering are shown in Figure 6. Thus to find the free energy difference, assuming all the *tgg* forms are similar to one another, we have:

$$36.76_{tgg} + 38.14n_{ggg} = 37.91$$

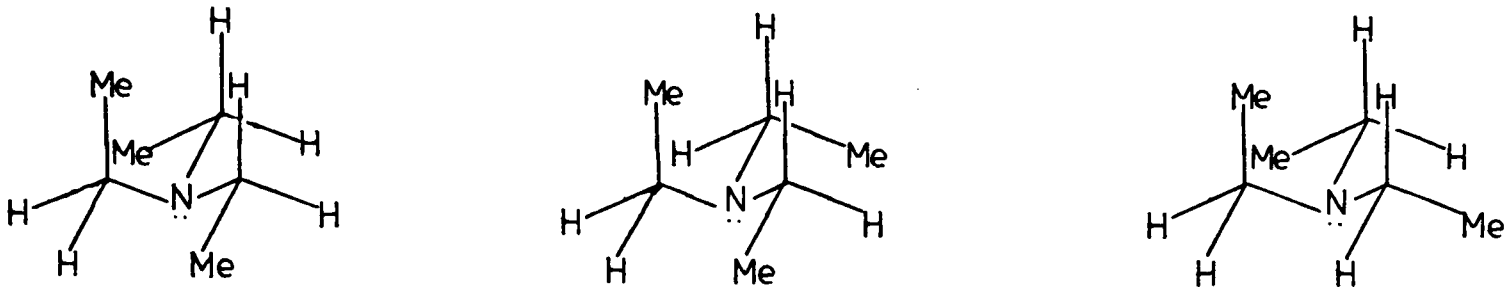
and $$n_{tgg} + n_{ggg} = 1$$

but $$k = 2n_{tgg}/9n_{ggg} = 0.044$$

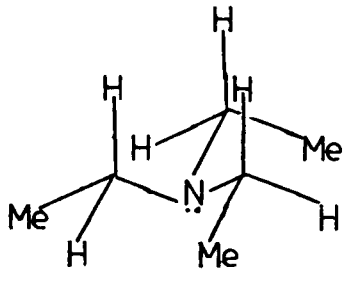
and $$\Delta G^{o} = -7.7 \text{ kJ}$$

Figure 6

(1) Conformers of triethylamine considered in calculation

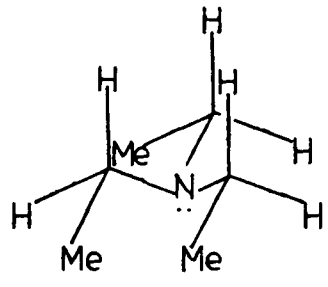


tgg. forms (X 3=9)



ggg form (+ enantiomer = 2)

(2) Example of sterically unfavoured form, not considered



Thus the *ggg* form is favoured by a large amount (ΔG^o is of the same order of magnitude as suggested by the result cited).

Although we knew that the ^1J values used here are only estimates, one can show how unlikely it is that the *tgg* is really the more stable conformer. Even if the *tgg* and *ggg* forms were only equally stable we should have:

$k = 1$, whence, assuming that the difference in ^1J between the two forms remains the same,

$$^1J_{ggg} = 39.04 \text{ Hz}$$

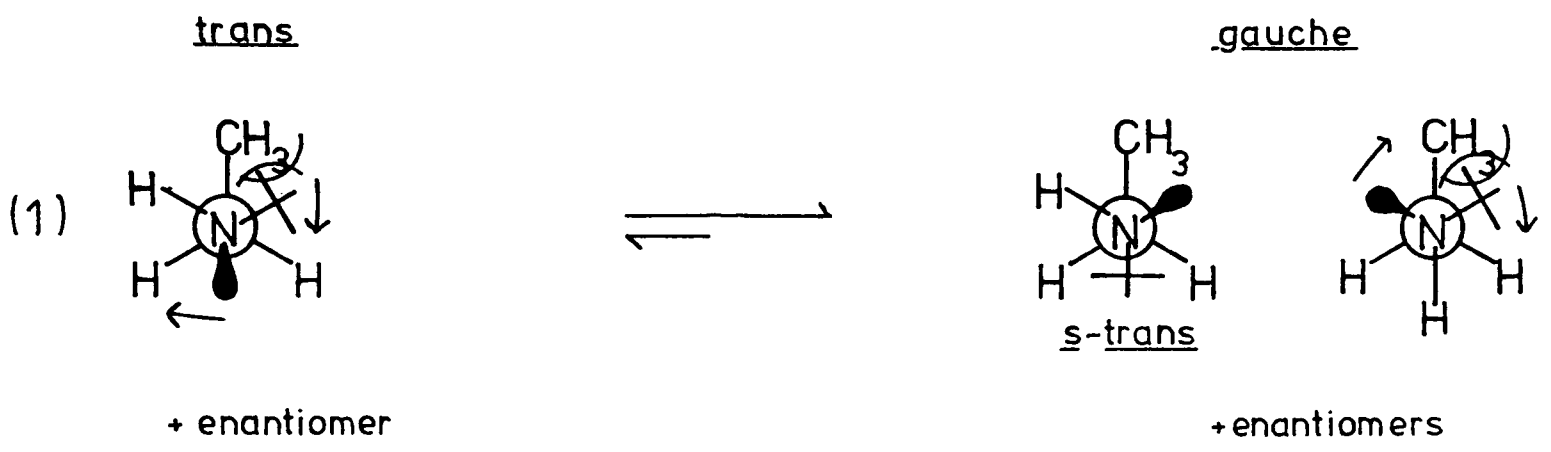
and $$^1J_{tgg} = 37.66 \text{ Hz}$$

These values are extremely unlikely, since such a value for a *gauche* type conformer only arises, it would appear from data to be discussed below, when the lone pair/C-C bond orientation is nearly *cis*. Thus we conclude that the *ggg* form is more stable but have not explained the fairly large value of $\Delta J/\Delta T$. This problem requires further work.

The ^1J values for the remaining compounds in Table 5 may be used to add to our understanding of how ^1J is affected by lone pair orientation. ^1J for *t*-butylethylamine is a little higher than for methylethylamine (37.26 vs. 36.92 Hz) indicating that the large *t*-butyl group forces the molecule to exist largely in the *gauche* form (the *s-trans* form very much predominating). This is illustrated in Figure 7. If there are, moreover, small amounts of the other *gauche* or the *trans* forms, these will have larger ^1J values than the analogous methylethylamine conformers. This is because the *t*-butyl group will enlarge the dihedral angle between itself and the vicinal methyl group relative to the angle between

Figure 7

The conformations of (1) t-butylethylamine, (2) its N-methylated analogue and (3) trimethylethylammonium iodide



two methyl groups. (Analogous effects in tetrasubstituted ethanes have been discussed[62]). Thus the *trans* lone pair interaction is weakened, thus raising ^{1}J while the *gauche* interaction will become more *cis* like, thus also increasing ^{1}J. The salt has a rather low ^{1}J which probably indicates the high proportion of the compound having a *trans* C-C bond/N-C bond orientation. Other, unidentified steric factors may also be involved and these may also affect the exact value of ^{1}J for the free amine. The methylated analogue provides further illustration of these ideas; the conformations are again shown in Figure 7. Only *gauche*-like forms are now encountered and in these, the unfavourable steric interactions will cause the lone pair/C-C bond orientation to be near to *cis*. The most favoured conformer also has an additional *gauche N*-methyl interaction compared to the unmethylated amine which raises ^{1}J still further. ^{1}J for the salt is 0.38 Hz larger than for the unmethylated analogue, showing the effect of the *N*-methyl group.

The quarternary ammonium salt also shown in Figure 7 completes the picture. This salt has a ^{1}J of 35.58 Hz, an increase of only 0.13 Hz compared to dimethylethylammonium chloride. Although the ^{1}J values were measured in the same solvent, the counter anion was different so no detailed interpretation of this result can be given.

The account given in this thesis of effects on $^{1}J_{CC}$ in terms of hyperconjugation of antibonding orbitals with lone pairs (and to a lesser extent with other, bonding orbitals) is at variance with an alternative theory proposed to account for stereochemical

variations in various coupling constants and chemical shifts. Gorenstein suggested that all observed effects could be accounted for by differing torsional angles between *trans* and *gauche* forms.[63] He predicted the effect of angle on $^{1}J_{CH}$ by use of a relation between $^{1}J_{CX}$ and s character. This relation, which originates in the extreme dominance of the Fermi contact term for such couplings, was an extension[64] of the earlier, better known work of Frei and Bernstein.[65] The relation involves the overlap integrals of the two involved orbitals and the percentage s character of the carbon orbitals. Gorenstein's calculations have been shown by the author and others[66] to be erroneous. It is clear, in any case, that the results shown here cannot be accounted for in terms of angles alone. This is particularly so when the amines and their salts are compared. Although differences in torsional angles between *trans* and *gauche* forms may be more pronounced in the free amines this would not account for the fact that ^{1}J values for the salts are so similar to one another. It is probable, though, that a refinement of the interpretation given here could be made if dihedral angles involving the relevant C-C bond were always taken into account.

In the discussion to be given later of $^{1}J_{CC}$ and conformation in heterocyclic ring systems, due reference is made to effects of angle change, which are much more pronounced on moving from open chain to cyclic compounds than amongst acyclic compounds themselves.

There is some hope that the work described above may be extended, for example, to the field of amino-acids and peptides where much use has already been made of $^{1}J_{CC}$ and $^{3}J_{CC}$. Most work

has involved gross changes in $^{1}J_{CC}$ occasioned by change in pH. As mentioned in the Introduction, however, there are other, conformational changes which might be better understood using the ideas described above.

Chapter 3

Nitrogen Inversion in Piperidine and Related Compounds

Although there is now no doubt in the minds of most of those concerned that in piperidine there is a preference for equatorial N-H, the equilibrium at nitrogen is still of current interest. As pointed out by Katritzky *et al.*[22a], there remains the possibility that the N-H axial form is preferred in polar solvents or, more particularly, in hydroxylic solvents such as methanol. In order to clarify this point and also to provide model compounds for various effects on $^{1}J_{CC}$, a series of measurements of $^{1}J_{CC}$ was made for piperidine and some derivatives, none of which has been made before. As described in the Experimental section, the preparation of piperidine containing double isotopic substitution in the ring led to the formation of some pyrrolidine, whose derivatives could also be studied. The results are drawn up in Tables 6 and 7. In Table 6 are shown results for compounds whose equilibria were only studied above the coalescence temperature (at the fast exchange limit). In Table 7 are shown results for equilibria that were slowed down enough at low temperatures to observe $^{1}J_{CC}$ values for the two separate conformers. For clarity, the formulae of the compounds are shown in Figure 8. Results for the hydrochlorides of the amines (only studied at room temperature) are included in Tables 6 and 7 near those for the parent amines.

Two points of interest emerge from the results for piperidine and *N*-methylpiperidine. First, both exhibit solvent effects on $^{1}J_{CC}$ of the same sense and those for *N*-methylpiperidine are at least as large as those for piperidine itself. Second, both show temperature dependent couplings but the coefficients have the opposite

Table 6

$^1J_{CC}$, $\Delta J/\Delta T$ and solvent effects on $^1J_{CC}$ for piperidine and related compounds

Compound[a]	Solvent	$^1J_{CC}$[b]	$\Delta J/\Delta T$[c]
1	CD_2Cl_2	34.925	-0.09
1	CD_3OD	34.752	-0.12
1	C_7D_8	35.102	-0.15
1	$(CD_3)_2SO$	35.045	-0.15[e]
1 HCl	D_2O[d]	34.16	-
2	CD_2Cl_2	35.907	+0.1
2	CD_3OD	35.487(5)	+0.08
2	C_7D_8	36.016(5)	+0.06
2 HCl	D_2O[d]	33.60	-
3	CD_2Cl_2/TMS[f]	34.846	0
3	CD_3OD	34.910	-
3	C_7D_8	34.827[j]	-
3 HCl	D_2O[d]	34.73	-
5	CD_2Cl_2	32.73[g]	-
5 HCl	D_2O	33.55	-
6 HCl	D_2O	33.46	-
8	CD_2Cl_2	32.90[h]	-
9	$CDCl_3$	33.15[i]	-

a Legend contained in Figure 8

b Precision $\pm$ 0.01 Hz for free amines and up to $\pm$ 0.05 Hz for salts (see Appendix 1)

c Change in $^1J_{CC}$ with temperature (Hz/K x 10^2)

d $^1J_{CC}$ was the same, within the precision, when the solvent was CD_3OD

e High temperature range used (300-400 K)

(Table 6 - footnotes)

f $CD_2Cl_2/(CH_3)_4Si$, 50/50 by volume

g Measured at 270 K (the others are for 298 K)

h Precision $\pm$ 0.04 Hz

i Precision $\pm$ 0.05 Hz, measured for the saturated solution using an isotopically normal sample by S.P. Kempsell using the method of double quantum coherence[67]

j Measured at 75.47 MHz. Value directly from print-out of Bruker computer but precision still $\pm$ 0.01 Hz (see Experimental for account of digital resoltuion).

Table 7

$^1J_{CC}$ for derivatives of piperidine for which two forms could be observed[h]

Compound[a]	Solvent	$^1J_{CC}$[b]	Ax[c]	Eq[c]
4	CD_2Cl_2/TMS	35.16	37.0[d]	34.1[d]
4	$CD_2Cl_2/CFCl_2H$	-	37.0[d]	34.0[d]
4	CD_3OD	35.18	36.3[e]	34.38[d]
4	C_7D_8	35.12	-	-
4 HCl	D_2O	-	34.27	35.14
7	CD_2Cl_2	33.18[f]	32.4[g]	33.09[f]

a see Figure 8; b Measured at ~ 260 K

c Ax refers to $^1J_{CC}$ for the form in which methyl or chlorine is axial with respect to the bond for which the coupling is measured (see Figure 8) and Eq to $^1J_{CC}$ for the form with an equatorial substituent

d Precision $\pm$ 0.1 Hz ; e Precision $\pm$ 0.2 Hz

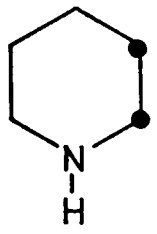
f Precision $\pm$ 0.02 Hz

g Value obtained from "peak picker" subroutine of Bruker WH90 program FT73EM (minor conformer)

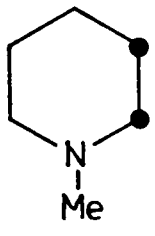
h Measured at low temperatures (200 to 150 K) except 4 HCl (~ 298 K).

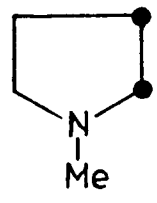
Figure 8

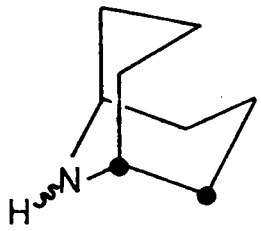
Legend for Tables 6 and 7

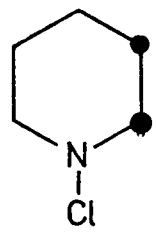
(1) 

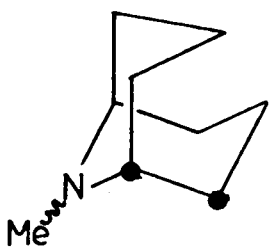
● denotes ^{13}C

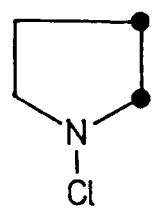
(2) 

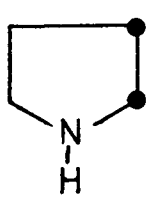
(6) 

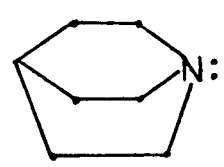
(3) 

(7) 

(4) 

(8) 

(5) 

(9) 

unenriched

sense and those for *N*-methylpiperidine are smaller on average. Bearing in mind the conclusions already drawn concerning the caution that must be used when interpreting such values of $\Delta J/\Delta T$, one may still be able to make some inferences. It is rather striking that the temperature effects for these two compounds are of opposite senses. It may be that those for *N*-methylpiperidine are due only to vibrational effects etc. Those for piperidine are likely to include such effects (giving a positive contribution to $\Delta J/\Delta T$) so the larger, negative $\Delta J/\Delta T$ may indicate a conformational change. If this were so, the temperature dependence of ^1J would be evidence that N-H equatorial is the more stable form in all solvents, as this form has the *gauche* lone pair/bond orientation. This is illustrated in Figure 9 where the conformations of piperidine and *N*-methylpiperidine are shown. The equatorial preference of the N-methyl has been in much less doubt than that of the N-H and it is now known[7] that the equatorial N-methyl conformer is favoured by approximately 12 kJ so that *N*-methylpiperidine acts as a model for the N-H equatorial form of piperidine.

Before the solvent effects are discussed it would be advantageous to show how the absolute values of ^1J show that the N-H equatorial conformer is favoured. This evidence is more reliable than that from temperature effects, as is shown later. First, as just mentioned, the model for N-H equatorial piperidine is *N*-methylpiperidine. The most suitable value of ^1J to use as a starting point for the model value is 36.017, the value for the latter compound just below room temperature in toluene. Out of

Figure 9

The equilibria at nitrogen in (1) piperidine and

(2) N-methylpiperidine

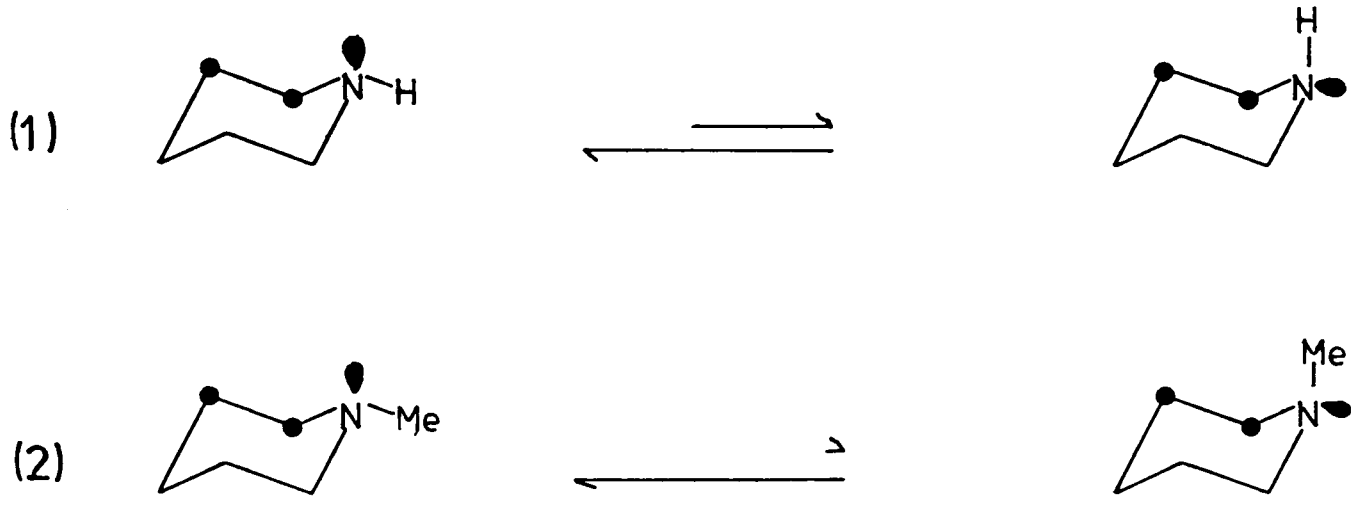
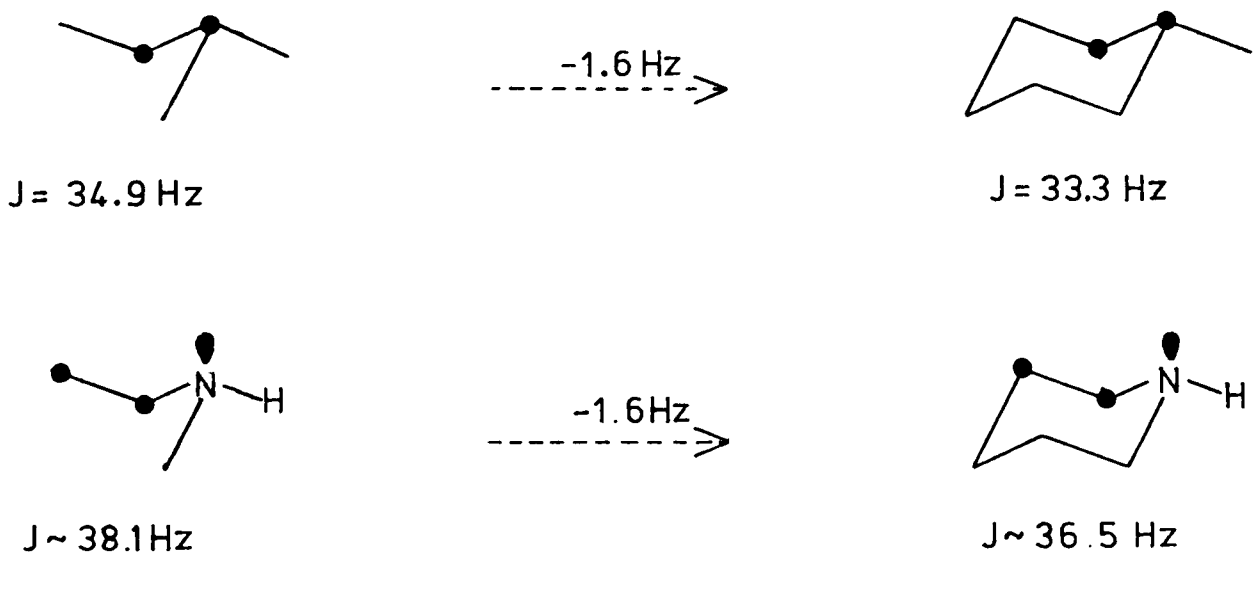


Figure 10

The effect of "ring formation" on $^{1}J_{CC}$



the solvents used toluene is the one of lowest dielectric constant and cannot interact very much with the amine. From this value we deduct the (negative) *N*-methyl substitutent effect of -0.5 Hz, thus obtaining 36.517 Hz. This is 1.6 Hz less than for the equivalent model for the ethylamines which is because the bond angle change on moving from a free ethyl group to a ring lowers ^{1}J considerably. This, using hybridization theory, would arise from increased p character in the orbitals forming the ring. Most importantly, this implies a concomitant increase in the s character of the exocyclic bonds. Such effects for $^{1}J_{CC}$ in hydrocarbons have been illustrated in a recent paper.[68] The effect of ring size on $^{1}J_{CH}$ for exocyclic bonds has recently been discussed.[69] It is of great interest that the effect on $^{1}J_{CC}$ seen in the hydrocarbon case was exactly the same as implied by the model used here. This is illustrated in Figure 10. This is further evidence that the present model for N-H equatorial piperidine is sound and also that the assumed *N*-methylation effects are of the correct order of magnitude. It should be noted that substitution β to the nitrogen must have a negligible effect on $^{1}J_{CC}$. It has been found that $^{1}J_{CC}$ for ethanol and 1-propanol is virtually the same while that for 2-propanol is significantly higher.[70] Thus α substitution has an effect while β substitution does not. These results may provide evidence that the steric theory of Summerhays and Maciel[71] is correct. That is, alkylation of the involved C-C bond only affects $^{1}J_{CC}$ significantly if it induces a change in bond angle.

The model for N-H axial piperidine is harder to find. One starting point is the same one as was used for the *trans* ethylamines. It is described in the next chapter and has a ^{1}J of 34.0 Hz and two *gauche* $_{N}$ -methyl interactions. The model has a free ethyl group while the model we require has the relevant bond in a ring. Therefore one subtracts an *N*-methyl effect of 0.5 Hz and a "ring" effect of 1.6 Hz giving 31.9 Hz for the new model value. This is necessarily a less certain value than that for the N-H equatorial model because the *gauche* *N*-methyl substituent effect we are subtracting is less precise. This is because *gauche* interactions cover a wider range than do *trans* ones, ("*trans*" implies a much more fixed orientation). Moreover,we have had to include the "ring" effect to arrive at the new model value. Fortunately, we have other evidence to use to find the model value of ^{1}J. The value of ^{1}J for quinuclidine (9 in Table 6) was 33.15 Hz. Quinuclidine represents a piperidine having some additional strain arising from the fact that three rings are fused at the position γ to nitrogen. There is also an additional *gauche* *N*-methylene interaction relative to piperidine itself and, moreoever, the measurement was made in a very concentrated solution. Subtraction of the *gauche* methylene substituent effect (assumed to be like an *N*-methyl effect) leaves a ^{1}J of 32.65 Hz. The fact that quinuclidine (and other [2,2,2]bicyclooctane ring systems) is likely to be twisted will render the orientation of the bond for which ^{1}J was measured and the lone pair not perfectly antiperiplanar. Subtraction of this effect would leave a still lower value of ^{1}J for the model derived from quinuclidine. The solvent effect is unknown.

The model value of ^1J finally arrived at is 32 Hz (uncertainty - 0.1 to + 0.3 Hz).

This leads to the equations:

$$32.0n_a + 36.517n_e = 35.102$$

where $n_a + n_e = 1$

n_a and n_e are the mole fractions of piperidine having N-H axial and equatorial respectively. 35.102 was the observed value of ^1J in Hz for piperidine in toluene at 298 K. This gives:

$k = 2.19$ and $\Delta G^o = 1.94$ kJ in favour of the N-H equatorial form. The range arising from the uncertainty in the value of 32.0 Hz for the axial form is:

1.69 to 2.02 kJ.

The range previously recorded[22a] for this free energy difference is 0.836 to 2.09 kJ. A recent determination at very low temperature gave 1.5048 kJ[72]. The agreement with the literature values is pleasing since at the moment our models are not as good as we should have liked. The models we had intended to use for axial and equatorial forms of piperidine which would also have shown *N*-methyl substituent effects in free amines were compounds (3) and (4) (see Figure 8). These are bicyclic piperidines, commonly known as granatanine and *N*-methylgranatanine. At present the *trans N*-methyl substituent effect we are using is based on two sources, first, the difference between ^1J for (1)HCl and (2)HCl in Table 6 (0.56 Hz) and second, the difference for (3)HCl and axial (4)HCl (Tables 6 and 7, 0.46 Hz). One of the sources for the

gauche N-methyl effect is the value for (3)HCl compared to equatorial (4)HCl, giving a difference of 0.41 Hz. The *gauche* effects seen in previous work[13] encompassed this value.

The intention was to observe separate conformers for not only *N*-methylgranatanine (Table 7) but also granatanine itself. This would have allowed one to find separate *N*-methyl substituent effects on ^{1}J for axial and equatorial species. The conformational equilibria are depicted in Figure 11 (the conformers are necessarily present in equal proportions). Using the available spectrometers and a variety of solvents it was found impossible to reach temperatures low enough to observe separate conformers for granatanine. This could be because:

(1) The barrier to interconversion is lower than in the *N*-methyl analogue.

(2) The proton can "tunnel" through the barrier even if it is high.

(3) The chemical shift difference between the methylenes in the two conformers is too similar. (The shift difference at the β methylenes in the two conformers of *N*-methylgranatanine is approximately 250 Hz or 11 ppm).

From extremely approximate measurements of line broadening for *N*-methylgranatanine (of the signal due to the methylenes β to nitrogen) a free energy of activation, $\Delta G^{\neq}$, of 40 kJ was estimated. From the literature values of $\Delta G^{\neq}$ for piperidine[72] and nortropane[73] (Figure 12a) a value of 28 kJ was estimated for granatanine. Thus, *ceteribus paribus*, a very low temperature would be needed to observe separate conformers for this compound, but one that might be

Figure 11

The conformations of (1) granatanine and (2) N-methylgranatanine

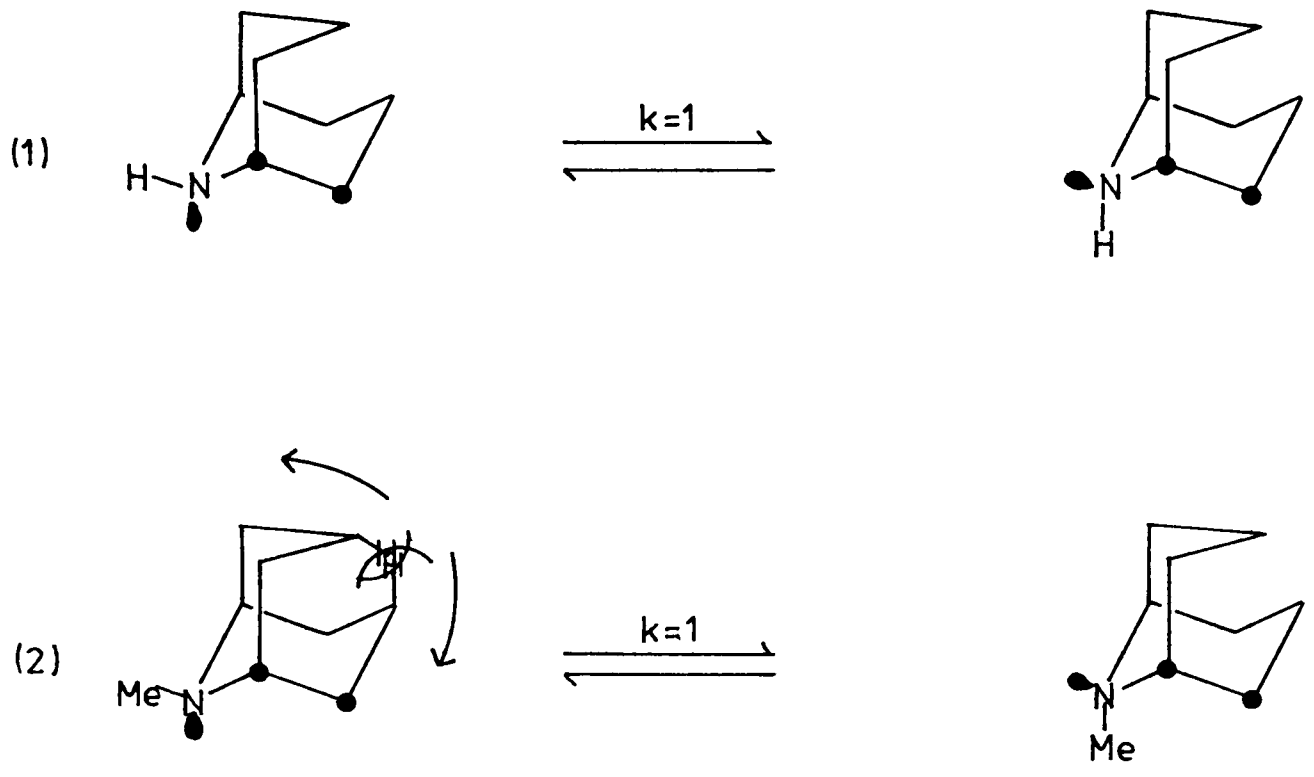
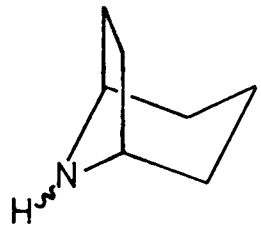
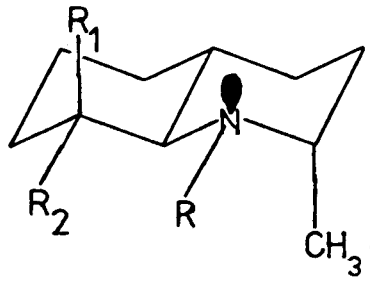


Figure 12

(a) Nortropane



(b) A trans-decahydroquinoline



R = H or Me

R_1, R_2 = H, Me or t-Bu

δ measured here

available in the future. However, it is possible that the experiment is not only technically but also physically impossible if the chemical shift difference for the β methylenes in granatanine is small or negligible. The latter point must remain problematic for the moment since the evidence is not sufficient to indicate what this shift difference would be. A rough estimate from the published low temperature carbon n.m.r. spectrum of piperidine[72] shows that the analogous shift difference for this compound is a little under 2 ppm. Eliel and Vierhapper, however, reported that there was no significant shift difference at an equivalent site in *trans* decahydroquinolines when the orientation of the N-H (and hence lone pair) was altered (see Figure 12b) by alteration of the substituents.[74] The latter workers only recorded such a shift difference when the nitrogen was methylated. One cannot tell to which compound granatanine would be similar in its chemical shift behaviour. For this reason, work to find an *N*-methyl substituent effect in a free amine is still required. Nevertheless, important results were obtained from the granatanines.

First, measurements were made on the salts which, as described above, led to estimates of *N*-methylation effects. Second, measurements on *N*-methylgranatanine provided some of the evidence for the models for both the ethylamines and piperidine. Third, important insights were gained into solvent and temperature effects.

If one examines the values of ^{1}J for compound (4) (*N*-methyl-granatanine) in Table 7, for the two relatively inert solvent mixtures at the top, one can see they are similar to those used for *gauche* and *trans* ethylamine models. The exact values reflect:

(1) *N*-methylation effects

(2) Effects of ring formation

(3) α-Substitution effects

(4) The partially exocyclic character of the bonds for which $^{1}J_{CC}$ is measured.

(5) The bending outwards of the rings caused by the steric interactions indicated on one of the formulae in Figure 11.

These factors add or subtract from one another, in a way one cannot define precisely, to give the observed values.

Temperature effects are shown by the fact that the low temperature ^{1}J values, though rather imprecise, do not average to the high temperature values. This is the clearest indication yet available that one must allow for inherent temperature effects in making detailed interpretations of values of $\Delta J/\Delta T$. Since the average ^{1}J is higher at low temperatures, we cannot in fact use $\Delta J/\Delta T$ for piperidine with any confidence to infer conformational behaviour, the absolute ^{1}J values being more useful.

Solvent effects on ^{1}J for *N*-methylgranatanine appeared small at room temperature. When the separate conformers were observed at low temperatures in methanol it became apparent that this might be because solvent effects on the two conformers cancel one another because they are of opposite sign for the axial and equatorial N-methyl species. However, at low temperatures the effects did not appear to cancel. ^{1}J for the axial species, having a *gauche* C-C bond/lone pair orientation was lowered by about 0.7 Hz in methanol. ^{1}J for the equatorial species which has a

trans C-C bond/lone pair orientation was raised by about 0.3 Hz. Since the value of ^{1}J at room temperature does not reflect these values, the solvent effect may itself vary with temperature.

The solvent effect is explained by the fact that, in the presence of an amine such as *N*-methylgranatanine, methanol acts as a hydrogen bonding acid. It withdraws electron density from the nitrogen lone pair thus weakening the latter's interactions with the bonds whose coupling constants are under observation. Thus, if the interaction is *gauche*, ^{1}J is decreased while if the interaction is *trans*, ^{1}J is increased.

For granatanine also the solvent effects on ^{1}J at room temperature appeared small; any slight differences were not in the same sense as for *N*-methylgranatanine. No account can be given for the effects of toluene vs. dichloromethane on ^{1}J for these amines, but these appear to be small. A variable temperature study of the (averaged) ^{1}J for granatanine showed no change, the solvent being the relatively inert mixture dichloromethane/tetramethylsilane. This suggests that the seemingly temperature dependent solvent effects on ^{1}J for *N*-methylgranatanine in methanol might be characteristic of the latter solvent. However, for *N*-methylgranatanine it was in the inert solvent mixture that the largest discrepancy was seen between the low and high temperature averaged values of ^{1}J. These results are curious. In any case, they imply that one can give no interpretation in conformational terms for the effect of methanol on piperidine. Methanol can lower ^{1}J for piperidine merely by changing the ^{1}J

values for the individual conformers, without changing the equilibrium between them. This idea would explain why methanol also lowered ^{1}J for *N*-methylpiperidine. For example, since at room temperature the effects of methanol on ^{1}J for the two conformers of *N*-methylgranatanine appeared to cancel, we may assume that the solvent effect is about $\pm$ 0.5 Hz. Thus, since *N*-methylpiperidine exists almost exclusively in the conformation having a *gauche* C-C bond/lone pair orientation,methanol should lower ^{1}J by 0.5 Hz. The observed effect is almost precisely this amount, which is also within the precision of the value found at low temperature for axial *N*-methylgranatanine (i.e. methanol lowered ^{1}J by 0.7 $\pm$ 0.3 Hz). For piperidine, we believe that 70% of the conformers will have a *gauche* C-C bond/lone pair orientation and 30% a *trans*, from the previously determined value of ΔG^{o}. Even if methanol affects the *gauche* and *trans* interactions equally it will nevertheless produce a solvent effect on ^{1}J. This should have a value of -0.2 Hz which, again, is close to the experimentally observed solvent effect of methanol on ^{1}J for piperidine. Thus, piperidine probably favours N-H equatorial in methanol the same as it does in less polar, non-hydroxylic solvents.

The other compounds referred to in Tables 6 and 7 are pyrrolidine derivatives and chloroamines. The values of ^{1}J for pyrrolidine and its derivatives illustrate how ^{1}J is decreased still further by decrease of ring size from the values typical for open chain ethylamines. (For pyrrolidine itself, ^{1}J is 32.73 Hz though the lone pair is not in a *trans* orientation with respect to the bond for which ^{1}J is measured). Interestingly, *N*-methylation

does not decrease ^{1}J for pyrrolidinium as much as it does ^{1}J for piperidinium. This is by now expected, since the relative orientation of the bond for which ^{1}J is measured and the N-methyl bond is not a true antiperiplanar one.

^{1}J values for the two conformers of *N*-chloropiperidine show that the electronic effect of the lone pair is balanced by that of the chlorine so the two couplings are very similar. From measurements at low temperatures of relative integrated intensities (of the signals due to both the isotopically substituted methylenes), ΔG^{o} for the chlorine axial/equatorial equilibrium was determined.

$\Delta G^{o} = 5.37 \pm 0.14$ kJ at 177.5 K was the value found. This is similar to the value found for 3,5-dimethyl-*N*-chloropiperidine (5.30 ± 0.1 kJ at 193 K) by Baldry and Robinson.[75] It is significantly different, however, from the more recently determined value for *N*-chloropiperidine itself (6.27 ± 0.42 kJ at 175 K).[76] The latter figure may be unreliable because not only was an unenriched sample used but measurements were made only of relative peak heights. (Relative integrated intensities, that is the areas of the peaks, are a more reliable parameter). ΔG^{o} for *N*-chloropiperidine is expected to be close to that for the 3,5-dimethyl analogue because the substituents in the latter are remote from the centre of inversion so they have no buttressing effect (see the next chapter).

The present work has shown the advantages of isotopic substitution and also that coupling constants may be useful in identifying conformers. With some understanding, values of $^{1}J_{CC}$ may be employed, for this purpose, more usefully than chemical shifts in some cases or as a supplement to shifts in others. The work

on the compounds described above has shown many effects of solvent, temperature and substitution on $^{1}J_{CC}$ that have not been well documented before. This information was additional to that derived about conformational behaviour. There is much promise in the idea of using $^{1}J_{CC}$ to study other cyclic molecules, a problem being the introduction of the isotopic carbon atoms. For some work the new methods for measurement of $^{1}J_{CC}$ at natural abundance might obviate this problem (see, for example the methods reviewed in reference 10 and the more recent one described in reference 67). Isotopic substitution is likely to remain necessary for work at low temperatures and in dilute solutions which are both of importance in conformational studies.

Chapter 4

Equilibria in Multiply Substituted Piperidines

In order to provide models for the possible conformations of the N-ethyl in *N*-ethylpiperidine, hindered piperidines were required. The first compounds made were the isomeric *cis* and *trans* 2,6-dimethyl-*N*-ethylpiperidines. Because, as described in the discussion of the preparations, these contained impurities, the 2,4,6-trimethyl analogues were prepared. The coupling constants of the ($^{13}C_2$)ethyl groups were studied as a function of temperature; the results are given in Table 8. These showed, as described in Chapter 2, that *N*-ethylpiperidine has a *gauche* orientation of the ethyl group and nitrogen lone pair. The close model was the *trans* compound (Figure 13). This had a coupling slightly higher than did *N*-ethylpiperidine itself but it also exhibited a very large $\Delta J/\Delta T$. This value suggests that the nature of the hindrance provided by the 2- and 6- ring methyls is such as to alter the preferred conformation somewhat with temperature. It may, however, be caused by large bending motions. The value of ^{1}J for the hydrochloride is remarkably close to that for the ethylamine hydrochlorides (in the same solvent). By contrast, ^{1}J at room temperature for the *cis* free amine is much lower, suggesting a preponderance of the conformer having the ethyl group *trans* to the lone pair. This is what we had expected of this model compound. What was quite unexpected was the de-coalescence phenomenon which was observed when the temperature of the sample was lowered. It appeared that this must be caused by a hindered rotation which would have no parallel in the analogous hydrocarbon. A hint that this compound may contain a very hindered ethyl group is given by the value

Table 8

$^{1}J_{CC}$ in hindered piperidines and their hydrochlorides

Compound	Solvent	$^{1}J_{CC}$ [a]	$\Delta J/\Delta T$ [b]
cis [c]	CD_2Cl_2 [e]	35.28	f
cis HCl	D_2O	36.18	-
trans [d]	CD_2Cl_2	38.34	+ 0.41
trans HCl	D_2O	35.49	-

a Value at 298 K, in Hz

b Change in ^{1}J with temperature (Hz/K x 10^2)

c *r*-2, *c*-4, *c*-6-Trimethyl-*N*-[($^{13}C_2$)ethyl]piperidine

d *r*-2, *c*-4, *t*-6-Trimethyl-*N*-[($^{13}C_2$)ethyl]piperidine

e The same behaviour was observed, for example, in CD_2Cl_2/TMS, 1:1 by volume.

f Not applicable; de-coalescence phenomen observed, see text.

Table 9

ΔG^{o} for the hindered rotation

Method [a]	ΔG^{o}/kJ [a]	Temperature/K
$^{1}J_{CC}$ - average	3.48	298
Line broadening	3.50	189
Area integration	3.7-3.8	156
δ-average 1 [b]	3.3-3.9	240-280
δ-average 2 [c]	6-8	240-260

a See text for details of methods and precisions

b Chemical shifts measured with respect to tetramethylsilane

c Chemical shifts measured with respect to the *N*-methyl signal in *N*-[(^{13}C)methyl]granatanine

Figure 13

The model for N-ethylpiperidine

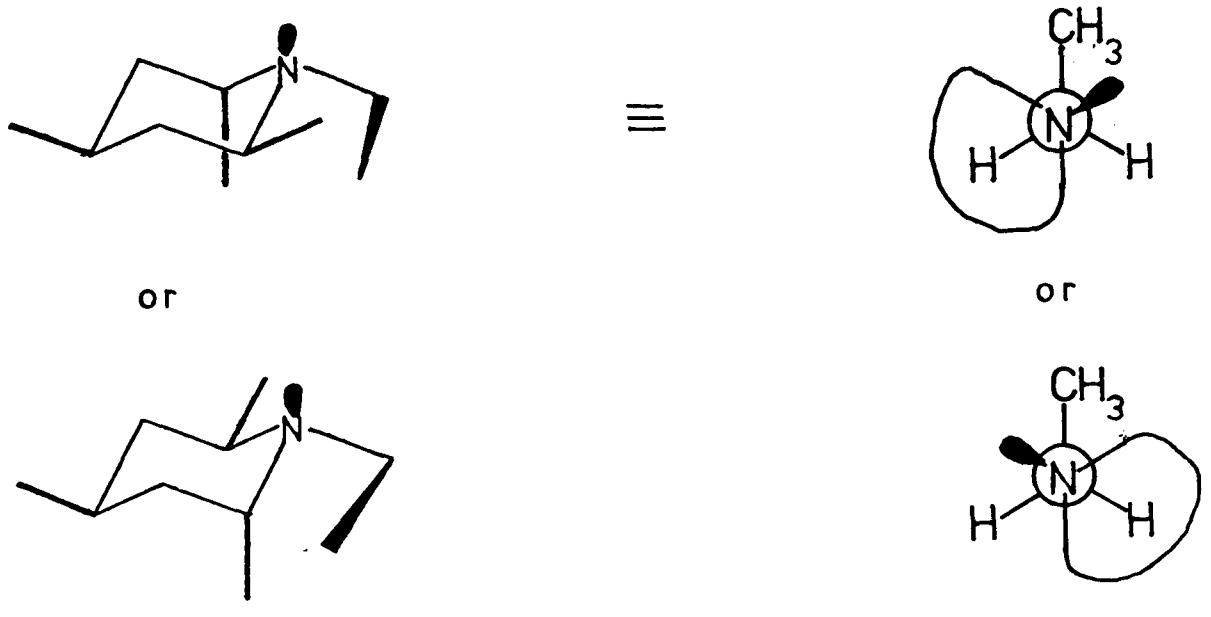
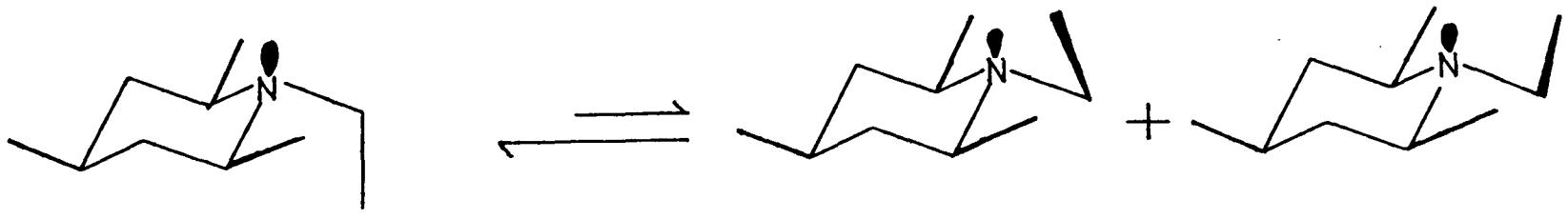


Figure 14

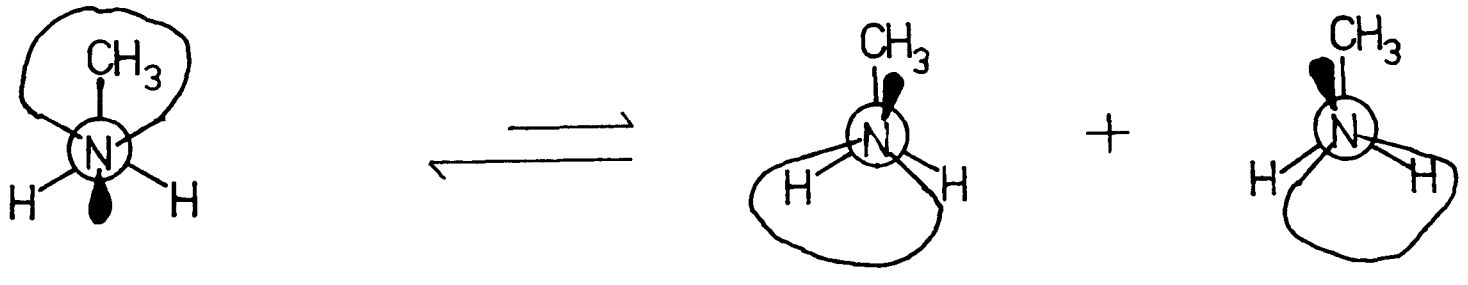
The hindered rotational equilibrium



J = 34.0 Hz

J= 40.5 Hz

i.e.



trans

gauche (nearly cis)

of ^{1}J for the amine salt. This is unusually high, suggesting that the hindrance may actually bend out the ethyl group which may increase the s character of the methylene carbon orbital and thus increase ^{1}J.

A similar de-coalescence phenomenon had been observed for the *cis*-2,6-dimethyl-*N*-ethylpiperidine but this was not studied in detail because of the presence of the impurities referred to above. Because these phenomena were of interest the one for the trimethyl compound was studied carefully. Samples were cooled sufficiently to observe separate conformers and a value of ^{1}J was obtained for each. The value for the major conformer was obtained precisely by curve fitting while that for the minor conformer was found with less precision. The results obtained led to the idea that the equilibrium was as shown in Figure 14. The major conformer has a ^{1}J of 34.0 Hz because it has a *trans* C-C bond/lone pair orientation. This value was used in the models for the *trans* ethylamines and N-H axial piperidine. The minor conformer has a ^{1}J of 40.5 Hz, the highest we have ever recorded for an amine. This is caused by a nearly *cis* bond/lone pair interaction. In fact the minor conformer is probably an enantiomeric pair of *gauche* type conformers. It was decided to study this equilibrium using several carbon n.m.r. methods. This would:

(1) Check that our idea was correct (and prove it was not, for example, an axial/equatorial equilibrium).

(2) Provide several estimates of the free energy difference between the conformers, ΔG^{o}, at different temperatures.

(3) Check the internal consistency of the group of methods.

It was necessary to show that this was not an axial/equatorial equilibrium since it was known that 2- and 6-methyl groups favour the axial form of *N*-alkylpiperidines. (Such behaviour for *N*-methylpiperidines has recently been discussed[22b]).

By providing other estimates of ΔG^{o} we could also, rather importantly, see how valid the method was that uses $^{1}J_{CC}$ values to find ΔG^{o}. At the same time, some other *N*-alkylpiperidines were also studied, to investigate the uses of the other carbon n.m.r. methods for determining ΔG^{o} values. The method using $^{1}J_{CC}$ values is analogous to that described in previous chapters, but the values of ^{1}J at low temperature for the two conformers are used, rather than model values for these. If we make the assumption that the individual values of ^{1}J remain constant with temperature we obtain the equations:

$$34.0n_t + 40.5n_g = 35.28$$

where $n_t + n_g = 1$

giving $k = 4.1$ and $\Delta G^{o} = 3.48$ kJ

at 298 K in favour of the *trans* conformer (Figure 14). An estimate of the precision of this value may be made by examination of the apparent temperature dependence of ^{1}J for *N*-methylgranatanine (Table 7). This appeared to be at most -0.4 Hz for the averaged value when the temperature was raised 100 K. Part of this large value may however, have been accounted for by the low precision of the low temperature measurements. At worst, therefore, the range of ΔG^{o} for the present equilibrium is:

2.6 - 4.6 kJ, allowing for an error of $\pm$ 0.4 Hz

in the ^{1}J values, (in the same sense on the value for each

conformer for each calculation). Since for *N*-methylgranatanine the temperature dependence appeared much smaller when methanol was the solvent, it may well also be much smaller for this compound. This would make the possible range for the true ΔG^{o} much smaller. The average value of ^{1}J cannot be used to find ΔG^{o} at temperatures much lower than 298 K (used in the above calculation). This is because on approaching the temperature at which de-coalescence occurs lineshapes become non-Lorentzian; using such lines one cannot find values of ^{1}J precisely. The value we have obtained is of some reliability because no models were used; the inaccuracy arises from the possible temperature dependence of ^{1}J. The inaccuracies associated with the use of models vs. those associated with temperature dependence have been discussed for the case of proton chemical shifts[77] (where both will be more serious).

The other methods used to determine ΔG^{o} employed singly isotopically substituted amines. The signal used in n.m.r. experiments was that due to the *N*-methylene (*N*-methyl for the *N*-methylpiperidines, see below). The first method used to study the rotational equilibrium further was measurement of line broadening. Anet *et al.*[78] showed that by measurement of the maximum broadening at half-height of a signal, one could find ΔG^{o} for the equilibrium causing the broadening. This method uses an approximation derived from the Gutowsky-Holm equation for the lineshape due to exchanging species in sites with non-equivalent populations. The full derivation has been given by Anet and Basus.[79] The approximation is supposed to be valid for very unequally populated sites, with a population difference of $> 10:1$. It leads to the equations:

$$\nu(\tfrac{1}{2}\ \text{max}) = p\Delta\nu$$

and $$\varkappa = 2\pi\Delta\nu$$

where $\nu(\frac{1}{2}$ max) = the maximum broadening at half-height in Hz,

p = the population of the minor isomer (conformer),

$\Delta\nu$ = the chemical shift difference for the nucleus in the two sites, in Hz

and $\varkappa$ = the rate of interconversion.

Anet and Basus explained that the approximation involved the assumption that the non-exchanging linewidths are negligible compared to $\Delta\nu$. This is equivalent to setting $1/T_2$ to zero, where T_2 is the transverse relaxation time, assumed to be the same for nuclei in the two sites. We have used the following approach in order to put this mathematical expression into practice. We derived values of the broadening by comparison of the relevant linewidths with those of two internal standards. These were the common chemical shift standard, tetramethylsilane (TMS), and *N*-methylpiperidine. The latter should be particularly suitable because it is of similar shape to the hindered piperidine, and the *N*-methyl, used to give the standard signal, is chemically similar to the *N*-methylene under observation. The internal standards are very useful because the breadth of signals due to them will include the effects of viscosity broadening, magnet inhomogeneities etc. The same would not be true if the room temperature width of the signal due to the compound under observation were used. We obtained the same value for the maximum broadening whether TMS or *N*-methylpiperidine was used as the standard.

It is of value to know that the amine and the non-polar and differently shaped TMS acted equally well in the region of interest. (Their broadening behaviour was not the same at either high or low temperatures).

The results were:

Maximum broadening = 19.6 Hz at 189 K

Chemical shift difference = 201.4 Hz

hence $p = 0.097$,

$k = 9.3$ and $\Delta G^{o} = 3.5$ kJ at 189 K, in favour of the *trans* conformer. Errors in measurement of temperature, broadening and chemical shift will produce an imprecision of not more than $\pm$ 0.1 kJ.

This value is very close to that obtained using the averaged value of $^{1}J_{CC}$ (see Table 9) but this does not imply the values are accurate. One might have expected ΔG^{o} to be higher by a significant amount at low temperatures since there will be a contribution from ΔS^{o} to ΔG^{o}. On a very simple basis, ΔS^{o} would be 6 eu, arising from a factor of R ln 2 due to the multiplicity of 2 of the *gauche* conformers (Figure 14). This factor would raise ΔG^{o} by 0.6 kJ if the temperature was lowered 100K. The temperature difference for the two determinations here is 109K. Since, however, the $^{1}J_{CC}$ method involved the assumption of temperature independent couplings, the agreement is encouraging rather than discouraging. The value obtained by the line broadening method showed the population difference was ~ 10:1 which is the supposed limit for which the method is valid. It will be

shown later that for population differences of greater than about 100:1 the line broadening method fails.

The rate of interconversion obtained by the line broadening measurement was:

$$\kappa = 1265 \text{ Hz.}$$

From this value we can derive a value for the activation energy using the approximation:

$$\kappa = \frac{kT}{h} \exp(-E_{act}/RT)$$

where k = Boltzmann's constant, h = Planck's constant and R, as usual, is the gas constant. This gives E_{act} = 34 kJ which is comparable to those values of $\Delta G^{\neq}$ found for nitrogen inversion processes (referred to in the last chapter).

The next method used to find ΔG^{o} for the hindered equilibrium was a very direct one, which was integration of signals at low temperatures (the method is described in the Experimental section). This method involves no assumptions and hence is very reliable. Uncertainties arise only from the difficulties of measuring areas accurately. The measurements made for this work used hand planimetry, but even repeated measurements produced a range of only 0.1 kJ for the ΔG^{o} value thus obtained (Table 9). More recent research has involved curve fitting which allows areas to be found more accurately and easily (see Appendix 1). The collected results in Table 9 show that the value of ΔG^{o} obtained by area integration at very low temperature is higher than the first two values. This may be because the entropy effect is showing up but we cannot use the latter result to show if the line broadening or $^{1}J_{CC}$ method is the better. It is, nevertheless, useful to be able to measure ΔG^{o} over a range of temperatures, as we have been able to do.

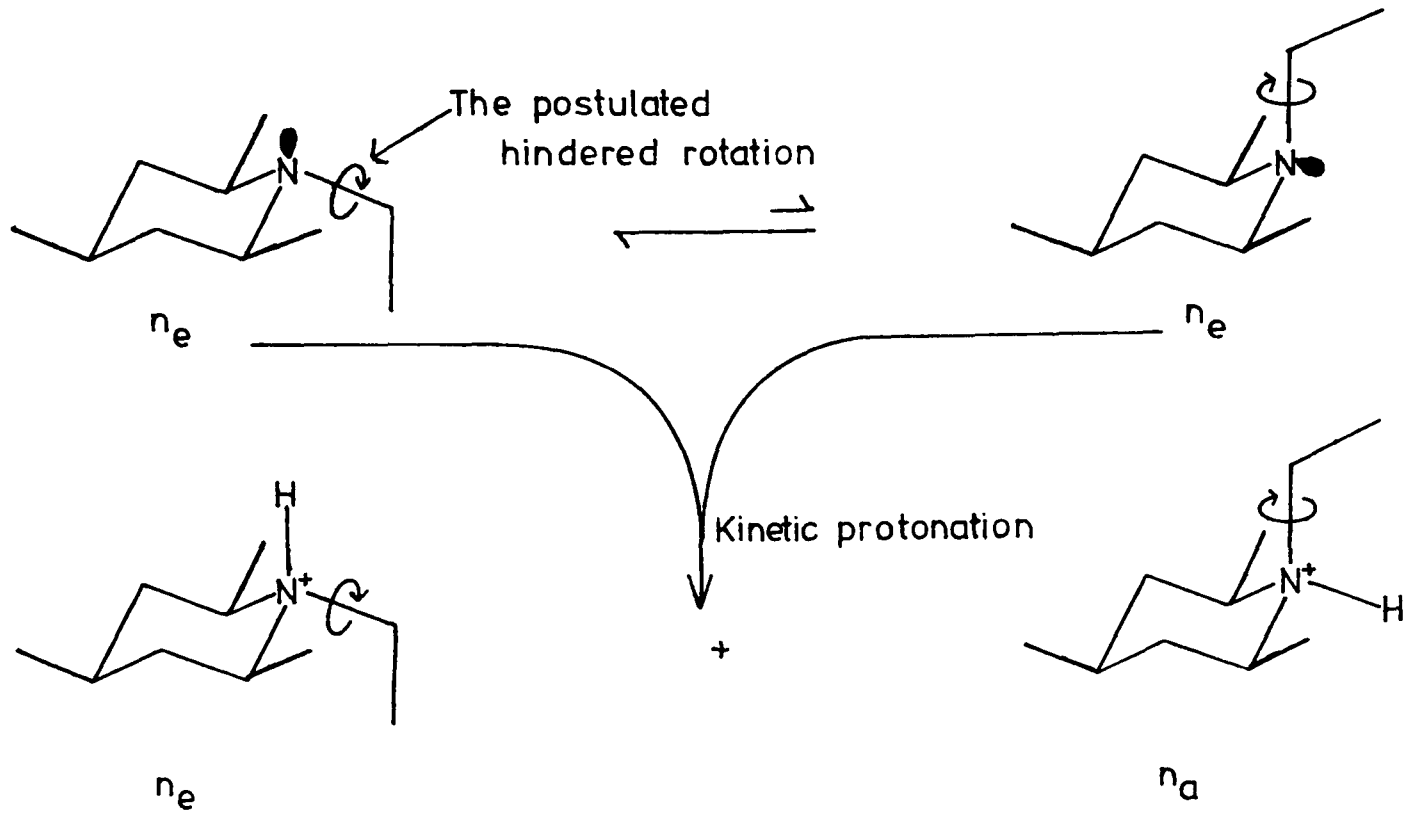
The last method used was not successful. This was similar to the first one, except that chemical shifts rather than coupling constants were used. The shifts of the two conformers were measured at low temperatures and then the averaged shift was measured over a series of higher temperatures. The value of ΔG^{o} thus obtained was found to be very sensitive to minor changes in the phasing etc. used in processing spectra to obtain chemical shift data. Moreover, when an attempt was made to use an amine as an internal standard having a shift close to that under observation, the results changed wildly. TMS, the usual standard, was at least more satisfactory in that the ΔG^{o} values obtained were in the correct region, compared to those obtained by the other methods. These results illustrate the point that coupling constants are much more suited than are chemical shifts to conformational work. Carbon chemical shifts are even less suitable for this use than are proton shifts because they have a greater inherent temperature dependence. This dependence has been measured, being for example for TMS, 0.012 ppm/K below 300 K.[80] Hence the "standard" commonly used is not a temperature independent standard.

The method used to show that the rotational equilibrium was not an axial/equatorial equilibrium was kinetic protonation.[7] This is described in the Experimental section in some detail. The method converts a mixture of axial and equatorial conformers into a mixture of axial and equatorial diastereomers by protonation. This process preserves the ratios of axial and equatorial species and so ΔG^{o} is found for the original equilibrium. If the equilibrium we observed previously was in a rotating equatorial ethyl group then

this will be irrelevant to the ΔG^{o} determined by protonation. This is illustrated in Figure 15. The method in fact showed that ΔG^{o} for the axial/equatorial equilibrium was very different from the previously determined ΔG^{o} values. Hence the equilibrium previously studied was not the axial/equatorial one. For comparison, ΔG^{o} measurements were made on some other amines, including *N*-methylpiperidines. The results are given in Table 10 and the amines are shown in Figure 16. The values obtained are in general precise and they all reflect the increasing amounts of axial conformers found at high temperatures. It is clear that ΔG^{o} for the axial/equatorial equilibrium is much higher than that for the equilibrium between the conformers we have been studying. Extrapolation shows that at 200 K (which lies within the temperature region used before) ΔG^{o} for compound (1) (Table 10, Figure 16) would be 9.77 kJ, nearly three times as high as ΔG^{o} for the rotational process. It is also interesting that ΔG^{o} for the inversion of the nitrogen bearing an ethyl group is only a little higher than that for one bearing a methyl group (compare (1) and (2)). Compound (3), containing a distant *t*-butyl group, shows that less axial *N*-alkyl group is present when the buttressing 2- and 6-methyl groups are removed. The values of ΔG^{o} obtained for (3), 4-*t*-butyl-*N*-ethylpiperidine, are close to those obtained by Robinson *et al.*[7] for the *N*-methyl analogue. They are in fact slightly lower, which may reflect that an ethyl group is more hindered in the equatorial position than is a methyl group. Compound (4), 2,4-dimethyl-*N*-ethylpiperidine, shows intermediate behaviour since one buttressing methyl group is present. The temperature dependence of ΔG^{o} for this compound is large. For

Figure 15

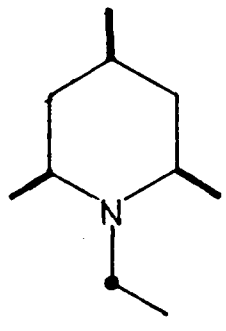
The differentiation of rotational and axial/equatorial equilibria

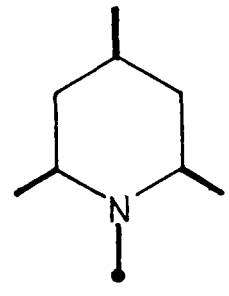


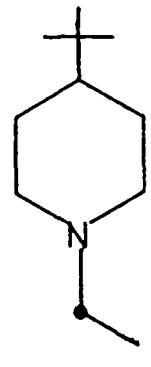
$\Delta G^\circ = -RT \ln(n_e/n_a)$ $\neq$ ΔG° for the rotation within the equatorial conformer

Figure 16

Legend for Table 10

(1) 

(2) 

(3) 

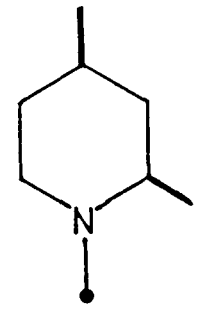
(4) 

Table 10

ΔG^{o} for axial/equatorial equilibria obtained by the kinetic protonation method

Compound[a]	ΔG^{o}/kJ	Temperature/K
(1)	8.71 ± 0.15	294
	8.00 ± 0.03	373
	7.56 ± 0.1	429
(2)	8.0 ± 0.3	293
	7.88 ± 0.58	373
	7.27 ± 0.77	429
(3)	12.27 ± 0.085	294
	11.68 ± 0.053	373
	10.57 ± 0.002	429
(4)	11.47 ± 0.2	293
	10.8 ± 0.2	373
	8.9 ± 0.3	429

a See Figure 16

some piperidines such dependence has been accounted for by postulating increasing amounts of twist-boat conformers at high temperatures[7] but this argument may not be relevant here. In any case, the true temperature dependence may not be quite as large as appears from Table 10 since the values for this compound are less precise than for some of the others. This was caused by problems associated with overlapping signals.

Attempts were made to study the axial/equatorial equilibria in compounds (2) and (4) by the line broadening method. For compound (2) the internal standard was *N*-methylazacycloheptane (*N*-methylperhydroazepine). The results were:

Maximum Broadening = 4.1 Hz

Chemical shift difference = 310.5 Hz

giving $k = 75.5$ and $\Delta G^{o} = 6.8 \pm 0.2$ kJ at 189.5 K.

This is in relatively poor agreement with the value derived from kinetic protonation results. Using the value of 8 kJ (from kinetic protonation) the expected maximum broadening would have been 1.9 Hz. Using a larger ΔG^{o}, to allow for the effect of temperature, would have produced an even smaller broadening. It is not known whether the kinetic protonation or the line broadening result is the more accurate.

For compound (4) the line broadening method failed entirely because no real maximum in the broadening was ever observed. Any slight broadening that occurred was obscured by viscosity broadening. The broadening was small because ΔG^{o} is so high and thus the population difference is very high. Thus the line broadening method is of limited utility because in part of the region where it is mathematically valid it is physically impracticable. The

equilibrium where we used the method most successfully would appear to be the one where the population difference was very nearly 10:1. In the case where the method was first used, ΔG^{o} was 7.9 $\pm$ 0.8 kJ at 213 K and k was 89, in good agreement with the results derived by kinetic protonation.[78] Thus, the line broadening method may be of most use in the region where the population difference is between 10:1 and 100:1.

The hindered rotation that we have studied is not an isolated phenomenon. The reason it has no parallel in hydrocarbon chemistry is that N-C bonds are shorter than C-C bonds. This also accounts for the much higher equatorial preference of *N*-methylpiperidine compared to methylcyclohexane.[7]

Hindered rotations analogous to the one that we observed have been found before. It has been found that rotations of N-R groups in 2,4,6-collidinium species have higher activation energies, $\Delta G^{\neq}$, than do those of C-R groups in analogous mesityl species.[81] Similarly, $\Delta G^{\neq}$ for the rotation of the amino group in a hindered *N,N*-dimethylanilinium compound is higher than that for the rotation in an analogous hindered isopropylbenzene.[82] The behaviour observed in our work is even more different from that of the analogous hydrocarbon because N-C bonds are usually shorter than $\overset{+}{N}$-C bonds[22b] and hence more different from C-C bonds.

Chapter 5

The Conformation of Ethylbenzene and its Derivatives

It is of interest to provide more evidence about the conformation of ethylbenzene as there has been much conflicting evidence in the past and this compound is the parent of a family of important species. Most of the earlier work on ethylbenzene has been reviewed by Schaefer *et al.* in a paper setting out a method using six bond proton-proton coupling constants ($^6J_{HH}$)[83]. More recent work has been reviewed by Schaefer and Parr in a summary of all the work achieved by the latter method.[5]

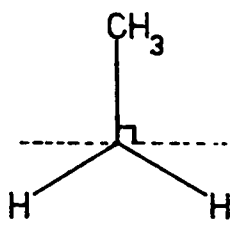
The possible favoured conformations are depicted in Figure 17. The first and third (perpendicular and parallel) are associated with a two-fold barrier to internal rotation of the ethyl group with respect to the phenyl ring. The second form involves a four-fold barrier as there are four equivalent 60^o positions. Most reliable evidence points to the perpendicular form as being the most stable but some methods necessarily involve the assumption that there is only one stable form and some that the barrier is two-fold.[5] Some workers have merely assumed the perpendicular form to be the most stable[84] while others have used only unreliable infra-red evidence[85] and thus have taken the preferred conformation to be parallel.[86]

We have tried to discover of what use $^1J_{CC}$ may be in illuminating this type of problem. For this purpose, model compounds were sought for the extreme forms, one for the perpendicular and one for the parallel. The latter is the more difficult to provide since in order to constrain the ethyl group to a parallel

Figure 17

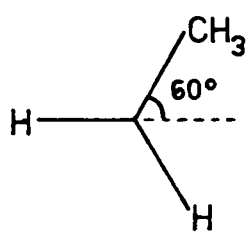
Possible conformations for ethylbenzene

(1)



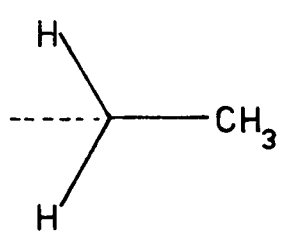
π plane

(2)



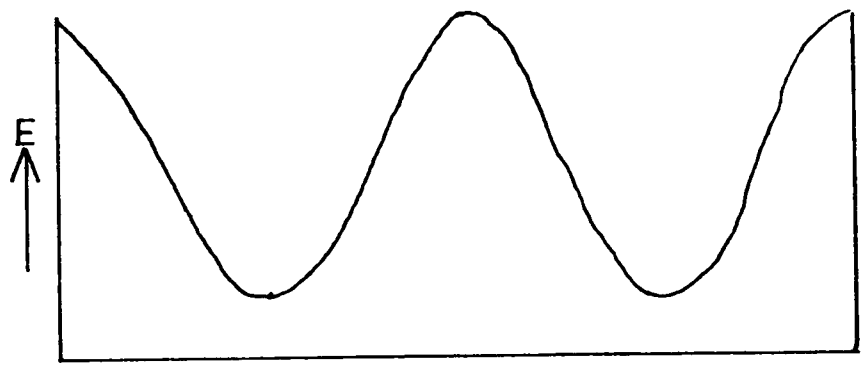
π plane

(3)



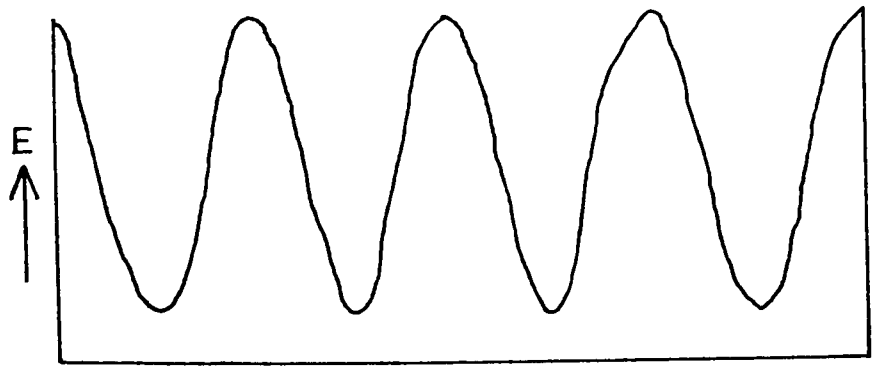
π plane

Associated potential functions (angles as depicted above)



(1) 0° 90° 180° 270° 360°

(3) 270° 0° 90° 180° 270°



(2) 60° 120° 240° 300°

position a cyclic compound is needed. As previously mentioned, $^1J_{CC}$ for a cyclic compound will include large strain effects and there may be significant substituent effects. Thus we have to estimate these effects for this model which makes it a relatively poor one. The compound used as a basis for the model was indan and that used for the perpendicular model was ethylmesitylene. Additional evidence was provided by various other compounds. $^1J_{CC}$ was measured for ethylbenzene, ethylmesitylene and indan over the usual range of 200-300 K. In addition it was measured at higher temperatures for the former two compounds. The results are given in Table 11; there is the expected agreement for ethylbenzene with the crude literature value of $^1J_{CC}$ (34 $\pm$ 1 Hz).[65]

It is immediately apparent that ethylbenzene has a higher ^1J than has ethylmesitylene while both show temperature dependences of their couplings that are greater than most of those seen for amines. The coupling in ethylbenzene, moreover, is the more sensitive of the two to temperature. The absolute value of ^1J for indan is irrelevant without allowing for other factors but it is notable that its $\Delta J/\Delta T$ is in the range previously classed as conformationally insignificant. We believe that these results show firstly that ethylbenzene and ethylmesitylene both have a hindered internal rotation and secondly that in ethylmesitylene the ethyl group is constrained more closely to a perpendicular position by the 2- and 6-methyl groups. Hence, hyperconjugation with the phenyl ring more effectively lowers ^1J for the latter compound and $\Delta J/\Delta T$ is smaller. The reasons for thinking the ^1J and $\Delta J/\Delta T$ values are conformationally significant are as follows:

Table 11

$^{1}J_{CC}$ and $\Delta J/\Delta T$ for ethylbenzene and some related compounds

Compound [a]	Solvent	$^{1}J_{CC}$ [b]	$\Delta J/\Delta T$
ethylbenzene	CD_2Cl_2	33.933	+ 0.29
ethylbenzene	C_7D_8	33.950	+ 0.28[d]
ethylmesitylene	CD_2Cl_2	33.413	+ 0.20
ethylmesitylene	C_7D_8	33.436	+ 0.20[e]
indan	CD_2Cl_2	32.942	+ 0.07
1-methylindan	CD_2Cl_2	33.374	-
ethylcyclohexane	CD_2Cl_2	34.870	0[f]
2,4,6-trimethylethylcyclohexane	CD_2Cl_2	34.820	-

a See Figure 18 for formulae

b Value at 298 K, in Hz. Precision $\pm$ 0.01 Hz

c Change in $^{1}J_{CC}$ with temperature, Hz/K x 10^2

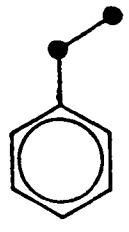
d Gradient of $\Delta J/\Delta T$ became less at high temperatures (300-360 K)

e Gradient of $\Delta J/\Delta T$ remained constant at higher temperatures

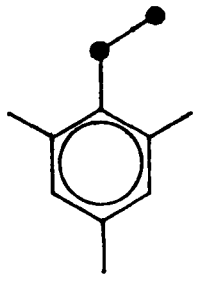
f i.e. within precision of data

Figure 18

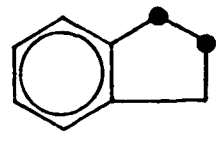
Legend for Table 11



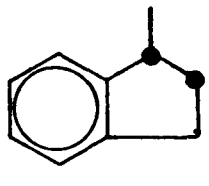
ethylbenzene



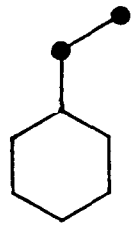
ethylmesitylene



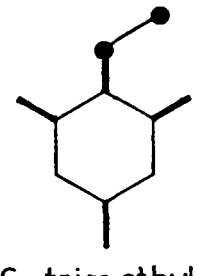
indan



1-methylindan



ethylcyclohexane



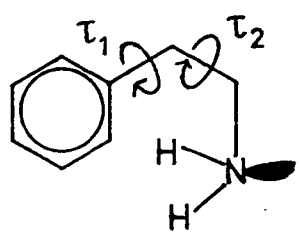
2,4,6-trimethylethyl-cyclohexane

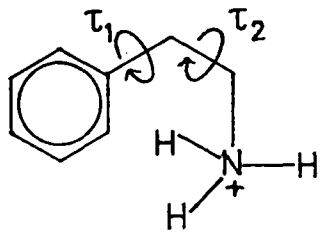
(stereochemistry as shown)

● denotes ^{13}C

Figure 19 (see p.87)

The conformations of phenylethylamine and the phenylethylammonium ion





$\tau_1 = 90°$

$\tau_2 = 180°, \pm 60°$

(1) Only a small change with temperature was seen in ^{1}J for indan, in which a phenyl ring is present but no rotation is possible.

(2) No change with temperature was seen in ^{1}J for ethylcyclohexane in which rotation is possible but there is no phenyl ring.

(3) The changes in ^{1}J are unlikely to be dipolar in origin because the solvent effect on ^{1}J was small and these species have small dipoles.

(4) The difference between ^{1}J for ethylbenzene and ethylmesitylene is in the expected direction.

(5) This difference is unlikely to be due to the methyl groups *per se* because such groups had a minute effect in the cyclohexane analogue.

(6) The difference in $\Delta J/\Delta T$ between ethylbenzene and ethylmesitylene is in the expected direction.

Before making a more quantitative interpretation one has to estimate ^{1}J for the parallel form of ethylbenzene. Using data from the pyrrolidinium compounds and the ethylammonium species one can estimate that if one "undid" the ring in indan (in which the relevant bond is near to parallel) ^{1}J would rise from 32.942 Hz to between 34.90 and 34.95 Hz. What effect removal of the substituent "methylene" would have is not so clear. Work cited in previous chapters suggested that introduction of a methyl group only seemed to have a large effect on ^{1}J if it had a steric effect. However, the datum for 1-methylindan shows that in this case, introduction of a methyl group raised ^{1}J by 0.43 Hz . Since it does not appear that this methyl group can have much effect on bond angles within the ring, the change in ^{1}J may be caused by

some unidentified electronic interaction. It is not clear whether one should deduct a similar quantity (e.g. 0.4 Hz), supposedly due to the "methylene", to produce the model value. It is possible that this hypothetical process, removal of the "methylene", would have no effect just as 1-propanol had a value of $^1J_{CC}$ close to that of ethanol.[70] An intermediate case would appear to be ethylcyclohexane, for which ^1J is 0.27 Hz greater than the published value for ethane.[87] Since this is currently such an uncertain field, the model for a hypothetical flat ethylbenzene has an imprecise value of ^1J of between 34.5 and 34.9 Hz. This is probably a realistic estimate and is much higher than the value observed for the real molecule. This provides evidence that the parallel form of ethylbenzene is probably a high energy intermediate rather than a stable conformer. If the stable form of ethylbenzene were flat, ^1J for ethylbenzene should approach the model value at low temperatures. In reality ^1J approaches the value of ethylmesitylene instead. Linear extrapolation shows that ^1J for ethylbenzene reaches the room temperature value for ethylmesitylene at 120 K which seems reasonable.

We thus believe that both the absolute value of ^1J and $\Delta J/\Delta T$ support the qualitative conclusion that the stable conformer of ethylbenzene is "near to perpendicular". The ideas embodied in this have been paralleled by those used in work on $^1J_{CN}$ for oximes. $^1J_{CN}$ has been used to investigate the barrier to internal rotation in mesitaldoxime[88] and $^1J_{CN}$ has been found to be higher in benzaldoximes than in mesitaldoximes.[89] We hope in

the future to make a quantitative estimate of $\Delta G^{\neq}$, the barrier to internal rotation in ethylbenzene, which will employ also the fact that $\Delta J/\Delta T$ for ethylbenzene showed a decrease in gradient at high temperatures while that for ethylmesitylene did not. This is believed to arise from the differing rotational averaging processes. The mathematical treatment we shall need has been more commonly used in electron spin resonance studies. It has been discussed by Schaefer and co-workers who used it in the method employing $^{6}J_{HH}$.[5,83]

The ethylbenzene problem is harder to treat than that of the amines discussed previously since we are attempting to find a barrier between two equivalent conformers rather than an energy difference between two non-equivalent conformers. However, the conclusion that ethylbenzene has an energy minimum in the perpendicular form is supported by evidence from $^{1}J_{CC}$ for derivatives of ethylbenzene. A brief study of these was made, including phenylethylamine and its *N*-methyl analogues which are of biological interest. The results obtained are given in Table 12 with some of those for the analogues containing no phenyl group. The phenyl compounds are β-phenyl derivatives of the monosubstituted ethanes; parent compounds include also ethane, acetic acid and acetonitrile. First, one may observe that when the parent compounds are substituted with phenyl there is a drop in the associated coupling constant. Thus in these derivatives the C-C bond is probably always in the "near to perpendicular" position. Second, one notices that there is an exception in acetonitrile. This seems very reasonable since one expects that for steric reasons

Table 12

$^{1}J_{CC}$ and $\Delta J/\Delta T$ for β-phenyl derivatives and parent compounds

	Parent		Derivative[d]	
Parent[a]	$^{1}J_{CC}$[b]	$\Delta J/\Delta T$[c]	$^{1}J_{CC}$[b]	$\Delta J/\Delta T$
$^{13}CH_3{}^{13}CH_3$	34.6[87]	-	33.933[e]	+ 0.29[e]
$^{13}CH_3{}^{13}CH_2I$	35.81	+ 0.12	34.80	+ 0.4
$^{13}CH_3{}^{13}CH_2OH$	37.33[g]	- 0.1	35.95	- 0.2
$^{13}CH_3{}^{13}CO_2H$	56.7[32]	-	55.3	+ 0.5
$^{13}CH_3{}^{13}CO_2Et$	58.8[32]	-	57.5	+ 0.6
$^{13}CH_3{}^{13}CN$	57.62	+ 0.25	57.7	+ 0.1
$^{13}CH_3{}^{13}CH_2NH_2$	36.01	+ 0.12	34.348[e]	+ 0.5[e]
$^{13}CH_3{}^{13}CH_2NH_3Cl$	35.25	-	34.45	-
$^{13}CH_3{}^{13}CH_2NHMe$	36.92	0	35.50	+ 0.2[f]
$^{13}CH_3{}^{13}CH_2NH_2MeCl$	35.10	-	34.35	-
$^{13}CH_3{}^{13}CH_2NMe_2$	38.14	0	37.00	+ 0.1[f]
$^{13}CH_3{}^{13}CH_2NMe_2HCl$	35.10	-	34.15	-

a The solvents were the same for both series except when parent compound values were obtained from the literature

b Value at ~ 298 K, in Hz

c Change in $^{1}J_{CC}$ with temperature, Hz/K x 10^{2}

d Results were not subjected to curve fitting and are not as precise as those quoted in the earlier Tables

e These results were obtained using curve fitting

f Temperature range was 260-360 K (usual range 200-300 K)

g In other solvents ^{1}J was close to the literature value (37.7 Hz)[20]

phenylacetonitrile can adopt a planar form and in this conformation the cyano group could hyperconjugate with a phenyl proton. Phenylacetonitrile therefore, by contrast with all the other species, may favour the parallel form.

The only data for parent compounds not previously discussed in this work is that for ethanol. Work on ethanol was postponed since its behaviour is more complex than that of amines, but substitution of a phenyl group appears to have the same effect on ethanol as on the other species. It is noticeable that the temperature dependences of ^{1}J associated with rotation with respect to the phenyl group are superimposed on those associated with the parent molecules. Thus $\Delta J/\Delta T$ is usually larger for the phenyl derivatives; (these changes were usually so noticeable that at the level of precision needed for this discussion it does not matter that curve fitting was not used in most cases). An exception is found again in acetonitrile for which the large $\Delta J/\Delta T$ was ascribed to large dipolar interactions. $\Delta J/\Delta T$ for phenylacetonitrile is smaller which may be because the temperature dependent dipolar interactions are balanced by conformational changes. This would be possible if the parallel form were more stable, as suggested above.

An interesting series is that of the phenylethylamines and their hydrochlorides; it is the latter which are generally studied by pharmacological chemists. It has been found for the phenylethylammonium ion that the preferred conformations have the C-C bond perpendicular to the ring[90] which is in agreement with the lowering we have found in $^{1}J_{CC}$ for both

ethylamine and the ethylammonium ion upon β substitution by phenyl. There then arises the question of whether the NH_2 (or $\overset{+}{N}H_3$) group is turned towards the ring or is in an extended position, that is, what is the value of τ_2 (Figure 19). The work just cited showed that although only the extended form ($\tau=180^o$) exists in the crystal, both folded ($\tau=\pm 60^o$) and extended forms exist *in vacuo* . The pair of forms comprising the "folded" one would, in our terminology, be almost *trans*. That is, the bond for which $^1J_{CC}$ is measured would be perpendicular to the phenyl ring and almost *trans* to the lone pair in the free amine. This seems an extremely plausible stable conformer in solution as the protons on nitrogen may hydrogen bond to the phenyl ring in this conformation. A preponderance of such a conformer would explain the extremely low value of ^1J seen for phenylethylamine and would also explain why ^1J for the salt was higher. Without more careful analysis, however, one cannot tell how much of the extended form is present.

The methylated and dimethylated amines should present a different picture because models show that increased methylation makes the folded form sterically crowded. (In any case, no favourable intramolecular hydrogen bonding can occur in the *N,N*-dimethylphenylethylamine). We notice indeed that $^1J_{CC}$ increases progressively upon methylation which would be expected if the extended form increasingly predominates. One must, however, allow for the *N*-methylation effects which are hard to assess accurately. One can make an estimate of these, which shows that the ^1J values do in fact support the idea that the extended forms are favoured. In *N*-methylphenylethylamine the difference in ^1J brought about

by a methyl group is unlikely to be more than + 0.6 Hz while the observed ^{1}J rises by more than 1.1 Hz. In *N,N*-dimethylphenylethylamine, a hypothetical folded form (probably sterically impossible) would have a ^{1}J raised by not more than 1.2 Hz. The observed ^{1}J is more than 2.6 Hz higher than that for phenylethylamine. ^{1}J values for the hydrochlorides are much more similar to one another, reflecting the fact that the effects of the lone pairs have gone and only the effects of the perpendicular phenyl ring and the *N*-methyl groups remain. The high values of ^{1}J for the methylated phenylethylamines arise because in the extended forms the lone pair can easily be in a *gauche* orientation with respect to the C-C bond. This idea is supported by the ^{1}J values for the salts which are lower than those for the free amines, in contrast to the value for the unmethylated amine salt which was higher than that of the free amine. (The methylated amines follow the pattern of the ethylamines).

Work on the related compounds, histamine and its side chain *N*-methylated derivatives, is in accord with these findings for phenylethylamines[91]. That is, *N*-methylation slightly increases the percentage of the extended form while dimethylation increases it further. (The trimethylammonium histamine derivative appeared to exist exclusively in the extended form).

Although we have not attempted to study the phenylethylamines in detail, it is encouraging that the present results are in agreement with those from other sources. This offers hope that measurement of $^{1}J_{CC}$ may be of value in conformational analysis of biological molecules, possibly quite large ones. In many cases it would be straightforward to synthesize these with the

appropriate carbon isotopic substitution, though any subsequent work will probably be confined, for the present, to *in vitro* studies.

Chapter 6

The Conformation of Diethylketone and *syn/anti* Isomerism in its Derivatives

Diethylketone is the only ketone that has so far been studied in this work. In our preliminary communication on stereochemical effects on $^{1}J_{CC}^{13}$ we reported that a bond *cis* to a carbonyl group had a coupling nearly 4 Hz larger than did one *trans* to a carbonyl group (see Figure 20a). $^{1}J_{CC}$ for diethylketone (see Figure 20b) was found to be 36.01 Hz, 1.6 Hz less than ^{1}J found for the *cis* isomer in the previous study and 2.2 Hz greater than that for the *trans* isomer.

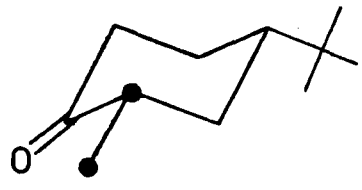
As mentioned in Chapter 3, exocyclic bonds have more s character than do those in comparable open chain species and hence have higher one bond couplings. A hydrocarbon example[68] is shown in Figure 20c; (the change for the exocyclic bond is much smaller than that for the cyclic bond shown in Figure 10). Bearing this in mind we may use the cyclic compounds as rough models for diethylketone conformers, though the conformation of the rest of the ring may not be the same as the models require. $^{1}J_{CC}$ for the exocyclic bonds will also, if anything, be increased by the substitution effect due to the ring methylenes. Qualitatively it appears that in diethylketone a *cis* orientation of the methyls and carbonyl group must be the favoured one. This conclusion is supported by the large negative value of $\Delta J/\Delta T$ which was -0.29 ± 0.09 Hz$^{\neq}$. Such a large negative $\Delta J/\Delta T$ is unique amongst

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$\neq$ The uncertainty was associated with the use of curve fitting to free induction decays rather than transformed spectra (see Appendix 1). Fitting to transformed spectra for diethylketone and most ethylbenzene derivatives could not be performed in reasonable time because a large mass of data was lost from magnetic discs and repetition of all the experiments was impracticable.

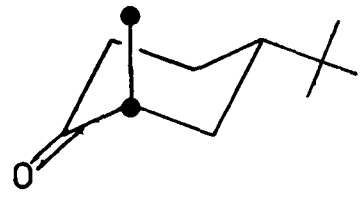
Figure 20

(a) $^1J_{CC}$ for diastereomeric cyclic ketones



cis

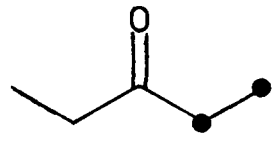
J = 37.6 Hz



trans

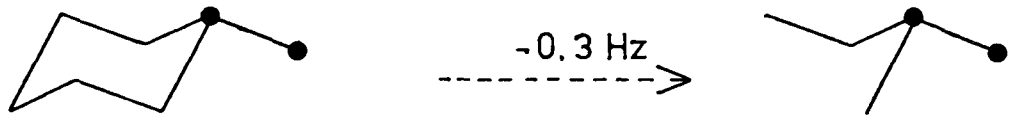
J = 33.8 Hz

(b) $^1J_{CC}$ for diethylketone



J = 36.01 Hz $\quad \Delta J/\Delta T = -0.29$ Hz/K $\times 10^2$

(c) Effect of "ring breaking" on $^1J_{CC}$



J = 35.7 Hz $\qquad$ J = 35.4 Hz

those values we have found. It is larger than any found for amines in which a *gauche* orientation of the lone pair and C-C bond was thought to be favoured. The only changes larger in magnitude were for the hindered *N*-ethylpiperidine (the third in Table 8) and for derivatives of ethylbenzene which were, however, in the opposite sense. The change seen here may indicate that for diethylketone there are two or more conformers in solution and that the *cis* one, being more stable, predominates increasingly at low temperatures. The conformer with such a *cis* orientation of the carbonyl and methyl groups is also known as the *trans-trans* or *s-cis* form. Variable temperature infra-red and Raman work has shown that this conformer is the more stable and that it is the only one in the solid.[92] Work using proton n.m.r. indicated that this was the most stable form but did not rule out the possibility that the carbonyl/methyl orientation might be *gauche*.[93] Other infra-red work showed that the *trans-trans* conformer was the only one in the solid but that various others might exist in the liquid and gaseous states.[94] A study combining infra-red, Raman and proton n.m.r. evidence indicated that there were at least two conformers in the liquid.[95]

There is another suggestion that may be relevant to our results, arising from examination of bandshapes in infra-red and Raman spectra of diethylketone and other molecules as a function of temperature. It was thought that variation of band structure might be caused by variation in intermolecular association mediated by dipole-dipole interactions.[96] The

variation in $^{1}J_{CC}$ with temperature for acetonitrile was ascribed to such interactions in Chapter 1. Diethylketone is of quite high polarity though it is less polar than acetonitrile (the dipole moment of acetone is 2.88 D while that of acetonitrile is 3.94 D). It is unlikely, however, that the large negative change in $^{1}J_{CC}$ with temperature for diethylketone is caused by changing intermolecular interactions. Whereas for acetonitrile the dipolar interaction involved one of the carbon atoms making up the bond for which ^{1}J was measured, for diethylketone it does not. The dipolar part of the molecule is the carbonyl group but ^{1}J was measured for the ethyl group. Moreoever, $\Delta J/\Delta T$ due to changing dipolar interactions would have the opposite sign to the one observed. It is unlikely, also, that $\Delta J/\Delta T$ is caused by solute-solvent interactions because the solvent was toluene which is of low polarity. Thus the conclusion is that the most stable conformer of diethylketone has a *cis* orientation of the methyl groups and carbonyl group. Further work on carbonyl compounds will require model compounds as did that on amines.

Syn/anti Isomerism

The *syn* and *anti* isomers of a constitutionally unsymmetrical oxime are not present in equal amounts. Proton n.m.r. has been used to find isomer ratios but identification of the isomers by their chemical shifts is difficult since the shifts may be very close to one another; lanthanide shift reagents have been used to alleviate this difficulty.[97]

It was mentioned in the Introduction that stereochemical effects on $^{1}J_{CH}$ are better documented than are those on $^{1}J_{CC}$.

Some of these effects relate to stereoisomerism such as *syn/anti* rather than to conformational differences. $^{1}J_{CH}$ has been found to vary between the *syn* and *anti* isomers of acetaldoxime[98] (see Figure 21). This can be explained in terms of lone pair/antibonding orbital overlap[44] as mentioned in Chapter 2. In oximes the relative orientations of the carbonyl type carbon to adjacent atom bond are *cis* or *trans* with respect to the lone pair. Thus the electronic effects will be at their extreme limits in the two forms (rather than diminished as, for example, in the *gauche* interactions found in amines). One might expect similar stereochemical effects on $^{1}J_{CC}$ as were found for $^{1}J_{CH}$ which may not, however, be larger than those seen in amines. This will be because the effects of the lone pair will be offset by electronic effects due to the hydroxyl group (or other groups in related species such as *N,N*-dimethylhydrazones). $^{1}J_{CC}$ has indeed been found to vary for a series of oximes in this manner[10] though the work has not been discussed.

We have observed a slightly different phenomenon; $^{1}J_{CC}$ for the ethyl in diethylketone derivatives varies according as the ethyl is on the *syn* or *anti* side of the derivative. The results found are given in Table 13; they are paralleled by those recently published for methylethylketonoxime.[10] For diethylketone the isomeric derivative pairs are chemically indistinguishable; only the isotopic substitution differentiates them. It is in the case of such a symmetrical ketone that values of $^{1}J_{CC}$ may be useful in assignment.

Carbon chemical shifts are more useful than proton chemical shifts in studying *syn/anti* isomerism because they vary more with

Figure 21

Stereochemical variation of $^1J_{CH}$ for acetaldoxime



Figure 22

Legend for Table 14

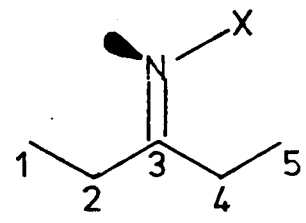


Table 13

$^{1}J_{CC}$ in *syn* and *anti* isomers of diethylketone derivatives[a]

Compound	Solvent	$^{1}J_{CC}$ *syn*	$^{1}J_{CC}$ *anti*
oxime	$CDCl_3$	33.12	34.43
N,N-dimethylhydrazone	$CDCl_3$	33.22	33.98
semicarbazone	CD_3OD	32.23	35.16

a *syn* and *anti* refer to the orientation of the group on nitrogen and the bond for which $^{1}J_{CC}$ (in Hz) was measured. Results were obtained directly from the print-out from the Bruker WH90.

Table 14

Chemical shifts for the derivatives, in ppm from TMS

	Carbon atom[b]				
Compound[a]	1	2	3	4	5
oxime	10.9	27.1	163.5	21.0	10.1
N,N-dimethylhydrazone	11.6	28.9	174.2	22.7	11.2
semicarbazone	10.9	30.2	158.2	23.0	9.9

a Solvents as for Table 13

b See Figure 22

stereochemical effects. However, there has been ambiguity in assigning the spectrum of diethylketonoxime for which the isomer ratio is 50:50.[99] The measurements of $^{1}J_{CC}$ resolve this because they prove which atoms are adjacent to each other. The chemical shift assignments are given in Table 14 and the explanation of the numbering system is contained in Figure 22.

This example shows the possibilities for using $^{1}J_{CC}$ for configurational assignments. By extension, it may be useful for studying conformational equilibria in systems containing double bonds. We expect that in general, $^{1}J_{CC}$ will be dependent on the orientation of a given bond and a centre of unsaturation, be it a double bond, aromatic ring, or lone pair.

Chapter 7

The Preparations

Some points of interest are discussed below, with references to the Reaction Schemes depicted on the adjacent pages.

Small, Open-Chain Ethyl Compounds and Ethyl Amines

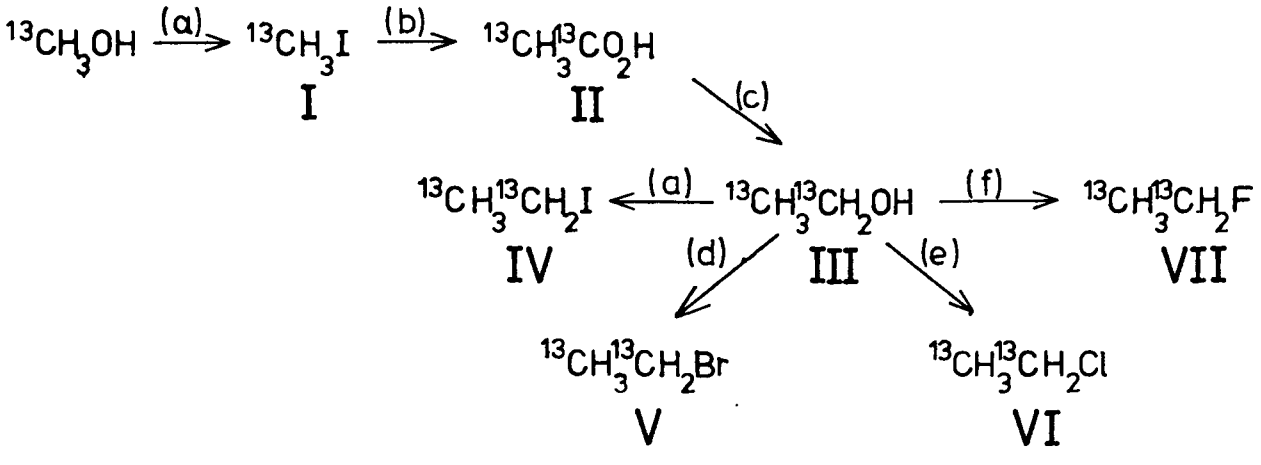
Reaction Schemes 1 and 2

The preparations of I,II, III and IV followed Hunt[100] but I and IV were redistilled from dry soda-lime then phosphorus pentoxide[101] rather than from dry alumina, yielding drier, more iodine-free products. Methods using hydrohalic acids were preferred for the preparation of V and VI since they gave higher yields of these simple halides than did methods using more complex reagents (e.g. thionyl chloride, phosphorus pentachloride). VII was made via the tosylate following a published procedure[102] but it was found unnecessary to use heating at 250°C for 5 hours as described, since no more fluoroethane (VII) was evolved after heating to 250°C during 2 hours. The more direct preparation from IV using potassium fluoride in the presence of a crown ether[103] was found to be unreliable. The preparation of VIII was based on analogous preparations[104] in which, however, the object was to prepare various *N*-alkylpiperidones rather than a simple dialkylamine as was desired here.

Reaction Scheme 3

IX was prepared from pyridine, rather than directly from piperidine, to avoid formation of the quarternary ammonium salt. X was prepared by an analogous route, the hindering 2- and 6-methyls necessitating more severe conditions for the ethylation.[105] The same route was used to prepare the 2,6-dimethyl analogue of X but an unidentified,

Reaction Scheme 1



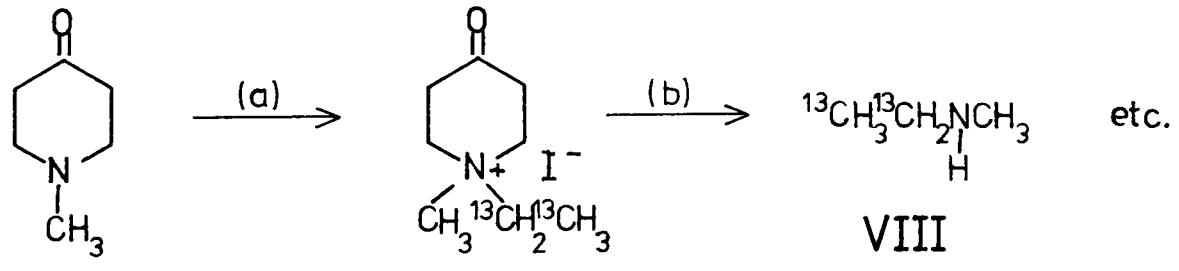
(a) HI/reflux (b) Mg/Et_2O; $^{13}CO_2/-40^{\circ}C$; H^+

(c) Dihydropyran/40°C; $LiAlH_4$/2-(tetrahydrofurfuryloxy)tetrahydropyran-/60°C; tetrahydrofurfuryl alcohol/110°C

(d) HBr/reflux (e) $HCl/ZnCl_2$/110°C

(f) Tosyl chloride/C_5H_5N/-20 to -40°C; H_2O; KF/heat to 250°C

Reaction Scheme 2



(a) $^{13}CH_3{}^{13}CH_2I/Me_2CO$

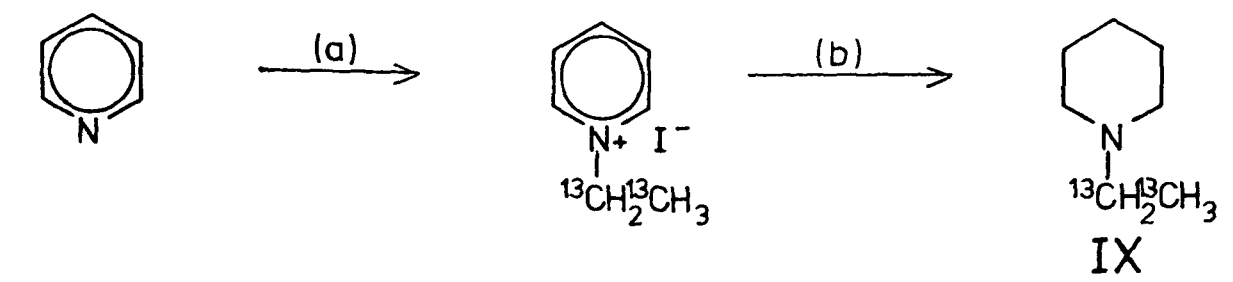
(b) $H_2O/H_2N(CH_2)_6NH_2$

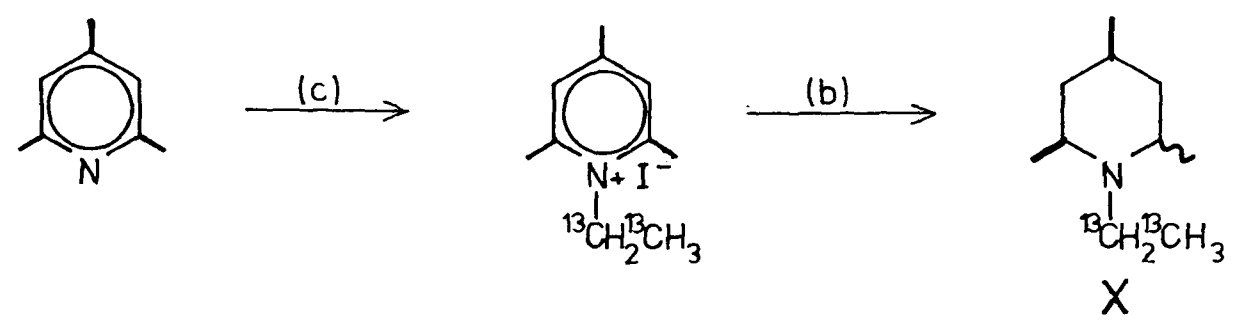
apparently isomeric, impurity was obtained in the final product (*cis/trans*-2,6-dimethyl-*N*[($^{13}C_2$)ethyl]piperidine). Attempts to remove possible traces of less hindered dimethylpyridines (which would undergo preferential ethylation) from the 2,6-dimethylpyridine using boron trifluoride etherate [106] did not help.

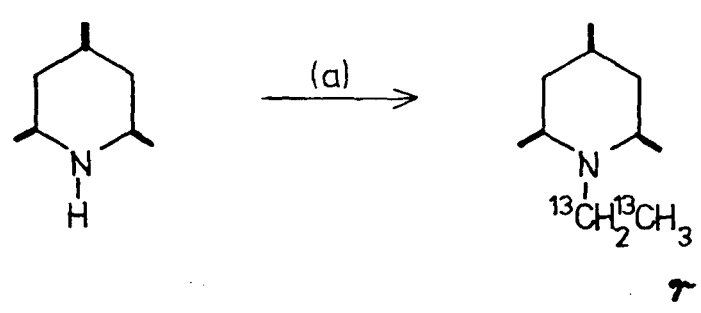
The hydrogenation produced X consisting of approximately 1:1 *cis:trans* isomers (*r*-2, *c*-4, *c*-6-X and *r*-2, *c*-4, *t*-6-X). *r*-2, *c*-4, *c*-6-X (and its *N*-methyl analogue) could be prepared directly from the available *N*-H piperidine, as shown. The hindering 2- and 6-methyls prevented purification of the amines by benzoylation (employed with other tertiary amines) since the unwanted secondary amine would not undergo benzoylation (or acetylation) under the mild conditions normally used. Hence these amines were merely separated from the crystalline hydriodide of the starting material. This rendered a slightly impure amine but recrystallization of the picrate of isotopically normal *r*-2, *c*-4, *c*-6-X gave an analytically pure sample. Moreover, the traces of secondary amine had no important effect on ^{13}C n.m.r. experiments.

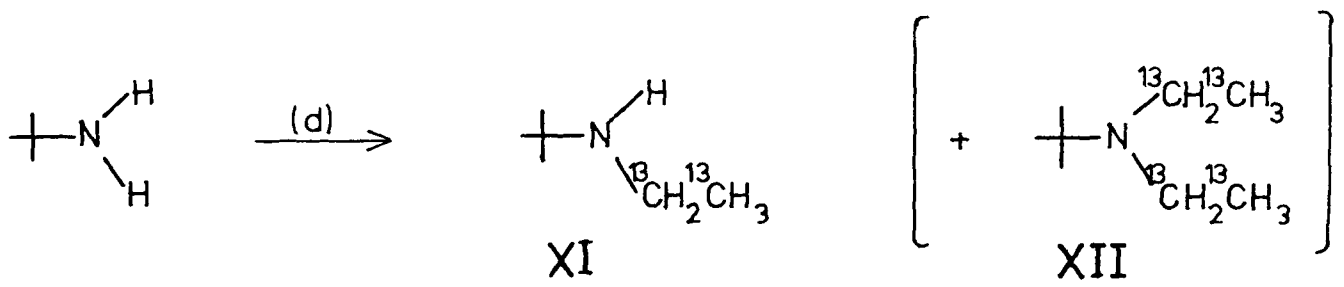
A high reaction temperature was needed to prepare XI which was sufficiently hindered to undergo little further ethylation. The small amount of XII formed was useful since it yielded an informative result in ^{13}C n.m.r. experiments. (XII was identified in the ^{13}C n.m.r. spectrum of XI by the observation of the three bond carbon-carbon coupling constant ($^3J_{CC}$) and by the chemical shift of the methylenes, which was similar to that of the methylene in *N*-methyl-*N*-($^{13}C_2$)ethyl-*t*-butylamine prepared from XI).

Reaction Scheme 3









(a) $^{13}CH_3{}^{13}CH_2I/Me_2CO$

(b) $NaBH_4/EtOH/reflux;\ H^+;\ H_2/Pt/AcOH$

(c) $^{13}CH_3{}^{13}CH_2I/PhNO_2/90^oC$

(d) $^{13}CH_3{}^{13}CH_2I/MeOH/90^oC$

Reaction Scheme 4

The oxidation step (b) in the preparation of XIII followed Brown[107]. This mild oxidation proved very convenient for small scale synthesis of fairly volatile compounds. The derivatives of XIII were not isolated but were characterized, in solution, by their ^{13}C chemical shifts by comparison with those obtained for isotopically normal analogues which were prepared and isolated on a larger scale for this purpose.

The preparation of XIV followed a published procedure.[108]

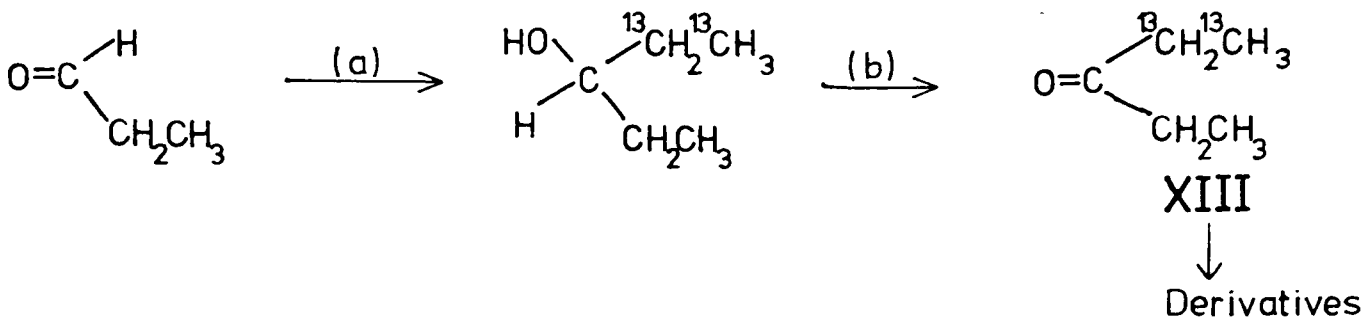
Ethylbenzene and Related Compounds

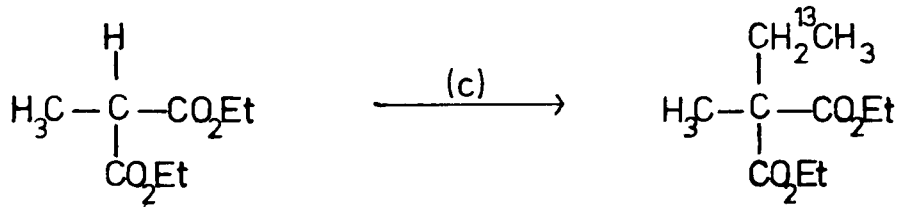
Reaction Scheme 5

The preparations of XV and XVI followed Hunt,[100] with the following modifications. In conducting a Grignard reaction with (^{13}C)carbon dioxide a larger excess of Grignard reagent (25% excess halide) was employed. This gave higher yields (based on (^{13}C)carbon dioxide) than the more usual ratios of reagents employed. (Obviously no excess halide was used when it was itself isotopically substituted). In the work-up stages of steps (a) and (b) sulphuric acid rather than hydrochloric acid was used since it is insoluble in ether. The lack of a totally water soluble complex (obtained with hydrochloric acid) after reduction with lithium aluminium hydride was not a disadvantage.

XXI was prepared by the route shown to enable study of the intermediate compounds XVIII, XIX and XX. However, it was subsequently found to be more satisfactory to prepare XVIII via XXII (steps (e) and (f) rather than (d)). Preparation of XVIII via a Grignard reaction using XVII tends to give low yields and large amounts of bibenzyl unless extreme care is taken to allow no heating of the mixture during

Reaction Scheme 4





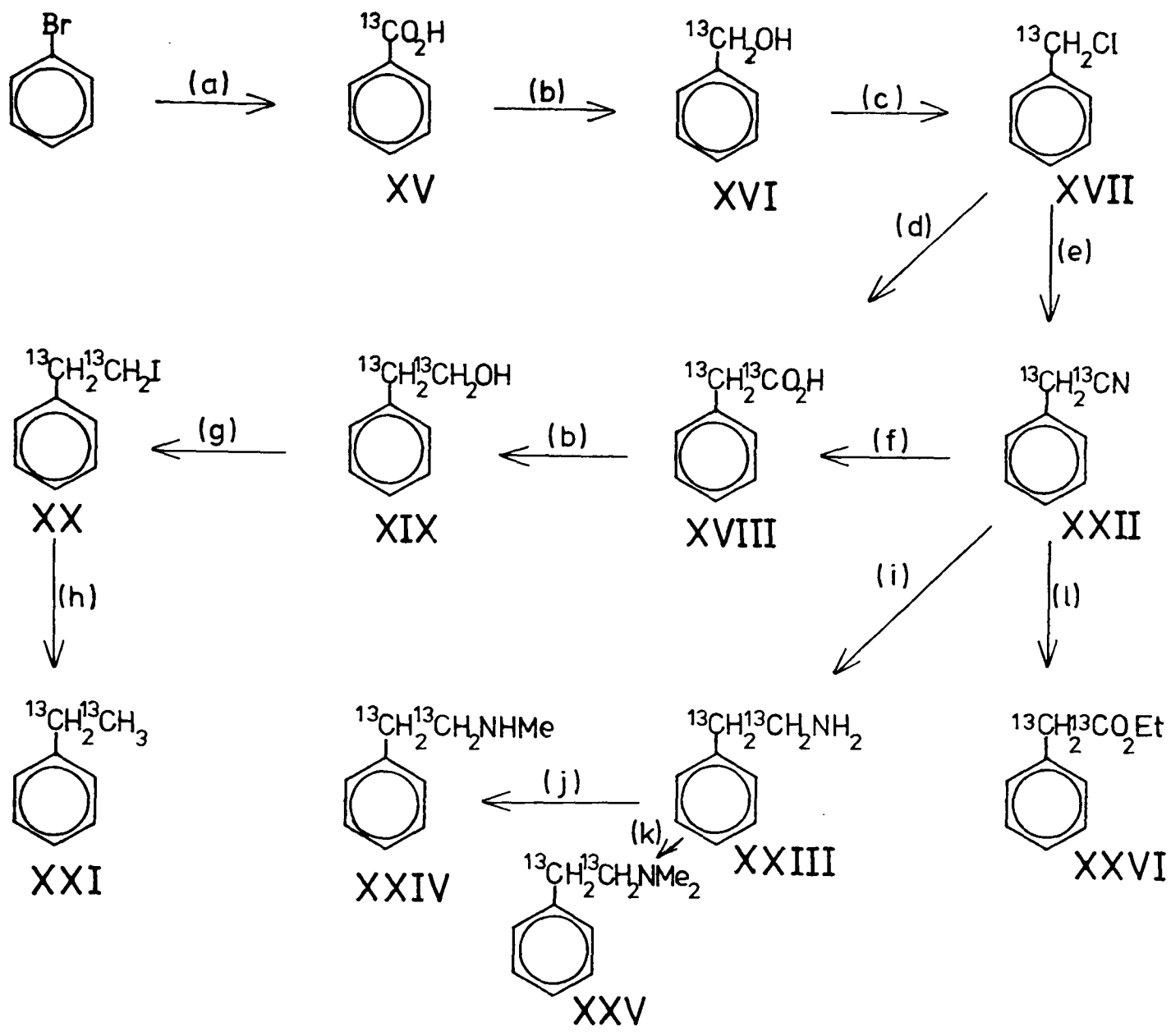
XIV

(a) $^{13}CH_3\,^{13}CH_2MgI/Et_2O$; NH_4Cl

(b) $H_2CrO_4/Et_2O/30^oC$

(c) NaH/DMF; $^{13}CH_3CH_2I$; H_2O

Reaction Scheme 5



(a) Mg/Et_2O/reflux; $^{13}CO_2$/-50 to -20°C; H^+

(b) $LiAlH_4/Et_2O$/reflux; H^+ (c) $HCl/ZnCl_2$/50°C

(d) Mg/THF; $^{13}CO_2$/-30°C; H^+

(e) $Na^{13}CN/EtOH/H_2O$/reflux (f) H_2O/H_2SO_4/130°C

(g) HI/reflux (h) $Zn/AcOH/HCl_{(g)}$/80°C

(i) BH_3:THF/60°C; H^+

(j) $ClCO_2Et/K_2CO_3/H_2O$; $LiAlH_4/Et_2O$/reflux 24h; OH^-

(k) $HCHO_n/HCO_2H$; OH^-

(l) H_2O/H_2SO_4/EtOH/130°C

preparation of the reagent.[109] ^{13}C n.m.r. spectra of XVIII and XIX prepared via (d) showed, moreover, that they contained gross impurities though XX and XXI appeared to be pure. The reduction of XX to form XXI followed Levine.[110]

The alternative procedure for preparing XVIII involved preparation of the nitrile XXII[111] and its subsequent hydrolysis[112]. The ester XXVI was prepared analogously.[113] XXII was shown by ^{13}C n.m.r. to contain some impurities but these did not seriously affect reactions carried out with it. (These may have arisen from impurities in the sodium (^{13}C)cyanide). The nitrile XXII also enabled preparation of the phenylethylamines. Reduction with diborane in tetrahydrofuran[114] gives better yields of XXIII than does lithium aluminium hydride which probably leads to undesired side reactions at the benzylic position.[115] (The latter reagent, however, was used successfully to convert acetonitrile to ethylamine). The preparation of XXIV from XXIII via the carbamate required a very long reaction time for the lithium aluminium hydride reduction (about 50% of the carbamate remained unreduced after 8 hours).

The Eschweiler-Clarke reaction used to prepare XXV required only a normal (2 hour) period of boiling (contrast the mono-methylation of *r*-2, *c*-4, *c*-6-trimethylpiperidine which required 8 hours,[116] owing to the hindrance discussed at Reaction Scheme 3).

The phenylethylamines were not distilled from barium oxide since an attempt at distillation of XXIII was shown by ^{13}C n.m.r. to have given at least two unsaturated products in low yield. (One was thought to be styrene since a value of $^{1}J_{CC}$ appropriate to this compound was observed in the ^{13}C n.m.r. spectrum of the distilled product. The other remained unidentified).

Reaction Scheme 6

The preparation of XXVII was analogous to that of XV and its homologues. The Grignard reaction used to form XXIX followed Fuson and Corse[117]; such a reaction at room temperature is only possible with a highly hindered acyl chloride, the method utilising a cadmium reagent being more general.[118] A general method for carbonyl halide to ketone conversion via a low temperature Grignard reaction has recently been published.[119] The vigorous Clemmensen reduction of XXIX to XXX[120] was necessitated by the same hindrance to which reference has just been made (contrast the preparation of indan, below).

Reaction Scheme 7

The Friedel Crafts reaction used to form indan-1-one, XXXIII, from XXXII[121] goes in better yield than does direct cyclisation of XXXI using polyphosphoric[122] or fluorosulphonic acids[123], though the first method was reported first. The facile Clemmensen reduction[124] was used to prepare indan, XXXIV, because hydrogenolysis failed, probably owing to the presence of iodine or sulphur impurities from the previous steps.

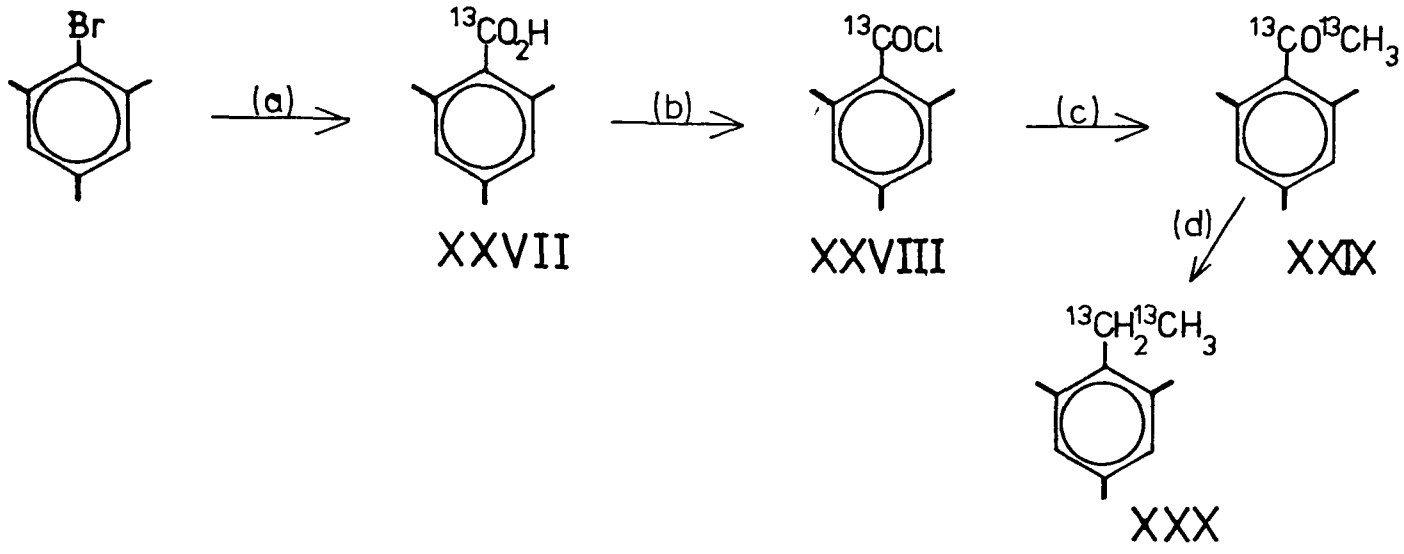
Formation of the conjugated bond in XXXVI by dehydration of XXXV was extremely facile (contrast 1-ethylcyclohexene, LV). Fortunately in the reduction to XXXVII the catalyst was not poisoned.

Piperidines Isotopically Substituted in the Ring

Reaction Scheme 8

The preparation of XXXVIII was exactly analogous to that of the lower iodides described. The preparation of XXXIX gave a much lower yield than did that of XXXI, leading to large amounts of the

Reaction Scheme 6



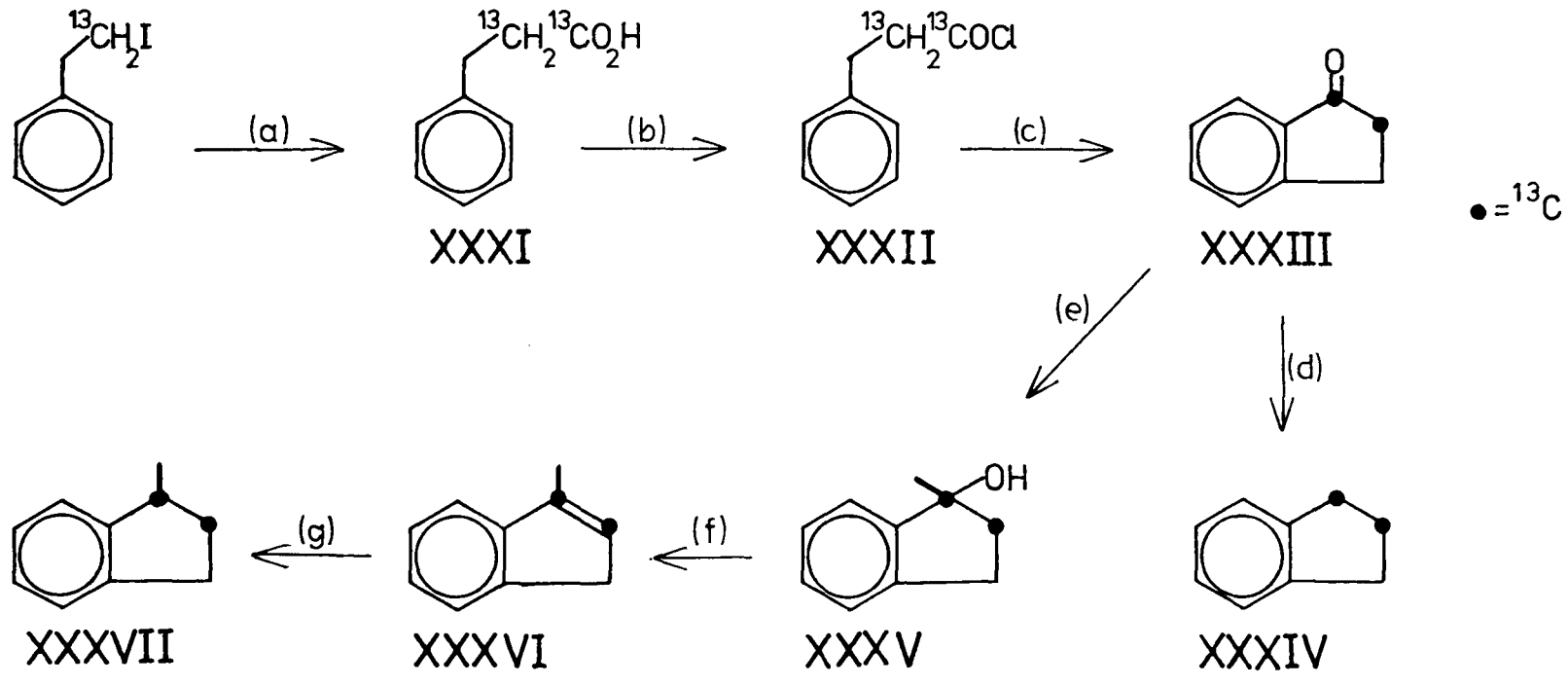
(a) Mg/Et_2O/reflux; $^{13}CO_2$/-50°C; H^+

(b) $SOCl_2$/reflux

(c) $^{13}CH_3MgI/Et_2O$; tartaric acid

(d) Zn:Hg/HCl(2.5M)/reflux 170h

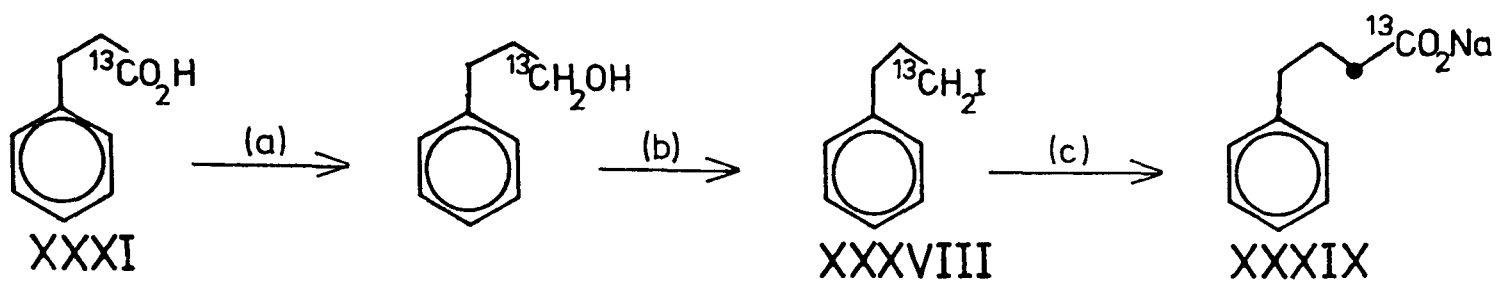
Reaction Scheme 7

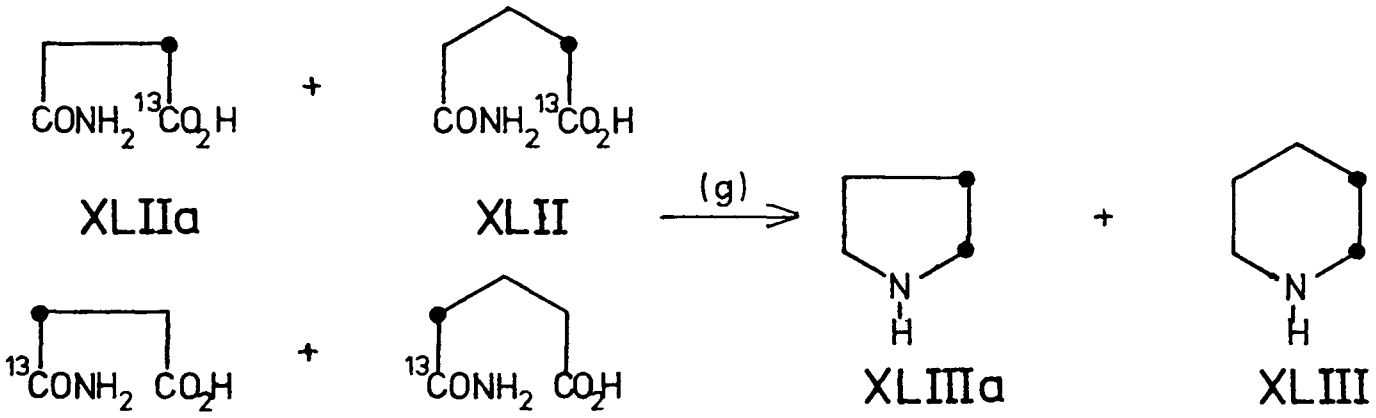


(a),(b) as above (c) $AlCl_3$/pentane (d) as above but 4h

(e) $^{13}CH_3MgI/Et_2O$/reflux; NH_4Cl (f) H_2SO_4 (g) $H_2/Pt/AcOH$

Reaction Scheme 8





(a) $LiAlH_4/Et_2O$/reflux; H^+

(b) HI/reflux

(c) Mg/Et_2O; $^{13}CO_2/-40^oC$; H^+; NaOH

(d) $RuCl_3/NaOCl$; H^+; H_2O_2/OH^-; H^+

(e) $(CF_3CO)_2O$

(f) $NH_{3(l)}$; H^+

(g) BH_3: THF; MeOH; HBr/heat; OH^-

dimer, 1,6-diphenylhexane. This behaviour was most unexpected, being analogous to that of the benzylic case discussed at Reaction Scheme 5, though yields on the previous steps were so high that this was not disastrous. The key step in the synthesis of (2,3-$^{13}C_2$)piperidine was the ruthenium tetroxide oxidation [125] which enabled the production of a chemically symmetrical, though isotopically unsymmetrical, difunctional compound (XL), a task which had proved very difficult using other routes (see below). The analogous oxidation of potassium 3-phenylpropanoate was reported to give 94% succinic and 6% benzoic acids [125] but in this case it was found that out of a total crude yield of 83% from the oxidation of sodium 4-phenylbutanoate not only were there traces of benzoic acid but also 15% of succinic acid (XLa). This suggests that the previous workers [125] might have been expected to produce some malonic acid (although this may have been further oxidised to carbon dioxide) by an analogous mechanism (attack at the benzylic position). Moreover the product was found, in this work, to be sticky and was treated with alkaline hydrogen peroxide [126] to try to remove traces of keto-acids thought to be present. The final yield of (2,3-$^{13}C_2$)piperidine (XLIII) was not as high as when commercial (isotopically normal) 4-phenylbutanoic acid was used. The reason for this is not obvious since the remaining steps were straightforward. The cyclic anhydrides (XLI and XLIa) were readily formed from the acids and trifluoroacetic anhydride. These were opened with ammonia to form the pairs of products XLII and XLIIa. The reduction of the acid-amides required vigorous conditions because the intermediate borane complexes were very insoluble in tetrahydrofuran. The work-up was readily adapted to form piperidine, XLIII, directly. The pyrrolidine, XLIIIa, was used

to advantage since a value of $^{1}J_{CC}$ could be obtained for it and its derivatives.

Other routes to (1,2-$^{13}C_2$)glutaric acid: Schemes 9 and 10

Scheme 9 was considered first but was eventually abandoned because many problems were encountered. The yield of XLV obtained by reduction of XLIV was never better than 75% (contrast with the aromatic acids for which yields were greater than 90% in all cases). Moreover no satisfactory method could be found for converting XLV into XLVI. No reported method of bromination[127] seemed to work well with this unsaturated alcohol nor did attempts at iodination of the tosylate.[128]

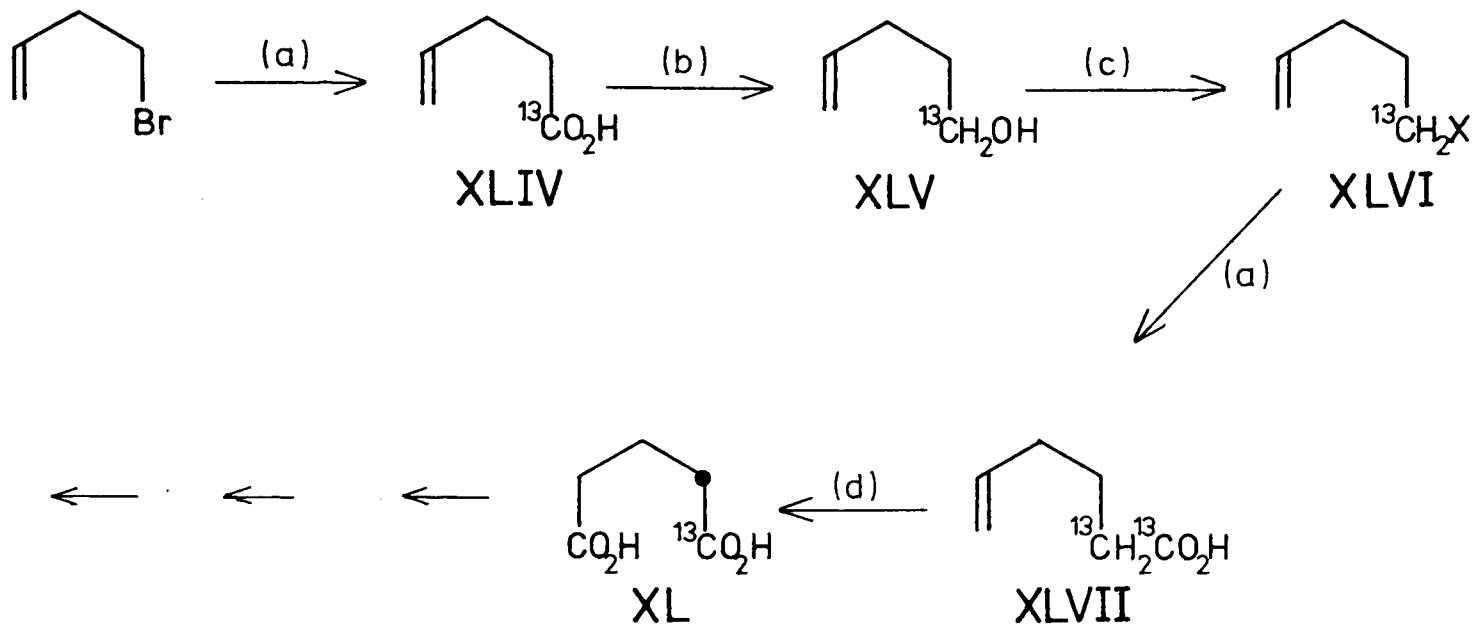
Scheme 10 was considered next but none of the published methods for alkylation of either lithium (or sodium) acetate or alkyl acetates was found appropriate for use with an isotopically substituted substrate since to obtain good yields excess acetate is employed.[129] In any case, yields with acetate are reported to be poor compared with those obtained via lithiation of higher acids.

Scheme 8, adopted finally, is analogous to Scheme 9, the double bond of XLIV being replaced by the phenyl group of XXXI. This proved a more convenient substituent to handle and was removed by ruthenium tetroxide in a manner analogous to the ozonolysis of the double bond[130] in Scheme 9.

Reaction Scheme 11

The use of neat oxalyl chloride with an amine catalyst on the free acid XL to form XLVIII has not been reported. It is analogous to the use of thionyl chloride/pyridine[131] but was used because the latter gave much lower yields in the subsequent reduction[132] (b). The improvement in yield for this non-catalytic reduction

Reaction Scheme 9



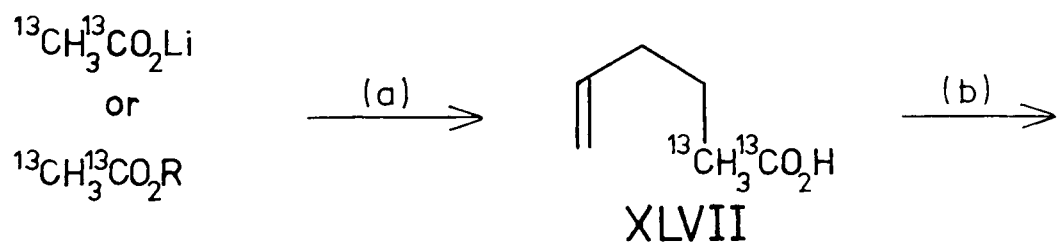
(a) Mg/Et_2O/reflux; $^{13}CO_2$/-30°C; H^+

(b) $LiAlH_4/Et_2O$/reflux

(c) X=Br: see text, X=I: tosyl chloride/C_5H_5N; H_2O; MgI_2/Et_2O

(d) O_3/MeOH/-70°C; H_2O_2/HCO_2H/reflux

Reaction Scheme 10



(a) Lithiation; allyl halide etc. : see text

(b) as for (d) above

was unexpected, though understandable in the Rosenmund-type reduction[133] (b^1) considered as an alternative. The latter failed entirely when thionyl chloride/amine was used to prepare XLVIII, presumably owing to the presence of sulphur impurities (though the catalyst was already modified by being supported on barium sulphate). When oxalyl chloride/amine was used the two reductions, (b) and (b^1) gave equally high yields of XLIX (isotopically normal, estimated as the 2,4-dinitrophenylhydrazone) but the subsequent pseudopelletierine synthesis[134] went in low yield following (b^1) despite attempts to remove *N,N*-dimethylaniline thoroughly. Crude pseudopelletierine (L) was readily reduced to give *N*-methylgranatanine (LI) by the Huang Minlon modification of the Wolff Kishner reduction.

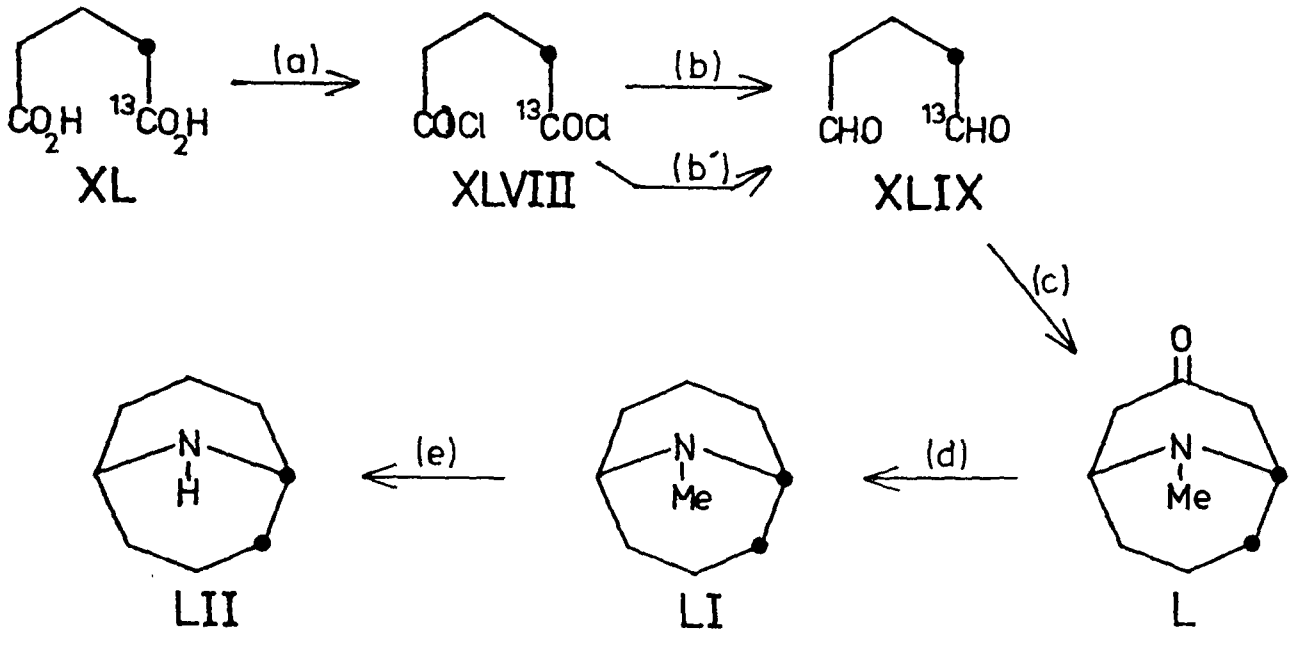
The work-up of the reduction, (b), to give an aqueous solution of glutaraldehyde (XLIX) was developed specially for this scheme by P.J.C. Harding.

The demethylation of LI to granatanine, LII, followed a recently published procedure[135]. LI and LII were obtained in a purer (drier) state than by previous workers because they were distilled at 10^{-3}mm from barium oxide. The melting points obtained were considerably higher than the literature values[136,137] because they were measured for the dry, distilled amines in a sealed tube under vacuum.

Reaction Scheme 12

Hydrogenation of XXX was very difficult; after 40 hours approximately 20% remained unreduced as judged by ^1H and ^{13}C n.m.r. analysis. The reduction appeared to give LIII with high stereoselectivity, the stereochemistry being deduced by comparison[8a] of the chemical shifts of the ethyl (and ring) carbon atoms with those of ethylcyclohexane[138]. (No three bond couplings ($^3J_{CC}$),

Reaction Scheme 11



(a) $(COCl)_2/Et_3N$/reflux

(b) $(PPh_3)_2CuBH_4/PPh_3/Me_2CO$; H_2O

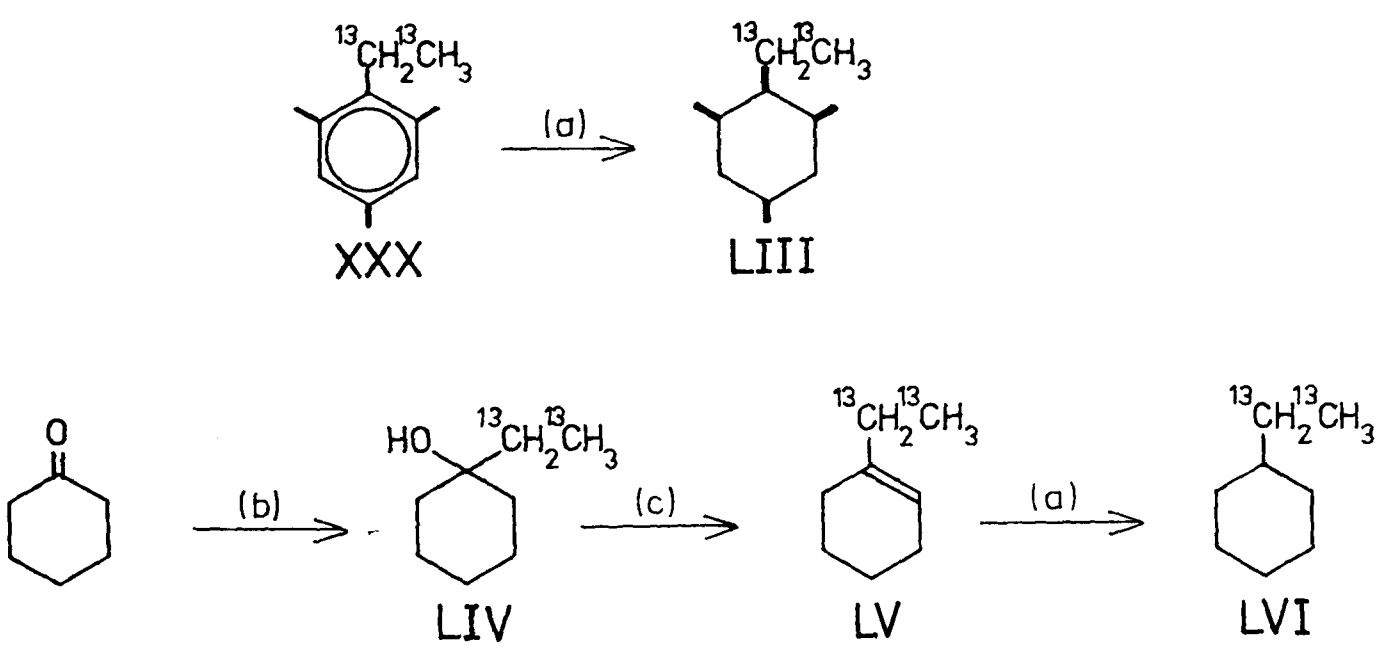
(b^1) $Pd:BaSO_4/H_2/Me_2CO/PhNMe_2$; H_2O

(c) $MeNH_4Cl/(CH_2CO_2H)_2CO/Na_2HPO_4/NaOH$; H^+; NaOH

(d) $N_2H_4/(HOCH_2CH_2)_2O/KOH$/distil

(e) PhSeH/150°C

Reaction Scheme 12



(a) $H_2/Pt/AcOH$

(b) $^{13}CH_3{}^{13}CH_2MgI/Et_2O$; NH_4Cl

(c) $KHSO_4$/100°C

expected to be 0 to 1 Hz, were observed).

By contrast, hydrogenation of the isolated, unhindered double bond in LV was very rapid. In the previous step, (c), the reaction was carried out in a sealed tube at 100°C for a long period rather than by slow heating in an open vessel to 150°C[139a] since the latter method was unsatisfactory on a small scale.

EXPERIMENTAL

^{13}C NMR

Most ^{13}C n.m.r. spectra were measured on a Bruker WH90 pulsed Fourier Transform spectrometer, operating at 22.63 MHz and employing a Nicolet B-NC 12 computer. Some preliminary measurements of one bond carbon-carbon coupling constants ($^{1}J_{CC}$) were made, using a Varian XL-200 spectrometer operating at 50.32 MHz, by A. Bax and S.P. Kempsell working in Dr. R.Freeman's group in the Physical Chemistry Laboratory. They used isotopically normal compounds (e.g. piperidine) in solutions of high concentration, employing the method of double quantum coherence.[67] These were room temperature (~ 296-301K) measurements.

In more recent work, when necessary, a value of $^{1}J_{CC}$ was measured or was verified using a Bruker WH300 spectrometer operating at 75.47 MHz.

Using the Bruker WH90 machine, spectra could be obtained at temperatures ranging from ~150-~ 420K. Temperatures between 150 and 300K were measured using a ^{13}C shift thermometer.[100] Higher temperatures were measured with a newly devised thermometer described in Appendix 2.

The following conditions were used for the different types of experiment as enumerated.

Determination of (1) ΔG^{o} from Measurement of Line Broadening as a Function of Temperature

Spectra were obtained using the following conditions:-

(a) Broad band proton decoupling

(b) Sweepwidth (SW) of 2000 Hz

(c) Free induction decays (FIDs) were collected in 4096 (4K) memory addresses.

(d) 4K zeroes were added to each FID before Fourier Transformation

(FT) giving a digital resolution of 0.488 Hz per address.

(e) Pulse repetition times were 2s and pulse angles were of the order of 50^{o}.

(f) Exponential multiplication (EM) was applied to FIDs before (d). This gave line broadening of, typically, 1.2 or 2.4 Hz.

Line widths were measured from peaks plotted on an expanded scale (~ 1.6 Hz/cm).

(2) ΔG^{o} from Integration of Resonances at Low Temperature

Similar conditions were used as for (1), (a)-(f). Areas were measured by hand planimetry and the experiments were repeated several times.

For (1) and (2) only 20 to 100 transients needed to be averaged for each experiment.

(3) ΔG^{o} from Kinetic Protonations

The method referred to here as 'Kinetic Protonation' is described below.

Spectra were obtained using the conditions described for (1) with the following differences:-

(a) Pulse repetition times were commonly 5s or more and pulse angles were approximately 90^{o}.

(b) Accumulations had to be much longer (smaller amounts of minor component) especially for those protonations carried out at room temperature. Thus 2 to 15 h accumulations were commonly used.

Spectra were processed in the same way as for (2). Relative areas of peaks were compared after applying several different amounts of line broadening (EM) to an FID before FT.

In (1), (2) and (3) *N*-ethyl or *N*-methyl piperidines were used with *N*- methylene or *N*-methyl respectively isotopically substituted with carbon-13 (~ 90 atom %).

(4) Chemical Shifts

These were measured for isotopically normal compounds. Shifts were measured for a series of piperidines (Table 15) using conditions similar to those for (1). When necessary chemical shifts were obtained for other types of compound using SW of 2000 Hz or 5000 Hz (carbonyl type) as appropriate.

(5) Coupling Constants

(i) One bond carbon-carbon coupling constants ($^1J_{CC}$)

Values of $^1J_{CC}$ were determined from compounds having two adjacent sites isotopically substituted in carbon-13 (90 atom % x 90 atom % = 81 atom %) of doubly substituted molecules). The following method was used:-

(a) Broad band proton decoupling was employed giving a spectrum consisting of an AB quartet.

(b) Using spectra run with a large SW (2000 or 5000 Hz) the appropriate offset for the carrier frequency was determined to allow use of a small SW.

(c) Usually a dwell-time (DW) of 7500 μs was employed (SW~ 66.67 Hz).

(d) FIDs were accumulated in 1K memory addresses and 7K zeroes were added before FT giving a digital resolution of 0.016 Hz per address.

(e) Pulse repetition times were long (1024 x 7500 μs = 7.68 s) and pulse angles were approximately 90^{o}.

(f) Decoupler power was optimized to give good line shapes.

(g) Sweepwidths of 50, 100 or 125 Hz were sometimes used with (e) correspondingly different.

These spectra included half of an AB quartet. Other, "folded" signals were strongly attenuated by the filters. When these conditions were impracticable (for example if the chemical shifts of the two halves of the quartet were similar) a larger SW was employed and, usually, the entire AB quartet was observed;

(h) EM was applied to FIDs before FT giving line broadening of, typically, 0.08 to 0.33 Hz.

(g) All measurements were repeated and the sample temperature was measured in between the first and second measurements of $^{1}J_{CC}$. (Measurement of $^{1}J_{CC}$ at 75.47 MHz employed SW=160 Hz. FIDs were accumulated in 512 (0.5K) memory addresses, line broadening of 0.2 Hz was used and 15.5K zeroes were added before FT).

(ii) $^{1}J_{CH}$ and $^{1}J_{CF}$

Values of $^{1}J_{CH}$ were measured from the quartets obtained for methyl carbon signals when no proton decoupling was applied ($^{13}CH_3I$, $^{13}CH_3Br$; octet for $^{13}CH_3{}^{13}CN$).

(a) SW of 500 or 625 Hz was used.

(b) FIDs were accumulated in 2K memory addresses.

(c) Line broadening was usually 1 to 2.5 Hz.

Values of $^{1}J_{CF}$ were obtained using a similar SW with proton decoupling.

There were no other important differences from (1).

For both (i) and (ii) the relevant data were transformed *via* a 16-bit parallel interface to a Hewlett-Packard 9825A calculator for further treatment. Least squares curve fitting to a Lorentzian line shape was used; the procedures employed are discussed in Appendix 1.

Table 15

Chemical shifts[a] of some *N*-ethylpiperidines and their hydrochlorides

Compound	Solvent	C_2	C_3	C_4	C_5	C_6	*N*-$\underline{CH_2}$-	*N*-CH_2-$\underline{CH_3}$	C_2-Me	C_4-Me	C_6-Me
Parent[b]	CD_3OD/H_2O	54.5	26.2	25.1	26.2	54.5	53.9	11.7	-	-	-
" HCl	TFA[c]	55.3	24.5	22.8	24.5	55.3	54.8	9.8	-	-	-
" "	CD_3OD/H_2O	53.5	23.9	22.4	23.9	53.5	53.1	9.6	-	-	-
cis-2,6-dimethyl	$CDCl_3$	54.3	35.5	25.0	35.5	34.3	41.0	7.0	21.1	-	21.1
" HCl	TFA	60.4	33.4	23.5	33.4	60.4	44.4	6.6	18.6	-	18.6
trans-2,6-dimethyl	$CDCl_3$	49.4	33.6	19.4	33.6	49.4	43.3	13.5	21.2	-	15.4
" HCl	TFA	57.5[d]	31.8[e]	18.3	30.1[e]	55.5[d]	46.3	10.7	18.3	-	12.5
r-2,*c*-4,*c*-6-trimethyl	$CDCl_3$	53.9	44.1[k]	31.1	44.1[k]	53.9	40.9	7.1	21.1	22.1	21.1
" HCl	TFA	60.5	42.0	30.6	42.0	60.5	44.7	6.7	18.6[j]	21.0[l]	18.6[j]
r-2,*c*-4,*t*-6-trimethyl	$CDCl_3$	49.7[f]	44.1[k]	33.1	43.0	49.4[f]	40.4	9.9	21.6	21.6	13.5
" HCl	TFA	57.9[g]	43.0[h]	25.1	39.5[h]	56.8 / 55.8[g]	47.5	10.7[i]	18.6[j]	21.0[l]	11.5[i]

a In ppm from TMS (tetramethylsilane); b Compare reference 143 (run as the neat liquid)

c Trifluoroacetic acid; d-i Ambiguous assignments

j-l Overlapping lines

KINETIC PROTONATION

The method of kinetic protonation has been fully described and discussed by Robinson *et al.*[7] A method was devised whereby *N*-alkylpiperidines were protonated in a strictly kinetically controlled way, such that the ratios of concentrations of protonated piperidines having axial and equatorial N-H in the final acid solution were the same as the ratios of concentrations of the chair conformers of piperidines having axial and equatorial N-lone pairs respectively. Thus ΔG^{o} for the N-alkyl axial/equatorial equilibrium could be determined. The method can be used at various temperatures at or above room temperature.

The following items were used in the experiments:-

(1) 82% sulphuric acid

(2) *n*-Dodecane, distilled from, and stored over potassium hydroxide

(3) Solutions of the amines in *n*-dodecane (0.25M)

(4) 10 mm n.m.r. tubes (used for subsequent n.m.r. measurements)

(5) Specially designed polytetrafluoroethylene (PTFE) or platinum/PTFE stirrers .

(6) Boiling solvent vapour bath employing water ($100^{o}C$) or bromobenzene ($156^{o}C$).

Method

N-Ethylpiperidines

(1) Room temperature: Sulphuric acid (1.25 cm^3) was carefully placed in the bottom of the n.m.r. tube with *n*-dodecane ($4cm^3$) on top. With the stirrer in place amine solution ($1cm^3$) was carefully added without mixing. After 5 min the mixture was stirred with vertical

movements for 1 min at 1 stroke/s. Dodecane was removed and ($^2H_2$)-sulphuric acid (50%; 0.25 cm^3) was added (to provide a deuterium lock for field stabilization in the Bruker spectrometer).

The experiment was duplicated.

(2) 100°C: As above except that the contents of the tube were heated for 1 min before addition of the amine and 1 min more after addition before stirring for 30s at ~ 2 stroke/s.

The experiment was repeated using 0.5 cm^3 of amine solution.

(3) 156°C: As for (2) but using 0.5 cm^3 of amine solution for each experiment.

N-Methylpiperidines

(1) Room temperature: As for (1) above except that the first experiment used 0.5 cm^3 of amine solution and the second used 0.25 cm^3.

(2) and (3) 100°C and 156°C: As for (2) and (3) above except that 0.25 cm^3 of amine solution were used for each experiment.

Chemical Shifts

To provide proof of the value of the chemical shift of the minor axial species under observation, a 50:50 axial: equatorial mixture of the appropriate piperidinium sulphate in sulphuric acid was made *via* the borane adduct. The latter was prepared by the general method described by Robinson.[7]

PREPARATIONS

General

Development of syntheses of isotpically substituted compounds was carried out using isotopically normal starting materials. Only the preparations involving isotopically substituted materials are described here. Characterization (e.g. m.p., ^{1}H n.m.r., i.r. and elemental analysis) was routinely performed on isotopically normal products. Elemental analysis results are given only for a new compound and m.p.s where they differed significantly from the literature values. Mass spectra were obtained for both isotopically normal and substituted products except for the most volatile ones (e.g. haloethanes, ethylamine and its methylated analogues). The expected molecular ions were observed. ^{13}C n.m.r. spectra were recorded for isotopically normal compounds when literature values for ^{13}C chemical shifts were lacking and the information was useful. Shifts for a series of piperidines and their hydrochlorides are given in Table 15. (Conditions used are described above). Isotopically substituted compounds were characterized by shifts and coupling constants obtained in the course of ^{13}C n.m.r. experiments. ^{1}H n.m.r. spectra were routinely recorded on a Hitachi Perkin-Elmer R24A or R24B spectrometer. To obtain more detailed information spectra were obtained using a Perkin-Elmer R32 spectrometer. Mass spectra were recorded using Varian CH7 or Vacuum Generators Micromass 16F machines. Melting points were recorded on an aluminium block and are uncorrected. Microanalyses were performed by Dr. F.B. Strauss in this department.

In the reactions described, room temperature is implied unless otherwise stated.

Commonly Used Chemicals

Barium (^{13}C)carbonate, sodium (^{13}C)cyanide and (^{13}C)-methanol were supplied by B.O.C. Prochem and were enriched to about 90 atom % in carbon-13.

Acetone and acetic acid were analytical grade. Hydrochloric acid and sodium hydroxide were 1M standard solutions (BDH) unless otherwise stated. Petroleum ether was the fraction with b.p. = 30-40°C (analytical grade).

Ethers were dried by distillation from lithium aluminium hydride. Other solvents were dried by standard methods.[140]

Soda-lime was dried at 10^{-3}mm for 4h.

Common Work-Up Procedures

The term reduced pressure is used to mean pressure obtained using a water pump while *in vacuo* implies 0.1-0.01 mm pressure.

Extracts in (diethyl) ether or petroleum ether were dried by shaking with brine then magnesium sulphate unless otherwise stated.

For amines the following standard procedures were used:-

Steam distillation: To a crude reaction product containing the amine salt was added water and potassium hydroxide to give a solution of pH 12-14 (universal indicator paper). Distillation in steam was followed by titration of the distillate with hydrochloric acid, using methyl orange as indicator, followed by removal of water at reduced pressure to give the pure amine hydrochloride. Quoted yields (in mmol) are based on such titrations. Amines were liberated just before use from a concentrated aqueous solution of their salts using potassium hydroxide followed by distillation from a large excess of barium oxide in a sealed apparatus at 10^{-3} mm. (For low-boiling amines,

Benzoylation: To free product tertiary amine from unwanted secondary amine a crude amine salt mixture was dissolved in water (25 cm^3 per mmol total amine) and an equal volume of ether was added. The aqueous phase was kept alkaline (phenolphthalein as indicator) by the addition of potassium hydroxide while the mixture was rapidly stirred with benzoyl chloride (added in two portions of 1 mmol equivalent each during 2 h). The pH was adjusted to 3 and water was removed at reduced pressure from the aqueous layer. The tertiary amine hydrochloride was isolated by titration after steam distillation of the amine.

N-Methylation (Isotopically normal): Secondary amines were methylated (primary dimethylated) using the following modification of the Eschweiler-Clarke reaction. The amine hydrochloride and potassium carbonate (0.5 mol equivalent) were dissolved in formic acid (98%; 1 cm^3 per mmol). Paraformaldehyde (3 mol equivalents) was added in two portions during 2 h boiling under reflux. (For hindered amines one more portion and 5-8 h boiling were used, see below). After cooling the mixture, hydrochloric acid (1 mol equivalent) was added, solvents were removed at reduced pressure and the amine was purified by steam distillation. (Yields were 70-90%).

For acids quoted yields (in mmol) are based on a titration of an ethereal extract of the acid (crude) with sodium hydroxide.

Isotopically substituted starting materials

(^{13}C)Iodomethane, sodium ($^{13}C_2$)acetate, ($^{13}C_2$)ethanol and ($^{13}C_2$)iodoethane were prepared using the method of Hunt[100] with slight differences in purification (described in the Discussion).

(1-^{13}C)Iodoethane and (2-^{13}C)iodoethane were prepared analogously.

($^{13}C_2$)Bromoethane

($^{13}C_2$)Ethanol (0.096g, 2 mmol) was gently boiled under reflux for 0.5 h with hydrobromic acid (48%, 2 cm^3). After cooling, ($^{2}H_2$)dichloromethane (1.4 cm^3) was added and the solution of ($^{13}C_2$)bromoethane was fractionally distilled onto dry soda-lime. The solution was dried over type 3Å molecular sieves before use.

(Yield determined from an analogous preparation using isotopically normal materials = 0.19 g, 87%)

($^{13}C_2$)Chloroethane

($^{13}C_2$)Ethanol (0.096g, 2 mmol) was sealed in a tube with hydrochloric acid (d.1.18; 2 cm^3) and zinc(II) chloride (1.4 g, 10 mmol). After stirring overnight at 110°C, the mixture was chilled (-196°C), the tube was opened, evacuated (10^{-3} mm) and the ($^{13}C_2$)chloroethane was distilled onto dry soda-lime then dried over 3Å molecular sieves.

Yield (isotopically normal): 0.11g, 87%

($^{13}C_2$)Fluoroethane

($^{13}C_2$)Ethanol (0.192 g, 4 mmol) and toluene-4-sulphonyl chloride (0.839 g, 4.4 mmol) were mixed and cooled to -40°C. Dry pyridine (4 cm^3) was added and the mixture was stirred at -40 to -20°C for 2 h. After warming to 0°C, ice/water (2 cm^3) was added, the mixture was stirred for 5 min then extracted with ether (3 x 20 cm^3). The combined ethereal extracts were washed with dilute ice-cold sulphuric acid, potassium hydroxide and then dried. Removal of

ether at reduced pressure gave ($^{13}C_2$)ethyl tosylate [($^{13}C_2$)ethyl toluene-4-sulphonate] .

Yield: 0.59g, 70%

The ($^{13}C_2$)ethyl tosylate was mixed with potassium fluoride (dried over P_2O_5 at 10^{-2}mm; 0.464 g, 8 mmol) and the pressure in the apparatus was reduced to 500 mm. The mixture was stirred and heated to 250°C over 2 h while the pressure was kept constant by allowing the gas formed to escape at intervals into a trap chilled to -196°C. After warming, the yield of ($^{13}C_2$)fluoroethane was found to be 60-70% by volume measurement. ^{1}H n.m.r. (of isotopically normal product) and ^{13}C n.m.r. showed it contained traces of impurities.

($^{13}C_2$)Acetonitrile

(^{13}C)Iodomethane (0.715 g, 5 mmol) was distilled at 10^{-3}mm onto sodium (^{13}C)cyanide (0.25 g, 5 mmol) in dry dimethylsulphoxide (7 cm^3). After stirring under vacuum for 48 h,($^{13}C_2$)acetonitrile containing a little dimethylsulphoxide was distilled out of the mixture.

Yield: 0.163g, 76% (crude)

The residue from the distillation yielded more ($^{13}C_2$)acetonitrile containing a higher proportion of dimethylsulphoxide.

N-Ethyl Amines

($^{13}C_2$)Ethylamine

($^{13}C_2$)Acetonitrile (0.163 g, 3.8 mmol), obtained as described, was added to dry ether (10 cm^3) containing lithium aluminium hydride (0.38 g, 10 mmol) and the mixture was boiled under reflux for 1 h. After cooling to room temperature the flask was chilled to -78°C

while excess solid carbon dioxide was added to destroy excess lithium aluminium hydride. While chilling continued, methanol/ hydrochloric acid was cautiously added until pH=1. After removal of solvents at reduced pressure the residues were chilled to $-196^{o}C$ and excess concentrated aqueous potassium hydroxide was added in an apparatus at 10^{-3}mm. Warming to room temperature and stirring yielded ($^{13}C_2$)ethylamine which was distilled into excess hydrochloric acid. Removal of solvents at reduced pressure gave ($^{13}C_2$)ethylammonium chloride.

Yield: 0.28g, 90%

A sample of the free amine was prepared by heating, with a small flame, the amine hydrochloride covered with a large excess of barium oxide at 10^{-3}mm.

N-Methyl-($^{13}C_2$)ethylamine

($^{13}C_2$)Iodoethane (0.316 g, 2 mmol) and freshly distilled *N*-methyl-4-piperidone (0.452 g, 4 mmol) were dissolved in acetone (1.4 cm^3) and left in a sealed tube overnight. This gave crystals of *N*-($^{13}C_2$)ethyl-*N*-methyl-4-piperidonium iodide (0.524 g, 96%) from which excess *N*-methyl-4-piperidone in acetone was removed by filtration. The crystals were dissolved in water (5 cm^3) with hexamethylenediamine (0.7 g, 6 mmol) and the mixture was left overnight in an apparatus at 10^{-3} mm.

N-Methyl($^{13}C_2$)ethylamine was distilled out of the mixture and treated in the same way as ($^{13}C_2$)ethylamine.

Yield (amine hydrochloride): 0.14 g, 84% from ($^{13}C_2$)iodoethane

N,*N*-Dimethyl($^{13}C_2$)ethylamine

Approximately 10 mmol of dimethylamine was liberated from its hydrochloride at 10^{-3} mm as described for ($^{13}C_2$)ethylamine. It was condensed onto chilled aqueous methanol(5 cm^3) containing ($^{13}C_2$)iodoethane (0.316 g, 2 mmol) and the mixture was stirred overnight. The amines were neutralized with hydrochloric acid (methyl orange as indicator) and methanol was removed at reduced pressure. Benzoylation, steam distillation and titration yielded *N*,*N*-dimethyl($^{13}C_2$)ethylammonium chloride.

Yield: 0.18 mmol, 90%

The amine was liberated in the way described for ($^{13}C_2$)-ethylamine.

(1,2-$^{13}C_2$)Triethylamine

Diethylamine (0.146 g, 2 mmol) and ($^{13}C_2$)iodoethane (0.158 g, 1 mmol) were dissolved in acetone (2 cm^3) and left in a sealed tube overnight. Hydrochloric acid (1 cm^3) was added and acetone was removed at reduced pressure. Benzoylation, steam distillation and titration yielded (1,2-$^{13}C_2$)triethylammonium chloride.

Yield: 0.9 mmol, 90%

The amine was liberated in the way described in the General section.

N-[($^{13}C_2$)Ethyl]piperidine

Pyridine (0.158 g, 2 mmol) and ($^{13}C_2$)iodoethane (0.158 g, 1 mmol) were dissolved in acetone (0.4 cm^3) and left in a sealed tube for 48 h. Addition of toluene (4 cm^3) gave solid *N*-[($^{13}C_2$)-ethyl]pyridinium iodide (quantitative yield). After drying, the salt was dissolved in ethanol (8 cm^3) and sodium borohydride (0.378 g, 10 mmol) was added in portions. After boiling under reflux for 1 h the solution was cooled and water followed by hydrochloric

acid was added (pH=3). After boiling 10 min, ethanol was removed and the pH was adjusted to 6. Steam distillation at this pH (to remove trace impurities) was followed by the general (alkaline) steam distillation and titration giving 0.9 mmol amine hydrochlorides (mixture of reduction products). Reduction was completed by hydrogenation of the amine salts in acetic acid (5 cm^3) using platinum oxide (40 mg). Removal of acetic acid at reduced pressure followed by steam distillation and titration gave *N*-[($^{13}C_2$)ethyl]-piperidinium chloride.

Yield: 0.8 mmol, 80%

The amine was liberated using the general method.

r-2,*c*-4, *c*/*t*-6-Trimethyl-*N*-[($^{13}C_2$)ethyl]piperidine

2,4,6-Trimethylpyridine (0.242g, 2 mmol) and ($^{13}C_2$)iodoethane (0.158 g, 1 mmol) were dissolved in nitrobenzene (0.5 cm^3) and heated at 90°C for 96 h. After cooling and adding a little ether, 2,4,6-trimethyl-*N*-[($^{13}C_2$)ethyl]pyridinium iodide precipitated. The salt was reduced as described for the un-methylated analogue above, and the product was purified in the same way.

Yield: 0.9 mmol, 90%

r-2,*c*-4,*c*-6-Trimethyl-*N*-[($^{13}C_2$)ethyl]piperidine

r-2, *c*-4, *c*-6-Trimethylpiperidine≠ (0.254 g, 2 mmol) and ($^{13}C_2$)-iodoethane (0.158 g, 1 mmol) were dissolved in acetone (0.5 cm^3) and left in a sealed tube overnight. After chilling and adding petroleum ether (5 cm^3) the crystals of *r*-2, *c*-4, *c*-6-trimethyl-piperidinium iodide were removed. Hydrochloric acid was added to neutralize the remaining amine and solvents were removed at

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≠ prepared by Dr M.J.T. Robinson for previous work

reduced pressure. Steam distillation and titration yielded *r*-2, *c*-4, *c*-6-trimethyl-*N*-[($^{13}C_2$)ethyl]piperidinium chloride (containing traces of un-ethylated material).

Yield: 0.96 mmol, 96% (crude).

The amine was liberated in the usual way. *r*-2, *c*-4, *c*-6-Trimethyl-*N*-[(1-^{13}C) ethyl]piperidine was prepared in an analogous manner.

A sample of isotopically normal amine was converted to the picrate.

m.p. = 124 - 126.5°C

Analysis: $C_{16}H_{23}N_4O_3$ requires C 50.13, H 6.01, N 14.62%

Found: C 50.16, H 6.22, N 14.65%

r-2, *c*-4, *c*-6-Trimethyl-*N*-[(^{13}C)methyl]piperidine

This was prepared in an analogous manner using (^{13}C)iodomethane in place of ($^{13}C_2$)iodoethane, but for every mmol of (^{13}C)iodomethane 4 cm^3 of acetone were used and chilling was required while the components were mixed.

The isotopically normal amine was prepared from *r*-2, *c*-4, *c*-6-trimethylpiperidine using the general Eschweiler-Clarke methylation. 8 h boiling under reflux and 3 additions of paraformaldehyde were used.

4-*t*-Butyl-*N*-[(1-^{13}C)ethyl]piperidine

This was prepared in an analogous manner from 4-*t*-butylpiperidine and (1-^{13}C)iodoethane but benzoylation was used before steam distillation.

Yield: 83%

N-[($^{13}C_2$)Ethyl]pyrrolidine

Pyrrolidine (0.142 g, 2 mmol) and ($^{13}C_2$)iodoethane (0.158 g,

1 mmol) were dissolved in methanol (2 cm^3) and left in a sealed tube for 48 h. After adding hydrochloric acid (1 cm^3) and removing methanol at reduced pressure, benzoylation, steam distillation and titration yielded *N*-[($^{13}C_2$)ethyl]pyrrolidinium chloride.

Yield: 0.85 mmol, 85%

The amine was liberated in the usual way.

N-($^{13}C_2$)Ethyl-*t*-butylamine

($^{13}C_2$)Iodoethane (0.158 g, 1 mmol) and *t*-butylamine (0.073 g, 1 mmol) in methanol (2 cm^3) were heated in a sealed tube at 90° for 48 h. Removal of methanol at reduced pressure was followed by steam distillation and titration to give *N*-($^{13}C_2$)ethyl-*t*-butylammonium chloride.

Yield: 0.8 mmol, 80% (crude)

The amine was liberated in the usual way. ^{13}C n.m.r. showed that it contained a little diethylated product (~ 15%).

N-($^{13}C_2$)Ethyl-*N*-methyl-*t*-butylamine

This was prepared from the amine described above by the general Eschweiler-Clarke method using boiling under reflux for 5 h and 3 additions of paraformaldehyde.

N-[($^{13}C_2$)Ethyl]trimethylammonium iodide

($^{13}C_2$)Iodoethane (0.078 g, 0.5 mmol) and trimethylamine (25% in water; 1 cm^3) were mixed and methanol was added to form a homogeneous mixture which was left in a sealed tube overnight. The product was obtained by removing solvents and excess trimethylamine at reduced pressure.

Yield: quantitative

(1,2-$^{13}C_2$)Diethylketone and Derivatives

($^{13}C_2$)Iodoethane (0.506 g, 3.2 mmol) was added to magnesium turnings (previously heated with iodine; 0.078 g, 3.25 mmol) in dry ether (10 cm^3). After stirring 2 h under nitrogen, propanal (freshly distilled; 0.295 g, 5 mmol) was added. After stirring 0.5 h the reaction was worked up with saturated aqueous ammonium chloride (10 cm^3); the ether layer was separated and the aqueous layer was extracted with more ether (2 x 10 cm^3). The combined ethereal extracts were dried and some ether was removed by fractional distillation.

The product in ether (5 cm^3) was stirred at 30°C for 2 h with chromic acid [sodium dichromate (4.4 g) and sulphuric acid (98%, 3.72 cm^3) made up to 25 cm^3 in water; 3 cm^3]. The ethereal layer was washed with 2% aqueous potassium hydroxide and dried. After removal of ether by fractional distillation, distillation at 10^{-3} mm gave (1,2-$^{13}C_2$)diethylketone.

Yield: 0.097g, 34%

(a) Oxime

(1,2-$^{13}C_2$)Diethylketone (0.0176 g, 0.2 mmol) and hydroxylammonium chloride (0.014 g, 0.2 mmol) were dissolved in methanol (0.3 cm^3) with one small drop of pyridine. The mixture was heated in a sealed tube at 80°C for 48 h. The resulting solution was used for ^{13}C n.m.r. experiments after dilution.

(b) *N,N*-Dimethylhydrazone

(1,2-$^{13}C_2$)Diethylketone (0.0176g, 0.2 mmol) and *N,N*-dimethylhydrazine (0.012 g, 0.2 mmol) were heated in a sealed tube at 80°C for 48 h. After cooling, excess barium oxide was added and the resulting *N,N*-dimethylhydrazone was distilled and extracted with

(^{2}H)chloroform to give a solution suitable for ^{13}C n.m.r. experiments.

(c) Semicarbazone

(1,2-$^{13}C_2$)Diethylketone (0.0176 g, 0.2 mmol) and semicarbazide hydrochloride (0.022 g, 0.2 mmol) were dissolved in methanol (0.5 cm^3) with one drop of pyridine and heated in a sealed tube for 48 h. The solution was used in the same way as that of the oxime.

Diethyl 1-(2-^{13}C)ethyl-1,1-ethanedicarboxylate

Sodium hydride (50% in oil; 0.24 g, 5 mmol) was washed with dry petroleum ether to remove oil. The dry powder was added under nitrogen to dry *N,N*-dimethylformamide (4 cm^3). The system was kept under nitrogen while diethyl 1,1-ethanedicarboxylate (0.87 g, 5 mmol) was slowly added with stirring, followed by more *N,N*-dimethylformamide (1 cm^3). After stirring for 15 min, water (5 cm^3) and ether (10 cm^3) were added. After separation of the layers, the aqueous layer was extracted with more ether (3 x 10 cm^3). The ethereal extracts were combined, washed with water (2 x 5 cm^3) and dried. The ether was removed by fractional distillation giving diethyl 1-(2-^{13}C)ethyl-1,1-ethanedicarboxylate.

Yield: 0.69 g, 68%

Ethylbenzene and Related Compounds

[($^{13}C_2$)Ethyl]benzene

(Carboxyl-^{13}C)Benzoic acid

This was prepared from phenylmagnesium bromide and (^{13}C)carbon dioxide by the method of Hunt[100] with modifications as described in the Discussion.

Yield: 92.5%

(*Methylene*-^{13}C)Benzyl alcohol

This was prepared by the method of Hunt [100] from (*carboxyl*-^{13}C)benzoic acid by lithium aluminium hydride reduction but sulphuric rather than hydrochloric acid was used in the work-up (see Discussion). The alcohol contained traces of ether.

(*Methylene*-^{13}C)Benzyl chloride

To (*methylene*-^{13}C)benzyl alcohol (2.452 g, 22.5 mmol) was added hydrochloric acid (d. 1.18; 3.5 cm^3) and zinc(II) chloride (6 g, 43 mmol). The resulting solution was stirred at 50°C for 6 h then left overnight at room temperature. The supernatant organic layer was extracted with petroleum ether (30 cm^3) and passed through a little potassium carbonate. Solvent was removed by fractional distillation giving (*methylene*-^{13}C)benzyl chloride.

Yield: 2.43 g, 85%

Phenyl($^{13}C_2$)acetonitrile

(*Methylene*-^{13}C)Benzyl chloride (1.805 g, 14.16 mmol) and sodium (^{13}C)cyanide (0.708 g, 14.16 mmol) in aqueous ethanol (water: 4 cm^3, ethanol: 3 cm^3) were boiled under reflux for 4 h. Most of the solvents were removed by fractional distillation and the product was extracted with ether (50 cm^3). After drying, ether was removed by fractional distillation giving crude phenyl($^{13}C_2$)-acetonitrile.

Yield: 1.53 g, 91%

Phenyl($^{13}C_2$)acetic acid

Phenyl($^{13}C_2$)acetonitrile (0.238 g, 2 mmol) was sealed in a tube with water (0.4 cm^3) and sulphuric acid (d. 1.84; 0.4 cm^3) and the mixture was heated at 130-140°C overnight. Extraction with

ether (3 x 10 cm^3), followed by drying and removal of ether at reduced pressure gave phenyl($^{13}C_2$)acetic acid.

Yield: 0.248 g, 90%

Ethyl phenyl($^{13}C_2$)acetate

This was prepared in an analogous way by including ethanol (0.4 cm^3) in the reaction mixture described directly above.

Yield: 81%

2-Phenyl($^{13}C_2$)ethanol

This was prepared by lithium aluminium hydride reduction of phenyl($^{13}C_2$)acetic acid in the same way that (*methylene*-^{13}C)benzyl alcohol was prepared from (*carboxyl*-^{13}C)benzoic acid.

2-Phenyl-1-iodo($^{13}C_2$)ethane

To 2-phenyl($^{13}C_2$)ethanol (3.72 g, 30 mmol) was added hydriodic acid (d.1.94; 30 cm^3). After boiling under reflux for 1 h the apparatus was set for distillation; after a little iodoethane (derived from traces of ether) had been removed in the distillate, the mixture was exhaustively distilled in steam with addition of water when required. The distillate was extracted with petroleum ether (2 x 50 cm^3) and the combined extracts were washed with 2% aqueous potassium hydroxide then passed through a short column of potassium carbonate. Petroleum ether was removed by fractional distillation giving 2-phenyl-1-iodo($^{13}C_2$)ethane.

Yield: 5.62 g, 80%

The compound was also prepared using the procedure described below for 3-phenyl-1-iodo(1,2-$^{13}C_2$)propane (i.e. using extraction from the reaction mixture *followed* by distillation). Its isotopic analogues were prepared by one or other of these methods, from 2-phenylethanol and from 2-phenyl(1-^{13}C)ethanol.

[($^{13}C_2$)Ethyl]benzene

2-Phenyl-1-iodo($^{13}C_2$)ethane (0.468 g, 2 mmol) was dissolved in acetic acid (2 cm^3) and zinc powder (0.65 g, 10 mmol) was added. The mixture was stirred at 80°C while hydrogen chloride gas was bubbled through it for a few minutes during each hour for 8 h. Alkaline steam distillation (cf. amines) yielded [($^{13}C_2$)ethyl]benzene and a little water from which it was separated by distillation from a large excess of barium oxide at 10^{-3} mm.

Yield: 0.135 g, 62.5%

Phenylethylamines

2-Phenyl($^{13}C_2$)ethylamine

Phenyl($^{13}C_2$)acetonitrile (crude; 0.65 g, 5.4 mmol) was dissolved in dry tetrahydrofuran (5 cm^3) and diborane in tetrahydrofuran (1M; 12 cm^3) was added under nitrogen. After heating at 60°C for 2 h under nitrogen, the mixture was cooled and excess methanol followed by hydrochloric acid was cautiously added. Removal of solvents at reduced pressure followed by the general steam distillation and titration gave 2-phenyl($^{13}C_2$)ethylammonium chloride.

Yield: 3.67 mmol, 68%

The free amine was extracted into an appropriate deuteriated solvent for ^{13}C n.m.r. experiments and not distilled from barium oxide since this caused complete decomposition.

N-Methyl-2-phenyl-($^{13}C_2$)ethylamine

2-Phenyl($^{13}C_2$)ethylammonium chloride (0.127 g, 0.8 mmol) was stirred overnight with a large excess of ethyl chloroformate

and saturated aqueous potassium carbonate. The mixture was extracted with ether (3 x 20 cm^3), the combined extracts were dried and most of the ether was removed by fractional distillation to give crude *N*-ethoxycarbonyl-2-phenyl($^{13}C_2$)ethylamine which was added to lithium aluminium hydride (0.114 g, 3 mmol) in dry ether (10 cm^3). After boiling under reflux for 24 h, the mixture was cooled, worked up with 50% aqueous potassium hydroxide and extracted with ether (3 x 10 cm^3). The combined extracts were dried and titrated with hydrochloric acid giving *N*-methyl-2-phenyl($^{13}C_2$)ethylammonium chloride.

Yield: 0.6 mmol, 75%

The amine was obtained in the same way as the unmethylated analogue.

N,N-Dimethyl-2-phenyl($^{13}C_2$)ethylamine

This was prepared from 2-phenyl($^{13}C_2$)ethylamine by the general Eschweiler-Clarke reaction.

Yield: 75%

[($^{13}C_2$)Ethyl]mesitylene :(2,4,6-trimethyl[($^{13}C_2$)ethyl]benzene)

(*Carboxyl*-^{13}C)Mesitoic acid

This was prepared from mesitylmagnesium bromide and (^{13}C)carbon dioxide in the same way that (*carboxyl*-^{13}C)benzoic acid was prepared from phenylmagnesium bromide and (^{13}C)carbon dioxide except that a little iodomethane was needed to initiate formation of the Grignard reagent.

Yield: 82.6%

(*Carbonyl*-^{13}C)Mesitoyl chloride

(*Carboxyl*-^{13}C)Mesitoic acid (1.52 g, 9.2 mmol) was boiled under reflux with thionyl chloride (7 g, 59 mmol) for 4 h and excess thionyl chloride was removed at reduced pressure, using evaporation with several portions of tetrachloromethane (analytical grade).

Yield: 1.647 g, 90%

Mesityl(^{13}C)methyl(*carbonyl*-^{13}C)ketone

(^{13}C)Iodomethane (1.287 g, 9 mmol) was added to magnesium turnings (previously heated with iodine; 0.24 g, 10 mmol) in dry ether (10 cm^3) at 0°C and the mixture was stirred for 0.5 h under nitrogen.

(*Carbonyl*-^{13}C)Mesitoyl chloride (1.647g, 8.26 mmol), obtained as described, was slowly added in ether (20 cm^3) at 0°C and the mixture was stirred 0.5 h. The reaction was worked up with excess saturated aqueous tartaric acid and the ethereal layer was separated. The aqueous layer was extracted with more ether (3 x 10 cm^3) and the combined ethereal extracts were washed with 2% aqueous potassium hydroxide before drying. Removal of ether by fractional distillation gave mesityl(^{13}C)methyl(*carbonyl*-^{13}C)ketone.

Yield: 0.72g, 54%

[($^{13}C_2$)Ethyl]mesitylene

The mesityl(^{13}C)methyl(*carbonyl*-^{13}C)ketone (0.72 g, 4.4 mmol), obtained as described, was boiled under reflux with amalgamated zinc granules [139b] (2.5 g) in hydrochloric acid (2.5 M, 8 cm^3) for 170 h. The apparatus was set for distillation and the distillate was extracted with tetramethylsilane (2 x 2 cm^3) which was evaporated to

give [($^{13}C_2$)ethyl]mesitylene.

Yield: 0.178 g, 27%

Indan and Related Compounds

3-Phenyl(1,2-$^{13}C_2$)propanoic acid

This was prepared from 2-phenyl-1-iodo(1-^{13}C)ethane *via* a Grignard reaction in the same way that (*carboxyl*-^{13}C)benzoic acid was prepared from bromobenzene.

Yield: 90%

3-Phenyl(1,2-$^{13}C_2$)propanoyl chloride

This was prepared from 3-phenyl(1,2-$^{13}C_2$)propanoic acid in the same way that (*carbonyl*-^{13}C)mesitoyl chloride was prepared from (*carboxyl*-^{13}C)mesitoic acid, except that only 2 h heating was employed.

Yield: 92%

(1,2-$^{13}C_2$)Indan-1-one

To 3-phenyl(1,2-$^{13}C_2$)propanoyl chloride (0.604 g, 3.2 mmol) in petroleum ether was added aluminium(III) chloride (1 g, 7.5 mmol) in portions, with stirring. After 10 min, water (5 cm^3) and ether (10 cm^3) were added. The ethereal layer was separated and solvents were removed at reduced pressure. Aqueous sodium carbonate was added and the mixture was distilled in steam. The distillate was extracted with ether (20 cm^3), the ethereal extract was dried and the ether was removed at reduced pressure to give (1,2-$^{13}C_2$)indan-1-one.

Yield: 0.351 g, 81%

(1,2-$^{13}C_2$)Indan

The (1,2-$^{13}C_2$)indan-1-one, obtained as described, was mixed with zinc amalgam (1.3 g) in hydrochloric acid (2.5 M; 1.5 cm^3) and the mixture was boiled under reflux for 4 h. Distillation from the mixture yielded (1,2-$^{13}C_2$)indan which was extracted directly into ($^2H_2$)dichloromethane for ^{13}C n.m.r. experiments.

1-Methyl(1,2-$^{13}C_2$)indan

(1,2-$^{13}C_2$)Indan-1-one (0.2 g, 1.5 mmol) in dry ether (1 cm^3) was added to methylmagnesium iodide prepared as described above from magnesium turnings (0.096 g, 4 mmol) and iodomethane (0.568 g, 4 mmol) . After boiling under reflux for 1 h, the mixture was cooled and worked up with saturated aqueous ammonium chloride (10 cm^3). The ethereal layer was separated and the aqueous layer was extracted with more ether (2 x 10 cm^3). The combined ethereal extracts were dried and removal of ether by fractional distillation gave 1-methyl(1,2-$^{13}C_2$)indan-1-ol which on shaking for 10 min with 2 drops of sulphuric acid (5 M) gave 1-methyl(1,2-$^{13}C_2$)-indene. (The latter two products were characterized by ^{13}C n.m.r. analysis). After hydrogenation in acetic acid (1 cm^3) using platinum oxide (20 mg), ether (10 cm^3) was added and the mixture was filtered and washed with 2% aqueous potassium hydroxide until the aqueous layer was alkaline (phenolphthalein as indicator). The ethereal layer was dried and the ether was removed by fractional distillation to give 1-methyl(1,2-$^{13}C_2$)indan.

Yield: 0.093 g, 46%

Piperidines Isotopically Substituted in the Ring

(2,3-$^{13}C_2$)Piperidine

3-Phenyl(1-^{13}C)propanol

This was prepared by lithium aluminium hydride reduction of 3-phenyl(1-^{13}C)propanoic acid, in a way directly analogous to the preparation of (*methylene*-^{13}C)benzyl alcohol. The acid was prepared from 2-phenyl-1-iodoethane (prepared as described above) via a Grignard reaction which was directly analogous to that used to prepare 3-phenyl(1,2-$^{13}C_2$)propanoic acid and homologous acids.

3-Phenyl-1-iodo(1-^{13}C)propane

3-Phenyl(1-^{13}C)propanol (12.475 g, 91 mmol) was boiled under reflux for 2 h with hydriodic acid (d. 1.94, 125 cm^3). After cooling, petroleum ether (30 cm^3) was added, the layers were separated and the aqueous layer was extracted with more petroleum ether (2 x 20 cm^3). The combined extracts were washed with 2% aqueous potassium hydroxide then brine, shaken with potassium carbonate, passed through a short column of neutral alumina and dried over magnesium sulphate. Removal of solvent by fractional distillation followed by distillation at 10^{-3} mm gave 3-phenyl-1-iodo(1-^{13}C)propane.

Yield: 19.74 g, 87.4%

Sodium 4-phenyl(1,2-$^{13}C_2$)butanoate

This was prepared, via a Grignard reaction, from the compound described directly above. However, unlike the analogous reactions used to prepare homologous acids, this reaction went in low yield. Large amounts of a byproduct, apparently 1,6-diphenyl(3,4-$^{13}C_2$)hexane, were formed.

(1,2-$^{13}C_2$)Glutaric acid: [(1,2-$^{13}C_2$)-1,5-pentanedioic acid]

Sodium 4-phenyl(1,2-$^{13}C_2$)butanoate (4.324 g, 23 mmol) and ruthenium(III) chloride (0.023 g) were dissolved in water (312 cm^3). Sodium hypochlorite (1.475 M; 218 cm^3) was added and the solution was stirred for 40 h. The pH was brought to 2 with hydrochloric acid (5 M) and the solution was flushed with nitrogen for 1 h. Sodium hydroxide (2 g) was added, followed by hydrogen peroxide (33%; 40 cm^3) and the solution was stirred for 24 h. The pH was brought to 1 with hydrochloric acid (5 M) and water was removed at reduced pressure. After desiccation, the residual solids were ground and extracted with dry ether (200 cm^3) in a Soxhlet extractor for 5 h, during which time the extraction was stopped twice to regrind the solids. Ether was removed at reduced pressure giving crude (1,2-$^{13}C_2$)glutaric acid.

Yield: 2.575 g, 83% (including traces of benzoic acid and approximately 15% of (1,2-$^{13}C_2$)succinic acid, as judged by ^{13}C n.m.r. analysis of (2,3-$^{13}C_2$)piperidine prepared subsequently).

Monoamide of (1,2-$^{13}C_2$)Glutaric acid

(1,2-$^{13}C_2$)Glutaric acid (crude; 1,206 g, 9 mmol) was stirred with trifluoroacetic anhydride (10 cm^3) for 0.75 h. Excess trifluoroacetic anhydride was removed *in vacuo*. The residues were dissolved in dichloromethane (30 cm^3) and poured into distilled liquid ammonia (50 cm^3). After allowing excess ammonia to evaporate, dichloromethane was removed at reduced pressure and water (50 cm^3) followed by hydrochloric acid (12 cm^3) was added. The aqueous solution was washed with ether (20 cm^3) then the water was removed at reduced pressure. Brine was added and water was removed again. This step was repeated, giving a product friable enough to be

transferred to a Soxhlet thimble. The product was extracted in the same way as described for (1,2-$^{13}C_2$)glutaric acid to give the crude monoamide of (1,2-$^{13}C_2$)glutaric acid.

Yield: 1.022g, 85%

(2,3-$^{13}C_2$)Piperidine

The monoamide of (1,2-$^{13}C_2$)glutaric acid (1.022 g, 7.68 mmol), obtained as described above, was dissolved in dry tetrahydrofuran (15 cm^3) and diborane in tetrahydrofuran (1 M; 50 cm^3) was added under nitrogen at 0°C. The mixture was boiled under reflux for 5 h, then cooled, and more diborane in tetrahydrofuran (1 M; 15 cm^3) was added. After boiling under reflux for 10 h the mixture was cooled and excess methanol was cautiously added, followed by hydrobromic acid (48%; 1.2 cm^3). After removing most of the solvents at reduced pressure, more hydrobromic acid (48%; 10 cm^3) was added. Traces of volatile material were removed by distillation then the general, alkaline, steam distillation and titration gave (2,3-$^{13}C_2$)piperidinium chloride containing approximately 15% of (2,3-$^{13}C_2$)pyrrolidinium chloride by ^{13}C n.m.r. analysis.

Yield: 3.7 mmol, 48% (34% from sodium 4-phenyl(1,2-$^{13}C_2$)-butanoate. Previous yield of piperidine from commercial 4-phenylbutanoic acid was 74%).

N-Methyl(2,3-$^{13}C_2$)piperidine

This was prepared from (2,3-$^{13}C_2$)piperidine using the general Eschweiler-Clarke reaction.

9-Methyl-9-azabicyclo(1,2-$^{13}C_2$)[3,3,1]nonane : [*N*-Methyl($^{13}C_2$)granatanine]

(1,2-$^{13}C_2$)Glutaryl dichloride:[(1,2-$^{13}C_2$)pentanedioyl dichloride]

Crude (1,2-$^{13}C_2$)glutaric acid, obtained as described above, was recrystallized several times from benzene. To the acid (1.34 g, 10 mmol) was added oxalyl chloride (4 cm^3) and 2 drops of triethylamine. The mixture was stirred and warmed while effervescence occurred then boiled under reflux for 2.5 h. Excess oxalyl chloride was removed *in vacuo* to give crude (1,2-$^{13}C_2$)glutaryl dichloride.

Yield: quantitative

(1,2-$^{13}C_2$)Glutaric dialdehyde:[(1,2-$^{13}C_2$)pentanedial]

The crude (1,2-$^{13}C_2$)glutaryl dichloride, obtained as described above, was dissolved in acetone (10 cm^3) and added over 10 min to a stirred slurry of bis(triphenylphosphine)copper(I) tetrahydroborate[132] (13.26 g, 22 mmol) and powdered triphenylphosphine (11.53 g, 44 mmol) in acetone (40 cm^3). The mixture was stirred for 2 h then filtered; the filter cake was washed with water (50 cm^3) and the combined acetone/water filtrate was refiltered. Acetone was removed from the filtrate at or below room temperature at reduced pressure leaving a solution of crude (1,2-$^{13}C_2$)glutaric dialdehyde in water (35 cm^3).

From previous experiments using isotopically normal materials the yield of glutaric dialdehyde (estimated as the 2,4-dinitrophenylhydrazone) was 60% from glutaric acid.

9-Methyl-9-azabicyclo(1,2-$^{13}C_2$)[3,3,1]nonan-3-one: [($^{13}C_2$)Pseudopelletierine]

To the solution of (1,2-$^{13}C_2$)glutaric dialdehyde in water (35 cm^3), obtained as described above, was added methylammonium chloride (recrystallized from ethanol; 1g, 14.8 mmol), 1,3-acetonedicarboxylic acid [3-ketopentanedioic acid] (freshly recrystallized from ethyl acetate; 1.665 g, 11.4 mmol), disodium hydrogen phosphate (0.71 g, 5 mmol) and sodium hydroxide (0.144 g, 3.6 mmol). The resulting solution was stirred under nitrogen for 20 h. Hydrochloric acid (d. 1.18; 0.67 cm^3) was added and the solution was stirred and heated at 70-80°C for 1 h (when evolution of carbon dioxide had ceased.) After cooling, sodium hydroxide (1.5 g) in water (2 cm^3) was added and the mixture was promptly extracted with dichloromethane (5 x 30 cm^3). The combined extracts were rapidly shaken with sodium sulphate then neutral alumina and the solvent was removed at reduced pressure to give crude ($^{13}C_2$)pseudopelletierine.

Yield: 0.45 g, 64.5%

N-Methyl($^{13}C_2$)granatanine

To the crude ($^{13}C_2$)pseudopelletierine, obtained as described above, was immediately added diethylene glycol (12 cm^3) and hydrazine hydrate (1.5 cm^3). After boiling under reflux for 10 min, the solution was cooled and potassium hydroxide (1.5 g) and more hydrazine hydrate (0.7 cm^3) were added. The mixture was slowly distilled until the still-head temperature was 200°C. The distillate was extracted with petroleum ether (50 cm^3), the extract was washed with water (3 cm^3) and this extraction

was repeated. The combined petroleum ether extracts were titrated with hydrochloric acid giving *N*-methyl($^{13}C_2$)granatanine hydrochloride.

Yield: 2.0 mmol, 20% from (1,2-$^{13}C_2$)glutaric acid

The amine was further purified by steam distillation and retitration then liberated in the usual way.

m.p. = 52-52.5°C lit.[136] 49-50°C

9-Azabicyclo(1,2-$^{13}C_2$)[3,3,1]nonane : [($^{13}C_2$)Granatanine]

N-Methyl($^{13}C_2$)granatanine (0.127 g, 0.9 mmol) and benzene selenol (0.2 cm^3) were sealed in a tube under nitrogen and heated at 150°C for 48 h. After chilling, the tube was opened and the contents were extracted with several portions of ether and water (total 30 cm^3 of each). After addition of hydrochloric acid to give pH=1 the aqueous layer was separated and the mixture was distilled in steam to remove impurities. This was followed by the general, alkaline, steam distillation and titration to give ($^{13}C_2$)granatanine hydrochloride.

Yield: 0.6 mmol, 67%

The amine was liberated in the usual way.

m.p. = 73-73.5°C lit.[137] 50-60°C

N-Chloro(2,3-$^{13}C_2$)piperidine

This was prepared by Dr. M.J.T. Robinson by his published method[75] using ($^2H_2$)dichloromethane as the solvent for reaction. The solution was used immediately for low temperature ^{13}C n.m.r. experiments (< 0°C) and the parent amine was recovered in 40% yield by hydrolysing the *N*-chloroamine by stirring the solution with hydriodic acid (d. 1.94) followed by the general alkaline steam distillation.

Ethylcyclohexanes

r-1,*c*-3,*c*-5-Trimethyl-*c*-6-[($^{13}C_2$)ethyl]cyclohexane

[($^{13}C_2$)Ethyl]mesitylene (0.09 g, 0.6 mmol) was hydrogenated during 40 h in acetic acid (0.25 cm^3) using platinum oxide (50 mg). ($^2H_2$)Dichloromethane (1 cm^3) was added and the mixture was washed with 2% aqueous potassium hydroxide until the aqueous layer was alkaline (phenolphthalein as indicator). The ($^2H_2$)-dichloromethane layer was removed and dried over potassium carbonate while the aqueous layer was extracted with more ($^2H_2$)dichloromethane. The second extract was dried and combined with the first. ^1H and ^{13}C n.m.r. analysis showed that about 20% of the product was unchanged starting material.

[($^{13}C_2$)Ethyl]cyclohexane

To magnesium turnings (previously heated with iodine; 0.053 g, 2.2 mmol) was added ($^{13}C_2$)iodoethane (0.316 g, 2 mmol) in dry ether (2 cm^3) with ice-cooling. After stirring for 1 h under nitrogen, saturated aqueous ammonium chloride (5 cm^3) was added and the ethereal layer was separated. The aqueous layer was extracted with ether (2 x 6 cm^3) and the ethereal extracts were combined and stirred with sodium hydrogen sulphite in water (nearly saturated; 5 cm^3) overnight. The ethereal layer was separated and dried. Ether was removed by fractional distillation then at reduced pressure to give 1-[($^{13}C_2$)ethyl]cyclohexanol (0.26 g, 72%). This was mixed with potassium hydrogen sulphate (freshly fused and ground; 4 g) and the mixture was heated in a sealed tube at 100°C for 60 h. 1-[($^{13}C_2$)Ethyl]-cyclohexene (0.08g, 50%) was distilled out of the tube at 10^{-3} mm.

This was hydrogenated during 2 h in acetic acid (0.7 cm^3) using platinum oxide (20 mg). The product was extracted in the manner described for the compounds directly above except that more concentrated potassium hydroxide was used. It was characterized by ^{13}C n.m.r. analysis.

APPENDIX 1

Techniques used in Least Squares Curve Fitting and the Measurement of $^1J_{CC}$ ($^1J_{CH}$, $^1J_{CF}$)

The methods used to obtain values of $^1J_{CC}$ as a function of temperature are described below. Initially it was thought that least squares fitting (LSF) to free induction decays would be a valuable method since in this way all the information gained during an accumulation would be used. It was found, however, that the method was only successful when quite exceptionally good resolution was available, so it was not used further. For most of the work LSF to the transformed spectra was used. The raw data consisted of real and imaginary parts of a spectrum which usually contained two major signals but sometimes up to eight. A program was written by Dr. M.J.T. Robinson to transfer the relevant data from the Nicolet B-NC 12 computer via a 16-bit parallel interface to the Hewlett Packard 9825A calculator, there to be recorded on tape before processing. The listing of the program is given below, under the title 'Transfer Program'.

The program transfers the real and imaginary parts of whichever signal is specified by the user; as many data points per signal as are required may be specified. This is shown schematically in Figure 23.

A second program, also written by Dr. M.J.T. Robinson, is listed under the title 'LSF to a Lorentzian'. This program uses a method for minimising the sum of the squares of the residuals involving the first and second derivatives of the sum of the squares with respect to the parameters (phase angle, baseline, line position,

Transfer Program

```
0: "Prosram 0810
 :31/5/80:MJTR:
 Variation for
 array data":
1: "Real/ima9.
 data transfer":
2: dim A,B,C,D,
 E,F,H,I,J,K,M,
 Q,T,U,W,X,Y
3: dim B$[12,
 16],C$[32],D$[3
 2],E$[16],Y$[16
 ],Z$[64],G[11]
4: for I=1 to
 12:" "→B$[I,1,
 16]:next I
5: "SF/MHz="→B$[
 1,1,7]:22.63→G[
 1]
6: "BW/ s="→B$[2
 ,1,6]:char(12)+
 B$[2,4,4]
7: "Real data="+
 B$[3,1,10]:4096
 →G[3]
8: "No. lines="+
 B$[6,1,10]
9: "No. segments
 ="→B$[7,1,13]
10: "+-  ="→B$[8
 ,1,5]:char(8)→B
 $[8,3,3]
11: "      Tape
    "→B$[9]:"
    JCJB FT 9"→Y$
12: "trk ="→B$[1
 0,1,5]
13: "File no.
 ="→B$[11,1,10]
14: "Real/imag
 data transfer
 (WH90) for o
 series of
 spectra"→Z$
15: "Start at
   K  Block size
 =   K "→D$
16: prt Z$:spc
 2:dsp Z$:stp
17: beep:dsp
 "Prepare for
 1st spectrum":
 stp
18: dsp "Enter
 conditions":
 wait 1000:sfg 1
19: for J=1 to
 10:fxd 0:if
 I=1:fxd 4
20: if I=9:prt
 B$[9]:Y$:spc :
 next I
21: if I=4 or
 I=5:next I
22: G[I]→X:dsp
 B$[I]:X:ent "",
 X
23: if I#1 and
 X#0:if X#int(X)
 :beep:jmp -1
24: if I=2:if
 X<80 or X>1000
 :beep:jmp -2
25: if I=5:if
 X<1 or X>4096:
 beep:jmp -3
26: if I=6:if
 X<1 or X>10:
 beep:jmp -4
27: if I=7:if
 X<1 or X>G[6]:
 beep:jmp -5
28: if I=8:if
 X<1:beep:jmp -6
29: if I=10:if
 (X#0)+(X#1)-1:
 beep:jmp -7
30: str(X)→B$[I,
 17-len(str(X)),
 16]
31: prt B$[I]:
 X→G[I]:if I=9:
 prt Y$:spc
32: next I
33: "F":fxd 0:
 dsp "Enter ",
 B$[11];ent "",X
34: X→G[11]:str(
 X)→B$[11,17-
 len(str(X)),
 16]:prt B$[11]:
 spc :""→Z$
35: ent "Title
 (<65 char.)",
 Z$:if fl≠13:
 beep:jmp 0
36: if fl≠1:dim
 P[40[6]],H[4,
 G[7]]
37: prt Z$:spc 2
38: dsp "Enter
 lines in increa
 sing M.A.":wait
  1000
39: prt " Li
 max. int. w
 ne          1/
 2":spc :fxd 0
40: 1→M
41: for I=1 to
 G[6]
42: " "→E$[1,16]
43: str(I)→E$[4-
 len(str(I)),3]
44: dsp "Line ",
 I," max. =";
 ent "",X:if
 fl≠13:beep:jmp
 0
45: cll '?m'(X,
 M,G[3],0):jmp 0
46: str(X)→E$[9-
 len(str(X)),8]
47: X→N→P[4]-1]
48: 0→X:dsp "Lin
 e",I," ipt.=";
 ent "",X:if
 fl≠13:0→X:jmp 2
49: cll '?m'(X,
 0,1000,0):jmp 0
50: str(X)→E$[14
 -len(str(X)),
 13]
51: X→P[4]-3]
52: 0→X:dsp "Lin
 e",I," wl/2→";
 ent "",X
53: cll '?m'(X,
 0,99,0):jmp 0
54: str(X)→E$[17
 -len(str(X)),
 16]:X→P[4]-2]
55: prt E$
56: next I
57: spc
58: 1→M:if G[0]=
 G[7]:for I=1
 to G[7]:I→H[1,
 I]:next I:sto
 70
59: prt "Seg.
 from  to":spc
60: " "→E$[1,16]
61: for I=1 to
 G[7]
62: dsp "Segment
 ",I,", line",M,
 " to line=";
 ent "",X
63: cll '?m'(X,
 M,G[6]-G[7]+I,
 0):jmp 0
64: X→H[1,I];
 str(I)→E$[4-
 len(str(I)),3]
65: str(M)→E$[10
 -len(str(M)),9]
66: str(X)→E$[16
 -len(str(X)),
 15]
```

Transfer Prog. contd.

```
67: prt E$;X+1→M
68: next I
69: spc:if M#G[
 6]+1;sto "?S"
70: 1→M;0→H
71: for I=1 to
 G[7]
72: P[4M-1]-G[8]
 →H[2,I]→X
73: H[1,I]→M
74: (P[4M-1]:
 G[8]→H[3,I])-X+
 1→W→H[4,I]:M+
 1→M
75: W+H→H
76: next I
77: if fl#1:cfl
 1;dim I[H],J[H]
 ;H→G[9]
78: H[2,I]→X:
 0→A:1024→Y
79: if X<1:jmp 5
80: for I=1 to 6
81: if X<A:A-
 Y→A:jmp 4
82: A+Y→A
83: next I
84: dsp "Error
 in H  array!";
 stp ;jmp 0
85: A→B:H[3,G[7]
 ]→X:if X<B:jmp
 -1
86: for I=1 to 7
87: if X<B:jmp 4
88: B+Y→B
89: next I
90: if B>8Y:jmp
 -6
91: jmp 2
92: "R"→Z$[len(Z
 $)+1,len(Z$)+1]
93: prt "   Bruk
 er TD:";spc
94: fxd 0:str(A/
 Y)→D$[14-len(st
 r(A/Y)),13]
95: str((B-A)/
 Y)→D$[30-len(st
 r((B-A)/Y)),29]
96: prt D$;spc
 2:dsp D$;stp
97: 0→C→E
98: for I=1 to
 G[7]
99: H[2,I]-A-1→D
100: if D=C:jmp
 5
101: dsp "Unwant
 ed data"
102: for J=C+1
 to D
103: for K=1 to
 4:rdb(9)→T:next
  K
104: next J
105: fxd 0:dsp
 "Segment";I
106: for J=1 to
 H[4,I]
107: cll 'rdb';
 T→I[J+E→N]
108: cll 'rdb';
 T→J[N]
109: next J
110: H[3,I]-A→C:
 H[4,I]+E→E
111: next I
112: dsp "Unwant
 ed data"
113: for J=C+1
 to B-A
114: for K=1 to
 4:rdb(9)→T:next
  K
115: next J
116: ent "Tr.
 complete:auto-
 rcf?";X:cll
 '?';jmp X
117: "rar":esb
 "ar"
118: trk G[10];
 rcf G[11],Y$,
 Z$,C[*]
119: rcf G[11]+
 1,P[*],H[*],I[*
 ],J[*]
120: prt B$[9],
 Y$,"trk",G[10],
 "rcfA",G[11],
 "rcfB",C[11]+1;
 spc
121: ent "Repeat
  spectrum?";X;
 cll '?';jmp X
122: prt "  *  *
   *  *";spc ;
 prt "Repeat";
 spc ;G[11]+2→G[
 11]→X;sto 92
123: "Next spect
 rum?"→E$:dsp
 E$;ent "",X;
 cll '?';jmp X
124: prt "  ****
 ********";spc ;
 prt E$[1,13];
 spc ;G[11]+2→G[
 11]→X;sto 34
125: ent "New
 conditions?";X;
 jmp X
126: dsp "RUN";
 stp
127: dsp "End";
 stp :end
128: "********":
129: "rdb":rdb(9
 )→T
130: if T<0:-T-
 1→T:jmp 2
131: 65535-T→T
132: rdb(9)→U:-
 U-1→U
133: 65536U+T→T
134: if T>524287
 :T-1048578→T
135: ret
136: "********":
137: "?n":1→C:
 if p1<p2 or
 p1>x3 or int(p1
 )#p1:-1→p4
138: ret
139: "********":
140: "?S":dsp
 "Segments do
 not incl. all
 lines";stp
141: ent "s. f.
 key 1 or 2",X
142: "********":
143: "?":if X#1
 and X#2:0→X
144: ret
145: "********":
146: "or":if
 fl#2:cfl 2:jmp
 5
147: dsp "Seekin
 g null file"
148: trk G[10];
 G[11]→W
149: fdf W:idf
 X,X,X,X:if X#0:
 W+1→W:fdf W:
 jmp 0
150: W→G[11]
151: 32(G[6]+
 G[7])+16H→G
152: dsp "mrk
 new files"
153: trk G[10];
 mrk 1,184,W:if
 W<0:sto "mrk"
154: mrk 1,G,X:
 if X<0:sto "mrk
 "
```

Transfer Prog. end

```
155: dsp "Ready
 for rcf in file
 s",G[11]:G[11]+
 1;stp
156: ret
157: "mrk":if
 G[10]=1;dsp
 "End of tape:
 trk 1 full";
 stp ;jmp 0
158: 1+G[10];
 ent "trk 0 full
 ; auto-rcf on
 trk 1?",X;cll
 "?":jmp X
159: rew;0+G[11]
 ;sf+ 2;gto "rdr
 "
160: dsp "Get
 new tape";stp ;
 jmp 0
+30570
```

LSF to a Lorentzian

```
0: "Program 0813
 ;22'9/80;MJTR":
1: "2 with Basel
 ine":
2: prt "Auto-
 KOMRU:LSF";"
 for Lorentzian
 ";"    lines with
 ";"baseline/2-
 files"
3: src ;rad
4: dim B$[4;16];
 C$[16];F$[13];
 0$[7];R$[9];
 Z[1;1]
5: for I=1 to 4;
 " "→B$[I;1;16];
 next I
6: "trk"→B$[1;1;
 3]
7: "ldf"→B$[2;1;
 3]
8: "Omit first"→
 B$[3;1;10]
9: "Omit last"→B
 $[4;1;9]
10: "      sesme
 nt"→C$[1;13]
11: cll 't&f'
12: dim Y$[16];
 Z$[64];G[11]
13: cll 'cf'
14: G[6]→L;G[7]→
 G
15: dim Y[4L];
 H[4;G];I[G[9]];
 J[G[9]]
16: cll 'df'
17: dim A[G];
 S[G];T[G];E[L];
 F[L];K[2;G]
18: cll 'M'
19: max(A[*])→Y
20: 3Y+2→H;0→M→V
 ;1→A
21: dim N[H];
 O[H];P[H];Q[H];
 U[H];V[H];W[H;
 H];X[H;H];D[1;
 H]
22: dim B[Y];
 C[Y]
23: ent "Auto?",
 X;cll '?';jmp X
24: cll 'ou'
25: "dr":ina S;
 0→M→V;dsp "Data
  reduction":
 cfg 1
26: for I=1 to
 G[7]
27: I[V+1]→X;
 J[V+1]→Z
28: for J=V+2
 to V+H[4;I]
29: Z+J[J]→Z;if
 I[J]→Y)X;Y→X
30: if Y>S[I];
 Y→S[I]
31: next J
32: S[I]-X→S[I];
 1/S[I]→Y;int(Z/
 H[4;I])→Z
33: for J=V+1
 to V+H[4;I]
34: (I[J]-X)Y→I[
 J];(J[J]-Z)Y→J[
 J]
35: next J
36: for J=1 to
 A[I]
37: Y[4(N+J)-1]-
 H[2,I]+1→X
38: V+X→X
39: I[X]>S;1+
 X→X;if I[X]>S;
 sfg 1;jmp 0
40: if flg1;X-
 1→X;jmp 3
41: I[X]→S;X-
 1→X;if I[X]>S;
 jmp 0
42: X+1→X
43: cll '1/2'
44: next J
45: V+H[4;I]→V;
 H[1;I]→M
46: next I
47: for I=1 to
 G[7];for J=1
 to A[I]
48: cll '?Y'
49: next J;next
 I
50: 0→M→V;1→A;
 if flg9;ret
51: "C":dsp "S.f
 .k.s";stp
52: "f2":cfg 9;
 cll 'CS'
53: "f3":cll
 's';0→r15→r16
54: ent "Limit
 data?",X;cll
 '?';jmp X
55: cll 'LD'
56: ent "Plot?",
 X;cll '?';jmp X
57: cfg 11,13;
 cll 'plt'
58: cll 'F3';
 sto 51
59: "f5":cll
 'plt';sto 51
60: "f7":cll
 'LD';sto 51
61: "f10":cll
 'Opt';cll 'prt'
 ;cll 'plt?';
 sto 51
62: "f11":cll
 'prt';sto 51
63: "f13":cll
 'rar';sto 51
64: "f16":cll
 'NS';sto 51
65: "f19":cll
 'au';sto 51
66: "f22":cll
 'j';sto 51
67: "f23":cll
 'pir';sto 51
68: "f15":sfg 7;
 fxd 0;prt "Segm
 ent";A;prt B$[3
 ],B$[4];src ;
 jmp 2
69: "F3":cfg 7
70: A[A]→Y;2+
 3Y→H
71: rdm N[H];
 O[H];P[H];Q[H];
 U[H];V[H];W[H;
 H];X[H;H];D[1;
 H]
72: rdm B[Y];
 C[Y]
73: W[2,A]→E
74: 0→P[1]→P[H]
75: for I=1 to
 A[A]
76: Y[4(M+I)-1]-
 E+1→P[3I]
77: Y[4(M+I)-
 2]→P[3I+1]
78: Y[4(M+I)-
 3]→P[3I-1]
79: next I
80: W[4,A]→F
81: cll 'Opt';
 cll 'prt'
82: if flg9;ret
83: if flg12;
 cll 'plt?'
84: ent "Re-opt
 with LD?";X;
 cll '?';jmp X
```

```
 85: cll 'LO';
  jmp -4
 86: cfg 11,12;
  if N<G[7];H[1,
  A]+W;V+W[4,A]+V
  'A+1+A;ret
 87: ent "Next
  Spectrum?";X;
  cll '?';jmp X
 88: r12+2+r12;
  cll 'if';cll
  'c1';cll 'df';
  sto 25
 89: dsp "END or
  use s.f.k.s";
  stp ;jmp 0
 90: "Z":0+Z;dsp
  P$&0$&R$
 91: for I=V+r15+
  1 to V+F-r16
 92: T[I]+R;J[I]+
  r1;-r1+Y[1];
  1+W[H];P+P[1]r1
  +R
 93: for J=1 to
  A[A]
 94: cll 'J'
 95: I-V-P[C]+B[J
  ]
 96: 1/(4B[J]B[J]
  /P[D]P[D]+1+C[J
  ])+V[B]
 97: R-P[B]V[B]+R
 98: next J
 99: R-P[H]+R;Z+
  RR+Z
100: if fl#1;
  next I;ret
101: U[1]-RV[1]+
  U[1]
102: U[H]-RV[H]+
  U[H]
103: for J=1 to
  A[A]
104: cll 'J'
105: U[B]-RV[B]+
  U[B]
106: U[C]-R(B[J]
  (8P[B]/P[D]P[D]
  C[J]C[J]+r7)+V[
  C])+U[C]
107: U[D]-R(V[C]
  (B[J]/P[D]+r3)+
  V[D])+U[D]
108: next J
109: for J=1 to
  H
110: for K=J to
  H
111: W[J,K]+V[J]
  V[K]+W[J,K]
112: next K
113: next J
114: if fl#2;
  sto 123
115: for J=1 to
  A[A]
116: cll 'J'
117: W[B,C]-RV[C
  ]/P[B]+W[B,C]
118: W[B,D]-RV[D
  ]/P[B]+W[B,D]
119: W[C,C]-R(V[
  D]^16/P[D]C[J]+
  r5)-r7)>W[C,C]
120: W[C,D]-R(r
  8V[D]r5>r6)-
  2V[C]/P[D])+W[C
  ,D]
121: W[D,D]-R(r3
  r6-3V[D]/P[D])+
  W[D,D]
122: next J
123: next I
124: for I=1 to
  H
125: for J=I+1
  to H
126: W[I,J]+W[J,
  I]
127: next J
128: next I
129: smpx 2U+U
130: smpx 2W+W
131: ret
132: "J":(3J+C)-
  1+B;C+1+D;ret
133: "PH":dsp
  "Rephasing"
134: sin(P[1])+X
  ;cos(P[1])+Y
135: for I=V+1
  to V+F
136: I[1]+R;J[1]
  +S
137: RY+SX+I[1];
  SY-RX+J[1]
138: next I
139: ret
140: "1/2":dsp
  "W1/2";rdm 0[3]
  ,U[3],X[3,3];
  ima X
141: 9+X[1,1];
  60+X[3,1]+X[2,
  2]+X[1,3];708+X
  [3,3];inv X+X
142: ima U
143: for G=-4
  to 4
144: 1/I[X+G]+Y
145: for F=1 to
  3;U[F]+Y+U[F];
  GY+Y;next F
146: next G
147: mat XU+0
148: X+0[2]/20[3
  ]-V+H[2,I]-1+Y[
  4(M+J)-1]
149: 1/(0[1]-
  (0[2]0[2]+Y)/
  40[3])+Y[4(M+
  J)-3]
150: r(Y+40[2]0[
  1]).0[3]+Y[4(M+
  J)-2]
151: rdm 0[H];
  U[H];X[H,H]
152: ret
153: "LO":fxd 0;
  dsp "Omit first
   n data=";ent
  "";X
154: if X<0 or
  X#int(X);beep;
  jmp -1
155: X+r15;fxd
  0;str(X)+B$[3,
  17-len(str(X))]
  ;prt B$[3]
156: dsp "Omit
  last n data:";
  ent "";X
157: if X<0 or
  X#int(X);beep;
  jmp -1
158: X+r16;str(X
  )+B$[4,17-len(s
  tr(X))];prt
  B$[4];spc
159: ret
160: "pip":sfg 4
161: "prt":if
  fl#1;prt "
  INITIAL";jmp 2
162: prt "
  FINAL"
163: prt "
  PARAMETERS";
  spc
164: 1e6/2G[2]G[
  3]+X
165: Z/(F-r15-
  r16-H)+T
166: for I=2 to
  H-3 by 3
167: fxd 4;prt
  "v=";(G[5]-P[I+
  1]-F+1)%+E[A];
  if fl#4;jmp 2
168: prt "+-";
  Xr(W[I+1,I+1]T)
  +F[A]
```

```
169:  spc 5;fxd 4;
 prt  "l=",le-
 3P[I]S[A]+Y;if
 fle1;jmp 2
170:  prt "+-",
 le-3S[A]r(W[I,
 I]T)
171:  spc 5;fxd 4;
 prt  "w1/2=",
 P[I+2]X+W;if
 fle4;jmp 3
172:  prt  "+-",
 X+W[I+2,I+2]T)
173:  prt  "l*w=",
 WY
174:  next  I;cfs
 4;ret
175:  "plto":0+r1
 7+r18;cfs 12
176:  "plt":dsp
 "Change pen";
 stp ;if fle12;
 r15+r17;r16+r18
 ;jmp 8
177:  sfs 12;0+r1
 7+r18
178:  pclr
179:  wrt 705,
 "ip 2000,1500,
 9000,6500"
180:  H[2,A]+E;
 H[4,A]+F
181:  scl E,E-F-
 1,-.1,1.1
182:  fxd 0;xax -
 .1,10,E,E+F-1,5
183:  fxd 2;yax
 E,.1,-.1,1.1,2
184:  for I=V+
 r17+1 to V+F-
 r18
185:  plt E-V+I-
 1,I[I]-P[H],-2
186:  next I
187:  pen
188:  if fle11;
 jmp 7
189:  sfs 11
190:  fxd 0;E+6F/
 7+r25
191:  plt r25;
 1.1,1;lbl Y$
192:  plt r25,1,
 1;lbl "trk";
 G[10]
193:  plt r25,.9,
 1;lbl "file";
 G[11]
194:  plt r25,.8,
 1;lbl "seg";A
195:  ret
196:  "plic":
197:  dsp "Change
  pen for calc.
 spectrum";stp
198:  for I=r17+
 1 to F-r18
199:  0+R
200:  for J=1 to
 A[A]
201:  cll 'J'
202:  I-P[C]+B[J]
203:  I/(4B[J]B[J
 ]/P[D]P[D]+1+C[
 J])+V[B]
204:  R+P[B]V[B]+
 R
205:  next J
206:  plt E+1-1,
 R,-2
207:  next I
208:  pen
209:  dsp "Plot
 ended!";stp
210:  ret
211:  "C9":"Go
 to "+C$[1,6];
 ssb "C5m"
212:  ret
213:  "C5a":dsp
 C$;ent "",A;if
 A<1 or A>G[7]
 or A#int(A);
 beep;jmp 0
214:  0+M+V;if
 A>1;for I=1 to
 A-1;V+H[4,I]+V;
 next I
215:  if A>1;M[1,
 A-1]+M
216:  ret
217:  "Split "+C$
 [1,6];ssb "C5a"
218:  0+M;if A>1;
 M[1,A-1]+M
219:  0+V;if A>1;
 for I=1 to A-1;
 V+H[4,I]+V;next
  I
220:  ret
221:  "Fl":for
 I=1 to H;U[]+D
 [1,I];next I
222:  mat D0+Z;
 mat X0+W;Z[1,
 1]+R
223:  for I=1 to
 H;Q[]+D[1,I];
 next I
224:  mat DV+Z;R-
 .5Z[1,1]+R;(W-
 Z)/R+R
225:  ret
226:  "Ma":2C-0
227:  "Mr":20+01
 fxd 0;sfs 3;
 ora X+W;ora
 0+P;ret
228:  "0":W[1,
 1]+Y;for I=2
 to H;if W[I,
 1]<Y;W[1,1]+Y
229:  if Y<0;-
 2Y+Y
230:  next I;ret
231:  "Om":sfs
 2;.5+0;0+W+Z
232:  "a":ora
 P+0;ima 0,W
233:  cfg 1;cll
 'Z';flt 5;Z+W;
 ora W+X
234:  "c":if .+1=3
 ;cll '0'
235:  sfg 14;inv
 W+W;if fle15;
 sto "Mat inv
 fail"
236:  mat WU+0
237:  for I=2 to
 H-1;if Q[I]>P[I
 ];cll 'Mr';sfg
 3;sto "c"
238:  ora P-0+P;
 cll 't';if fle1
 ;cfg 1;ret
239:  sfg 1;cll
 'Z';cfs 1;flt
 5;dsp "z",Z;if
 fle5;stp
240:  cll '2';
 cll "Fl";cll
 '$';dsp P$80$0R
 $;if R>.75;cll
 '2'
241:  if R<0;cll
 'Ma';sto "c"
242:  if R<.25;
 cll 'Mr';sto
 "c"
243:  "b":T[A]+
 P[1]+T[A];cll
 'PH';0+P[1];
 sto "a"
244:  "d":if Q>1;
 .50+Q;ret
245:  if Q=1;.50+
 Q;cfg 3
246:  ret
247:  "?";if X#1
 and X#2;0+X
248:  ret
```

```
249: "L":if fl=3
 :ret
250: Z^(F-r15-
 r16-H)→T
251: for I=1 to
 H:if (W[I,I]→S)
 <=0:ret
252: if abs(Q[I]
 )>1e-2r(ST):
 ret
253: next I
254: sfs 1:ret
255: "2":if abs(
 (W-T)^Z)=0:cfs
 2
256: ret
257: "$":cll
 'P$':cll '0$':
 cll 'R$':ret
258: "P$":" z"→P$
 [1,1]:" "→P$[2,
 13]:flt 5:str(Z
 )→P$[2,13]:ret
259: "0$":" "→0$
 [1,7]:"0"→0$[2,
 2]:fxd 1:" "→0$
 [3,7]
260: if 0<1e3:
 str(0)→0$[8-
 len(str(0)),7]:
 ret
261: "!"→0$[4,
 4]:ret
262: "R$":" "→R$
 [1,3]:"R"→R$[2,
 2]:fxd 3:" "→R$
 [3,9]
263: if R<100
 and R>-10:str(R
 )→R$[10-len(str
 (R)),9]:ret
264: "!"→R$[4,
 4]:ret
265: "ne":dsp
 B$[6]:ent "",X:
 if X#0 and X#1:
 jmp 0
266: X→r16
267: dsp B$[7]:
 ent "",X:if
 X<0 or X#int(X)
 :jmp 0
268: X→r17:fxd
 0:prt "trk",
 r16:prt "ldf",
 r17:spc
269: gto 20
270: "f22":cll
 'j':gto 51
271: "j":cll
 'j?'(N,0)
272: cll 'jj'(N,
 0):ret
273: "jj":fxd 4;
 prt "J=":E[p1]-
 E[p2]
274: prt " +-";
 r(F[p1]F[p1]+
 F[p2]F[p2])
275: ret
276: "Mat inv
 fail":dsp "MATR
 IX INV. fail,
 CS used?":cfs
 15:stp
277: ent "Ruto:
 last control
 file=":X:cll
 '?n':jmp 0
278: X→r12
279: cll 'LD'
280: 0→Y→M
281: "cf":trk
 r11:ldf r12,Y$,
 2$,G[≠]
282: prt "
 TAPE":spc :prt
 Y$
283: for I=64
 to 1 by -1:if
 2$[I,I]#" ";
 jmp 3
284: next I
285: prt "No
 title!":dsp
 "??":sfs 1:ret
286: prt Z$[1,
 I]:spc
287: ret
288: "df":trk
 r11:ldf r12+1,
 Y[≠],H[≠],I[≠],
 J[≠]:ret
289: "if":trk
 r11:fdf r12;
 idf X,X,X,X:if
 X=0:dsp "End
 of trk":stp
290: ret
291: "t&f":fxd
 0:for I=1 to 2:
 dsp B$[I]
292: ent "",X
293: cll 'trk':
 jmp 0
294: cll 'rI';
 next I
295: spc :ret
296: "trk":1→Q
297: ret
298: "rI":X→r(10
 +I):str(X)→D$[I
 ,17-len(str(X))
 ,16]:prt B$[I]:
 ret
299: spc :ret
300: "au":ent
 "Ruto: last
 control file=":
 X:cll '?n':jmp
 0
301: X→r14
302: ent "on
 trk=":X:cll
 'trk':jmp 0
303: X→r13
304: cll 'LD'
305: ent "Prt
 Js?":X:cll '?':
 jmp X
306: cll 'JJ'
307: dsp "Check
 entries before
 CONTINUE":stp
308: "0→":sfs 9;
 0→M→Y
309: cll 'dr'
310: for A=1 to
 G[7]
311: cll 'f15';
 cll 'Opt'
312: H[1,A]→M;V→
 H[4,A]→V
313: next A
314: for I=1 to
 r20:cll 'jj'(K[
 1,I],K[2,I]);
 next I
315: spc
316: r12+2→r12
317: if r11=r13;
 if r12>r14:dsp
 "END":stp :jmp
 0
318: fdf r12;
 idf X,X,X,X:if
 X=0 and r11=0;
 1→r11:0→r12
319: cll 'cf';
 cll 'rdm':cll
 'df'
320: gto "0→"
321: "rdm":ret
322: "M":0→p1;
 for I=1 to G;
 (H[1,I]→p2)-
 p1→A[I];p2→p1;
 next I:ret
323: "?Y":ret
```

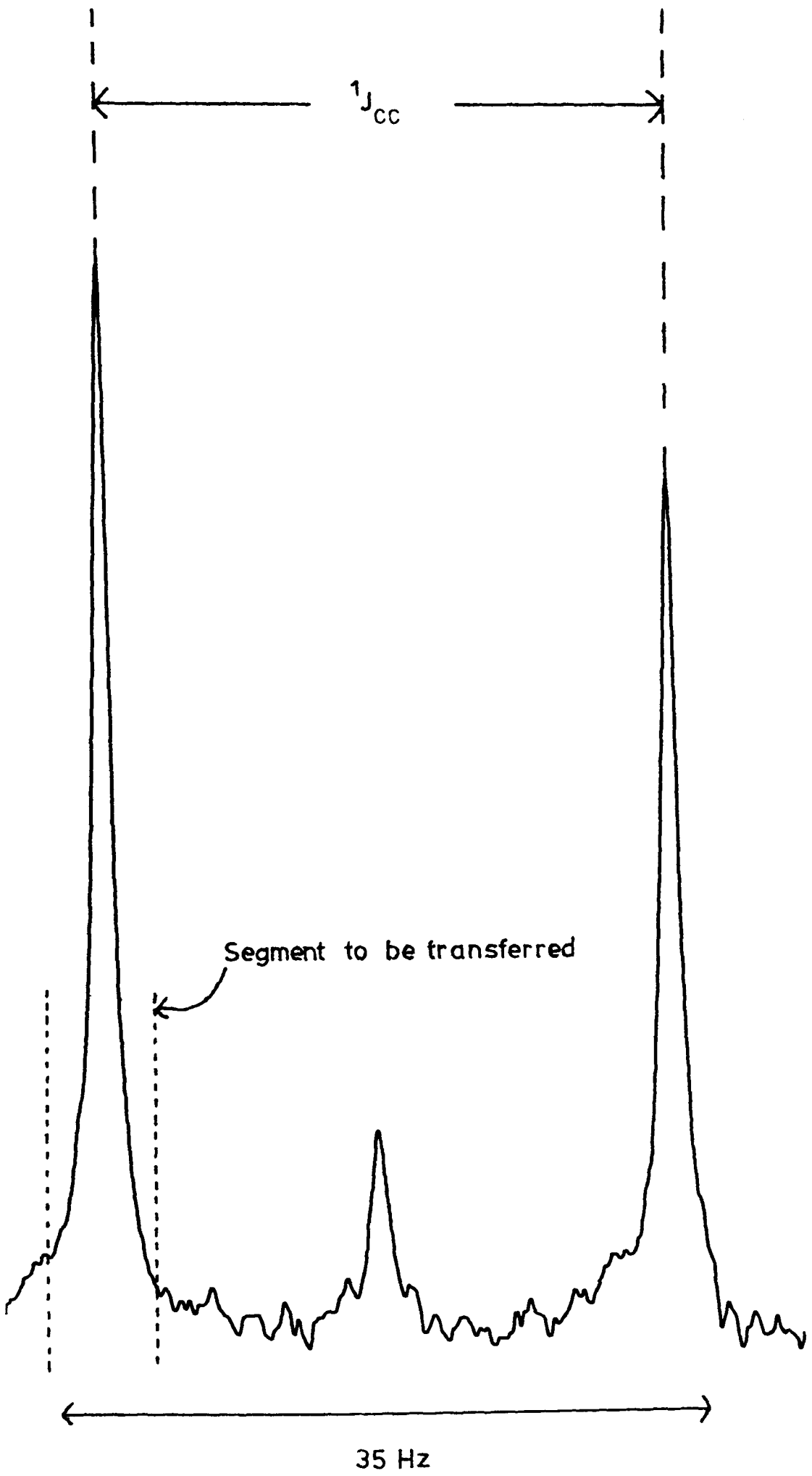
LSF end

```
324: "plt?":ent
 "Plot?";X;cll
 '?';jmp X
325: cll 'plt';
 cll 'plic'
326: ret
327: "s":fxd 0;
 prt "Segment";
 A;ret
328: "?n":ret
329: "J?":ent
 "Calc J for
 line";P;
330: ent "and
 line";P2;ret
331: "JJ":ent
 "No. of Js=";X;
 cll '?n';jmp 0
332: X+r20
333: for I=1 to
 r20;cll 'J?'(K[
 1,I],K[2,I])
 next I
334: ret
+14211
```

Figure 23

The real part of a spectrum

(the right half of an AB quartet)



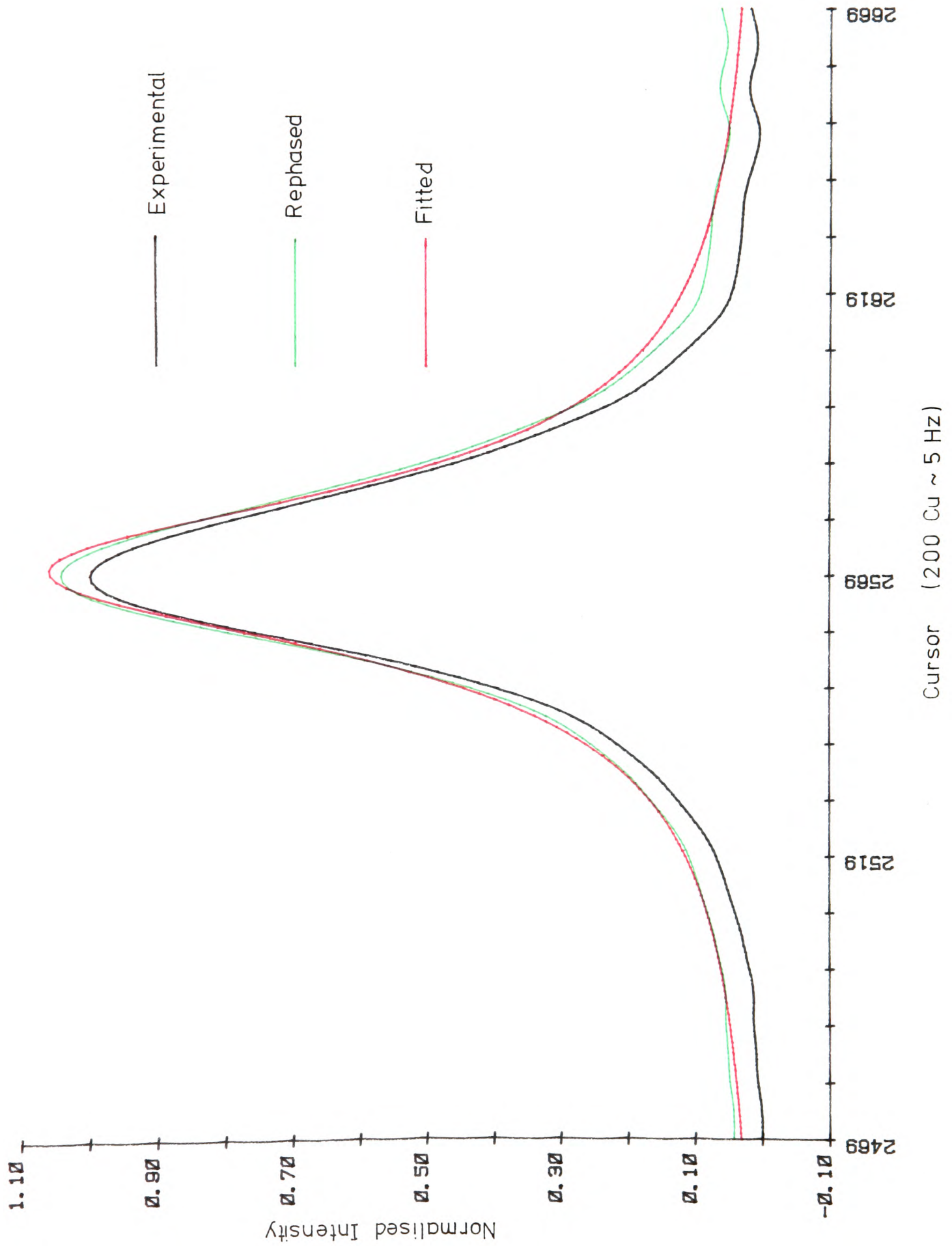
intensity and halfwidth). The matrix of second derivatives at the minimum leads to estimates of the errors. The optimization method used is an improvement of Fletcher's[141] modification of the Marquardt routine.[142] The program allows for varying degrees of user interaction; it provides phase correction to each line, fits it to a Lorentzian and gives line positions, intensities and halfwidths as output. Only the line positions are needed to find $^{1}J_{CC}$ (which can also be computed via the program). A visual indication of the fit is given by an interfaced plotter; an example is shown in Figure 24.

The calculated error for each coupling constant was generally only a few thousandths of one Hertz but the difference between any two measurements at a given temperature was generally greater. Hence the quoted precision is $\pm$ 0.01 Hz. This refers to the precision that could be obtained when the spectra were of good quality which was the case for most compounds at temperatures down to approximately 200 K. In certain cases, particularly for measurements of $^{1}J_{CC}$ for amine and acid salts and for all compounds at low temperatures, the precision is less. (At low temperatures lines are broadened because solvents become viscous and intermolecular interactions, such as hydrogen bonding, increase. This is particularly noticeable for methanol where lines due to amines were broad even at moderately low temperatures). Because of the several factors that give poor resolution, no measurements were made of $^{1}J_{CC}$ as a function of temperature for amine salts and the precision for sodium acetate is lower than for most covalent compounds.

Having obtained usually two values of $^{1}J_{CC}$ for each temperature (T)

Figure 24

Fitting to a Lorentzian

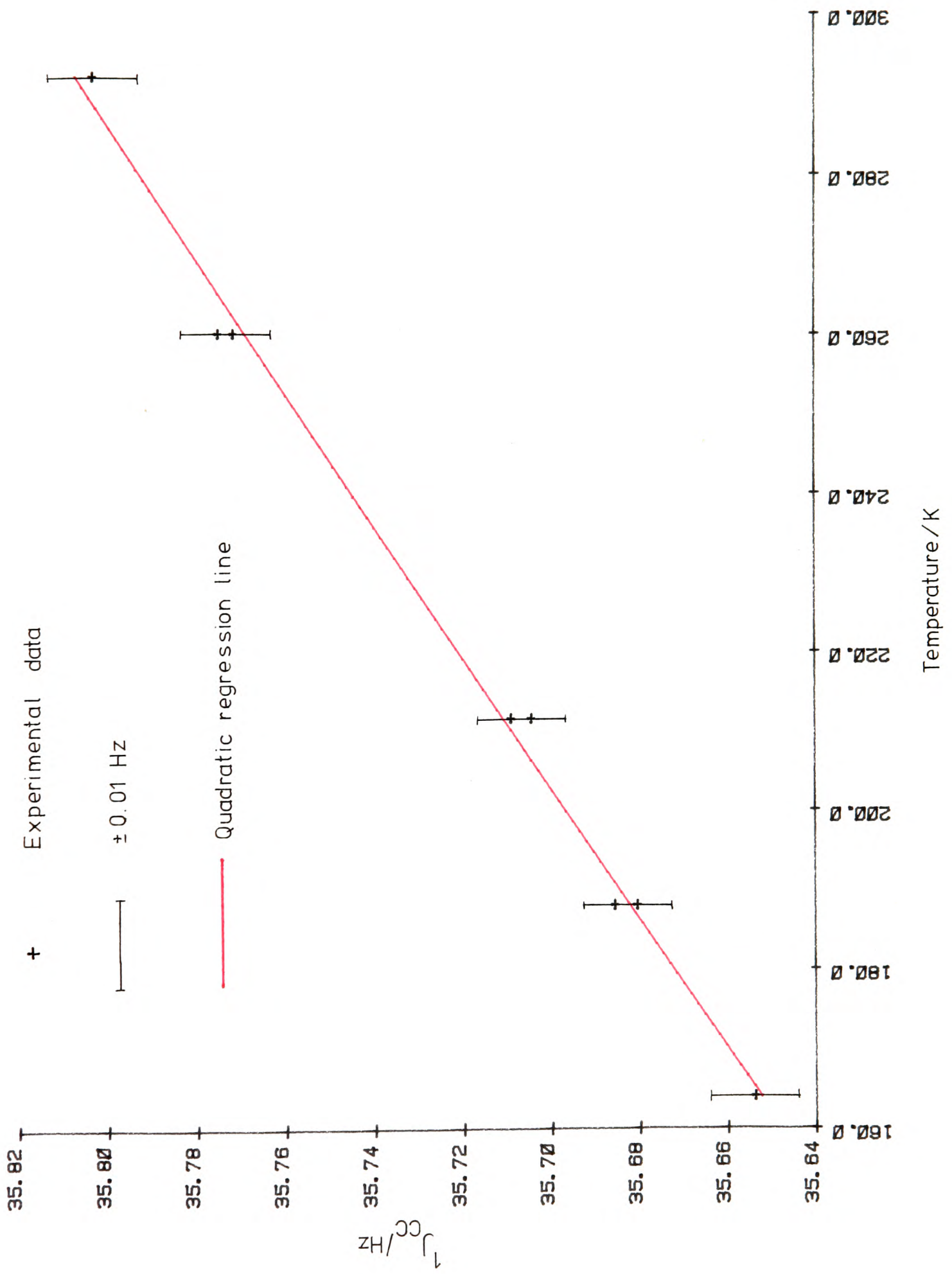


the data for $^{1}J_{CC}$ vs. T were subjected for some sample compounds to both quadratic and linear regression procedures. This showed that any curvature in the data tended to be insignificant compared with the quoted precision of $\pm$ 0.01 Hz for each data point. (See Figure 25 for an example). For this reason changes in $^{1}J_{CC}$ with T are quoted as a single number, implying the slope of a linear change. In a few cases the changes showed definite, pronounced curvature and reference to this fact is made in the text. Experiments repeated on successive occasions showed, however, that the chief reason for the detection of slight curvature from one experiment was usually experimental error; in other words, as stated above, the curvature was generally insignificant.

Preliminary experiments used at least ten different temperatures (usually at approximately 10 K intervals). When these had shown that changes in $^{1}J_{CC}$ encountered were linear, some later experiments could be performed using as few as five temperatures.

Figure 25

$^{1}J_{CC}$ vs. Temperature for iodoethane



APPENDIX 2

Temperature Measurement

The carbon-13 chemical shift thermometer used at low temperatures employs iodoethane.[100] When it was desired to find out how accurate the temperature controller on the Bruker WH90 machine was at high temperatures, a new thermometer was sought. The compound(s) used had to be less volatile than iodoethane as well as being thermally stable. 2-Phenyl-1-iodoethane seemed a likely candidate since a large temperature dependence of the chemical shift of the methylene adjacent to iodine had been observed for it. The shift difference between the two methylene carbons in the molecule was, however, considered too large to use this compound alone. (A large shift difference provides for less precise determination of temperature, moreover the benzylic position gives rise to a signal that would interfere with many spectra).

A compound having a chemical shift nearer to that of $-\underline{C}H_2I$ in 2-phenyl-1-iodoethane was sought, preferably a shift having a negligible temperature dependence. A readily prepared compound, having a suitable signal, was found to be diethyl 1-ethyl-1,1-ethane-dicarboxylate. The appropriate signal is due to the methyl carbon of the 1-ethyl group.

The calibration of the thermometer took the same form as that of the iodoethane thermometer. A 1:1 mixture (by mole ratio) of the two compounds was prepared, containing 10% of each compound having one isotopic substitution (ie. 2-phenyl-1-iodo-(1-^{13}C)ethane and diethyl 1-(2-^{13}C)ethyl-1,1-ethanedicarboxylate). This mixture was used as the thermometric liquid in a specially constructed conventional liquid in glass thermometer. Next, the meniscus height was

measured for this thermometer simultaneously with the shift difference of the two relevant carbons. This was done by supporting the thermometer in a 10 mm n.m.r. tube (containing some deuteriated solvent to provide field stabilization) which was spun in the n.m.r. probe at various temperatures. Since the thermometer and tube assembly could be spun, the resolution was good.

Lastly, the meniscus height was measured as a function of temperature using an oilbath and a copper-constantan thermocouple. The latter was checked for accuracy in ice (273 K), steam (373 K) and boiling bromobenzene vapour (429 K). These three temperatures encompassed the range required of the eventual thermometer.

Now a plot of chemical shift difference ($\Delta\delta$), in Hertz, against temperature T(K), in Kelvin, could be made. This was found to be linear, giving the following relationship:-

$$T(K) = 3.62\ (\Delta\delta) + 62.6$$

(The shift difference in Hz was measured at 22.63 MHz)

The precision of this equation is not as good as that obtained for the one derived from the iodoethane thermometer. This is because it was impossible to reproduce accurately the ambient heating effects in the probehead, within the magnet of the spectrometer, by using an oilbath for the second half of the calibration. The same problem was not encountered during the calibration of the low temperature thermometer. The precision of the high temperature thermometer is thus only $\sim \pm$ 1K but this did not matter as this thermometer was used only rarely in this work. It is unlikely, moreover, that elevated temperatures will be required to be known with high precision in the future, because measurements of ΔG^{o} are likely to be made by carbon n.m.r. only at low temperatures.

Despite the relatively low precision, the thermometer showed that the temperature controller may be in error by up to 10 K at high temperatures. (Such error arises because the exact position of the thermocouple involved is not well controlled and is in any case somewhat distant from the sample. The iodoethane thermometer showed that much worse errors, up to 20 or 30 K, occur at low temperatures).

For routine use the high temperature thermometer is made up in the same way as the low temperature one. A small amount of the two isotopically substituted compounds, in a 1:1 mixture, is sealed in a narrow glass capillary. The capillary is supported coaxially within a 10 mm n.m.r. tube containing the sample. Hence the temperature of the sample may be measured while conducting the n.m.r. experiment. When, as for the measurement of $^{1}J_{CC}$, a narrow sweepwidth is used to measure the parameter of interest, the carrier frequency offset and sweepwidth are altered each time the temperature is measured but the sample remains undisturbed.

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