Multi-metallic lanthanide complexes – using kinetic control to define complex multi-metallic arrays

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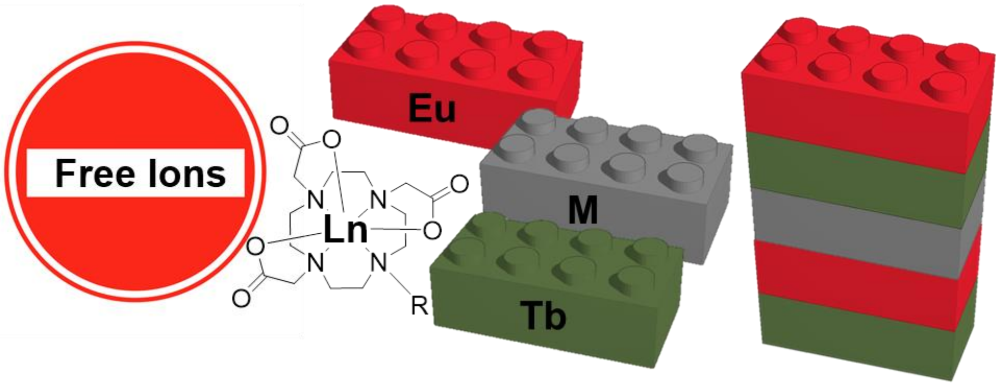


Conspectus: Kinetically inert lanthanide complexes are proving to be highly effective building blocks for the preparation of complex heterometallic architectures, allowing complete control of metal ion domains, which cannot be achieved under thermodynamic control. Kinetic stability may render perceivable labile coordination bonds, more durable than several types of covalent interactions. For complexes in clinical use, the significance of kinetic stability cannot be overstated, and this account treats the topic accordingly.

Kinetically inert complexes can be used as building block for elaborate synthesis. For instance, it is now possible to prepare heterometallic lanthanide complexes containing two or more different lanthanide ions by linking kinetically robust complexes together. This approach can yield bimetallic (*f*-*f*' or *d*-*f*) and trimetallic (*f*-*f*'-*f*'') lanthanide complexes.

In this Account, we describe our studies exploiting the slow dissociation of lanthanide complexes derived from 1,4,7,10-tetraazadodecane-1,4,7,10-tetraacetic acid (DOTA) derived ligands to link complexes together through synthetic manipulation of pendent groups on the ligand skeleton or through coordination of bridging donor groups to a *d*-block metal centre. In the course of this work, we have developed a variety of such methods, ranging from peptide coupling and diazotisation to Ugi and Click chemistry, and have also explored the use of alternative strategies that combine orthogonal protecting group chemistry with sequential complexation of different lanthanide ions, or that use self-assembly to deliver well-defined multi-metallic systems.

These well-defined bimetallic systems also have considerable scope for exploitation. Since the earliest studies, it has been clear that there is potential for application in the burgeoning field of molecular imaging. Heterometallic lanthanide complexes can be used as single-molecule bimodal imaging agents through incorporation of MRI active and luminescent components.

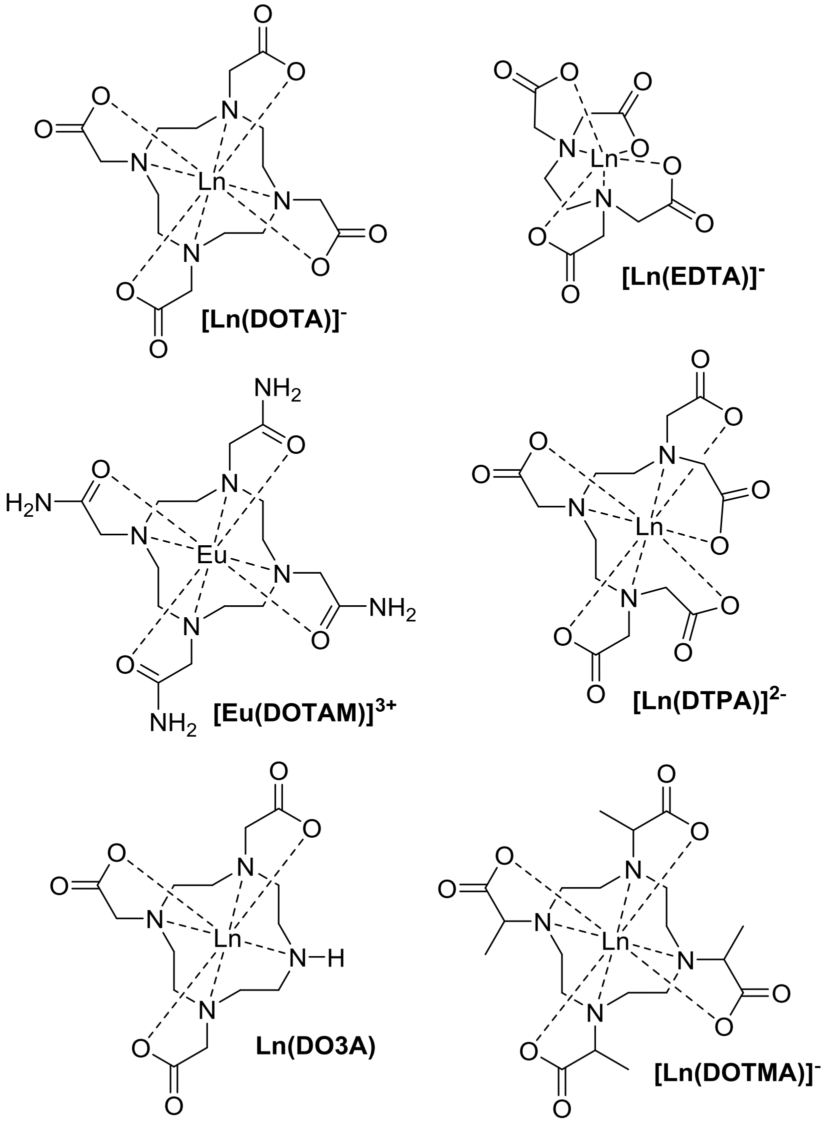
Alternatively, conventional luminescence methods can be exploited in conjunction with lanthanide luminescence. In the simplest cases, a single lanthanide can be used to achieve a switchable response in combination with a transition metal complex. Bimetallic *f*-*f*' complexes allow the full potential of the approach to be realised in systems in which one lanthanide responds to changes in the concentration of an analyte, while a second lanthanide centre can be used to define the concentration of the probe itself. This offers a new solution to the old dichotomy of ratiometric imaging that can potentially be applied widely.

Introduction

Undergraduate chemistry textbooks consider two forms of bonds, inert covalent bonds and labile ionic bonds.[1] We teach that molecular constitution is maintained for organic molecules in solution, while salts dissociate when dissolved. Inorganic textbooks introduce the transition between these extremes, with coordinate bonds that define the behaviour of *d*-block elements in the solid state and in solution.[2-4] Some coordinate bonds are labile, while others are so inert that they may be compared to the covalent bonds in organic molecules.[5] The kinetics determine how fast equilibrium is reached. The classic example is the spontaneous combustion of table sugar: thermodynamically favored yet impossible due to kinetics.

In the *f*-block, and in particularly for the lanthanides, [2,6,7] there is negligible orbital overlap involving *f*-orbitals. Thus bonding must be essentially ionic: from this, it follows that lanthanide complexes with simple ligands must be highly labile even if they are highly thermodynamically favoured.[5] Indeed, complexes with ligands such EDTA and DTPA were studied around sixty years ago, and it was established that lanthanide complexes were more labile than their *d*-block counterparts.[8-10]

The size and ionic character of lanthanide(III) ions favours high coordination numbers and complexes commonly involve 8-10 donor atoms binding to the lanthanide. For macrocyclic ligands with seven of more donor atoms, the rapid exchange kinetics inherent for the lanthanide(III) ions can be suppressed. In 1980, Desreux reported that complexes between 1,4,7,10-tetraazadodecane-1,4,7,10-tetraacetic acid (DOTA, see Scheme 1) and lanthanide(III) ions behaved as if kinetically inert.[11,12] This inertness underpins the safe use of gadolinium(III) complexes with macrocycles in magnetic resonance imaging applications.[12,13]



Scheme 1. Structure and abbreviated name of lanthanide(III) complexes of some common polyaminocarboxylate ligands. Lanthanide ions in systems such as these generally have coordination numbers around 9, and the remainder of the coordination sphere is filled by coordinated solvent molecules

Kinetically inert complexes control the solution phase properties of lanthanide complexes on timescales that are compatible with common characterization techniques.[14] For such complexes, the solid state structure and solution structure can be expected to be similar.[12,14] Further, as the the complexes are well-defined in time, these molecular building blocks can be used multistep syntheses just as kinetically stable organic compounds can be used.

In this account, we show how kinetically inert complexes in solution can be controlled to access the complicated architectures we have made using kinetically inert lanthanide(III) complexes as molecular building blocks. We have restricted this account to the discussion of small molecules, but the concepts described are equally relevant to the decoration of nanoparticles: and indeed to any system in which it is desirable to control speciation.

Labile or Inert?

Equilibrium considerations may suffice for describing coordination complexes in isolated systems, but in many situations, and particularly for biological applications, the actual speciation of a coordination complex must be known. It is important to appreciate that speciation in systems that are not at equilibrium will invariably be a function of time: for kinetic control, we would ideally wish to be far from equilibrium.

Peptide hydrolysis in water at neutral pH occurs with a unimolecular rate constant: $k_{\mathrm{obs}} = k_0$, with $k_0 \sim 1\cdot10^{-10}$ $\mathrm{s}^{-1.}$ Thus peptide bonds are inert. Peptide bond hydrolysis may be accelerated by addition of base or acid. The acid catalyzed process can be described by a bimolecular rate constant and the observed rate constant of hydrolysis must be expressed as: $k_{\mathrm{obs}} = k_0 + k_1[\mathrm{H}^+]$, with $k_1 \sim 2\cdot10^{-6}$ $\mathrm{s}^{-1}\mathrm{M}^{-1}$.[15] As $k_{\mathrm{obs}} < 1\cdot10^{-5}$ s^{-1} at pH =1 covalent peptide bonds are kinetically inert in the absence of a peptidase enzyme, and cleavage occurs on a timescale of days, even at extreme pH. In contrast, the bond between a lanthanide ions and a simple monodentate ligands is labile, and the exchange of ligands occur on the nanosecond timescale.[5] Note that the covalent peptide bond is inert despite a limited thermodynamic stability.[16] In contrast, lanthanide complexes exhibit high thermodynamic stability, but also high lability. However, if rigid polydentate macrocyclic ligands are used, kinetically inert lanthanide complexes can be made by creating a high activation energy barrier to demetallation.

Table 1. Thermodynamic and kinetic parameters of dissociation for a four lanthanide complexes contrasted to those of a dipeptide, The table report the rate constants of dissociation $k_{\mathrm{obs}} = k_0 + k_1[\mathrm{H}^+]$, the stability constant K = [LnL)]/([L][Ln(III)]), and the observed rate constant for dissociation at pH = 1 and pH = 7 at 298 K.

Molecule/complex	association constant K M^{-1}	ΔG kJ/mol	k_0 s^{-1}	k_1 s^{-1}M^{-1}	$k_1[\mathrm{H}^+]$ at pH=7	$k_1[\mathrm{H}^+]$ at pH=1
(phenylacetyl)glycyl	0.8 (pH = 5)[e]	0.56	$9 \pm 6 \cdot 10^{-11}$	$2 \pm 1 \cdot 10^{-6}$	$2 \cdot 10^{-13}$	$2 \cdot 10^{-7}$
$[\mathrm{Ln.EDTA}]^-$ [a]	$10^{17.35}$	-100	-	149±8	$1.5 \cdot 10^{-5}$	15
Ln.NOTA[b]	$10^{13.9}$	-80	$8.3 \cdot 10^{-6}$	$2.3 \cdot 10^{-2}$	$2.3 \cdot 10^{-9}$	$2.3 \cdot 10^{-3}$
$[\mathrm{Ln.DOTAM}]^{3+}$ [c]	$10^{13.7}$	-79	$1.5 \cdot 10^{-7}$	$5.6 \cdot 10^{-7}$	$5.6 \cdot 10^{-14}$	$5.6 \cdot 10^{-8}$
$[\mathrm{Ln.DOTA}]^-$ [d]	$10^{23.6 \pm 1}$	-136±6	$< 5 \cdot 10^{-8}$	$5 \cdot 10^{-6}$	$5 \cdot 10^{-13}$	$5 \cdot 10^{-7}$

[a] K value reported from Ln: Gd^{3+},[17] kinetics for Eu^{3+}.[18] [b] K value reported from Ln: Eu^{3+},[17,19] kinetics for Ce^{3+}.[20,21] [c] K value and kinetics reported from Ln: Eu^{3+}.[22] [d] K, value reported average from all Ln^{3+} from 36 determinations,[17,19,23] kinetics for Gd^{3+}.[24,25] [e] From reference [26].

If we consider thermodynamically stable lanthanide complexes ($K > 10^{10}$), we must consider the rates for dissociation to classify them as kinetically inert or labile. For a one step equilibrium, K represents the ratio of the rate constants for association and dissociation. However, a single value of K can define very different rates of dissociation; since a variety of processes (mediated by pH, other metal ions or competitive binding of other ligands) contribute to dissociation, which is inevitably going to be a multistep process given the difficulty of removing all the donor atoms from the lanthanide. For a system to be kinetically inert to dissociation, it needs to be rigid and pre-organised to ensure that it exists in a deep potential well with a high activation barrier to dissociation of any donor atoms. As such, one must be prepared to accept relatively slow association kinetics.

As with peptide bonds, the dissociation of lanthanide complexes can occur spontaneously (k_0), and through mediated processes.[25,27] By far the most important process in aqueous solution is the protonation mediated de-complexation k_1. The thermodynamic and kinetic stability of several complexes between multidentate aminocarboxylate ligands and lanthanide(III) ions have been studied in great detail and is collated in Table 1.[17,19,20,23] The information on the kinetics of dissociation and the association constants allows us to simulate the rates of de-complexation using commercial software,[28] the results are shown in Figure 1. The figure shows the effect of pH on the speciation of three thermodynamically stable lanthanide complexes in the presence of a scavenger (e.g. precipitation on glass surfaces, coordinating biomacromolecules, inclusion in bone). These simulations show that DOTA complexes are stable for hours at pH = 1 conditions, while the other complexes dissociate within minutes. Even at neutral pH, the labile complexes between EDTA, DO3A and lanthanide ions dissociate within 2 hours.

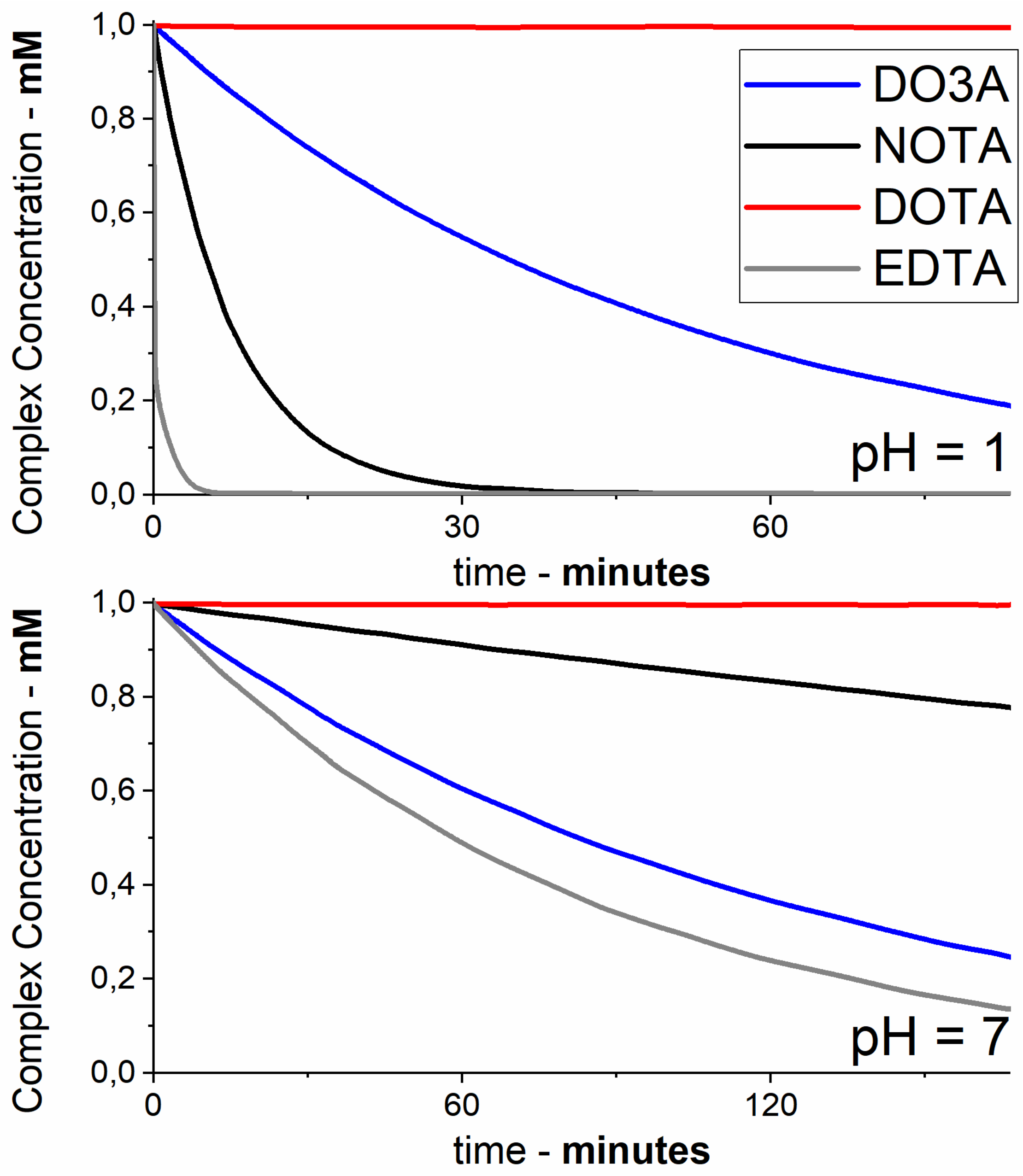


Figure 1. Modelled change in concentration of lanthanide complexes of DOTA, DO3A, NOTA and EDTA dissolved in the presence of an irreversible scavenger for lanthanide ions at pH = 1 and pH = 7.

Thermodynamic vs. Kinetic control

[Ln(DOTA)]$^-$ complexes are kinetically inert. [Ln(EDTA)]$^-$ must be considered to be labile. Thus, applications and physicochemical studies of [Ln(EDTA)]$^-$ must rely on thermodynamic control. Biological applications cannot be considered for complexes that rely on thermodynamic control. The simulations in Figure 2 show the speciation when a complex under thermodynamic control is dissolved in an NMR tube or cuvette. The speciation depends on concentration; there will be a significant concentration of free ions present at equilibrium, even for complexes with very high thermodynamic stability.

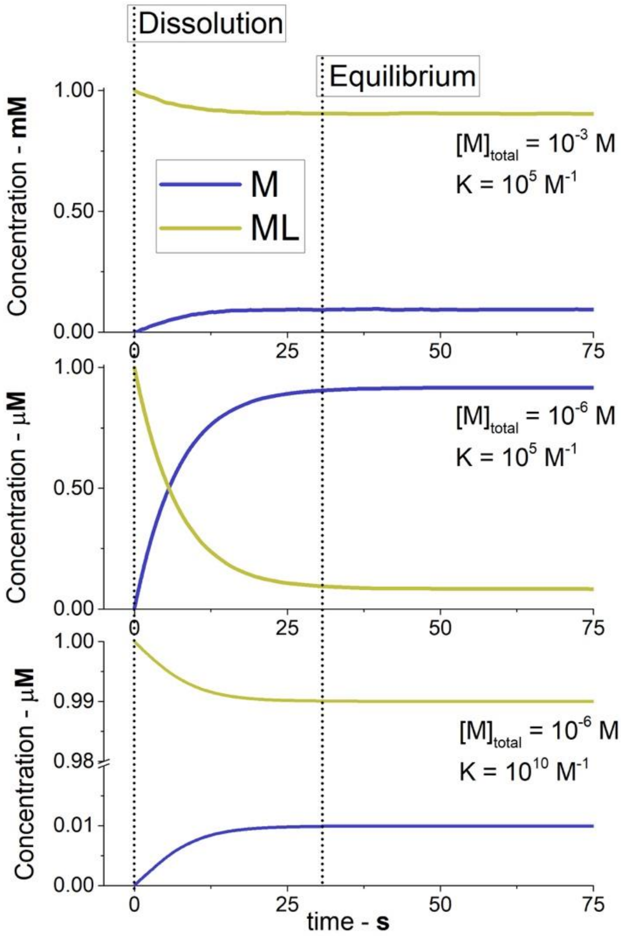


Figure 2. Modelled temporal changes in the concentration of two lanthanide complexes with association constants of 10^5 M^{-1} and 10^{10} M^{-1} at milli- or micro-molar concentrations using: **M + L = ML ; K = [ML]/[M][L] =** $\boldsymbol{k_1/k_{-1}}$, the changes are modelled with a dissociative rate constant of $k_{-1} = 10^{-3}$ $M^{-1}s^{-1}$ and the value of K indicated on the graphs.

In stark contrast, complexes that rely on kinetic control can be used in biological systems, and the speciation is simple when dissolved in a cuvette. This should not be surprising, as a chemist would never assume that peptides or other organic molecules fall apart when dissolved. Figure

3 show the speciation of two complexes when dissolved in a medium where free ions will precipitate immediately. Two complexes are simulated, one under partial kinetic control, and another under kinetic control (with dissociation kinetics similar to [Ln(DOTA)]$^{-}$) The speciation is unchanged over days for the complex that is under kinetic control, while the other complex dissociates after the first hour. That is applications or measurements on this complex must be complete within the first second. For [Ln(DOTA)]$^{-}$, and other complexes under kinetic control, no constitutional changes occur in days.

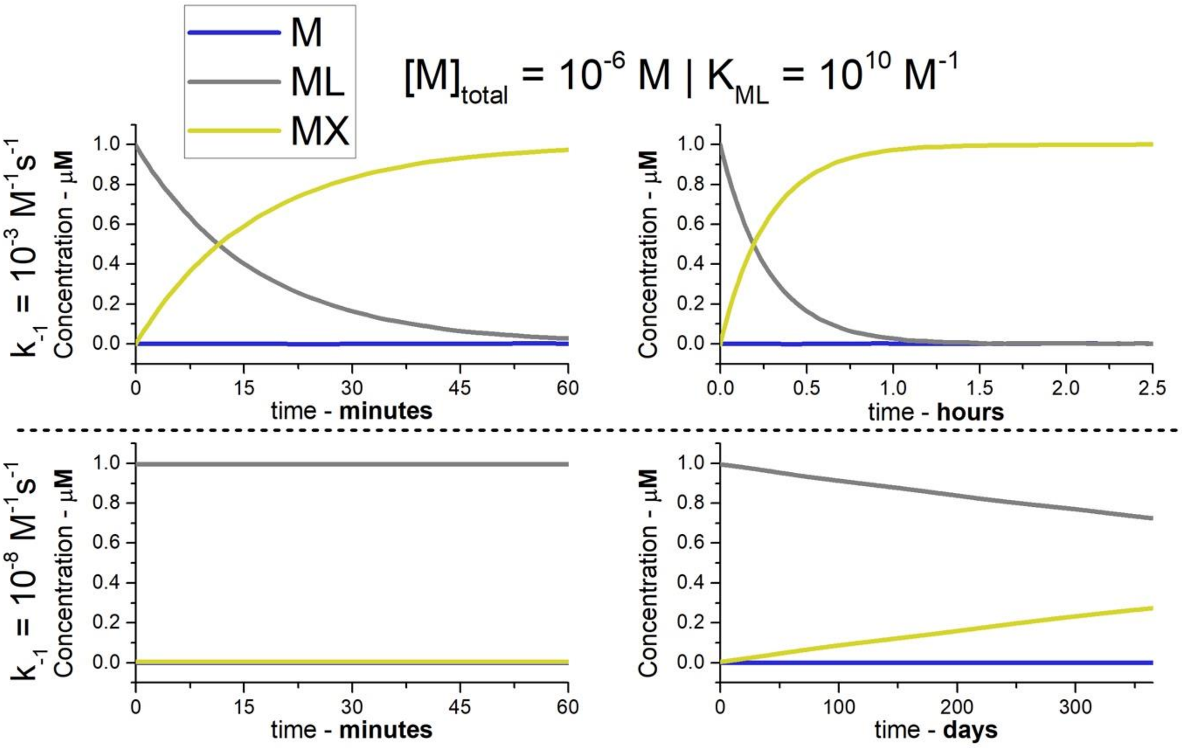
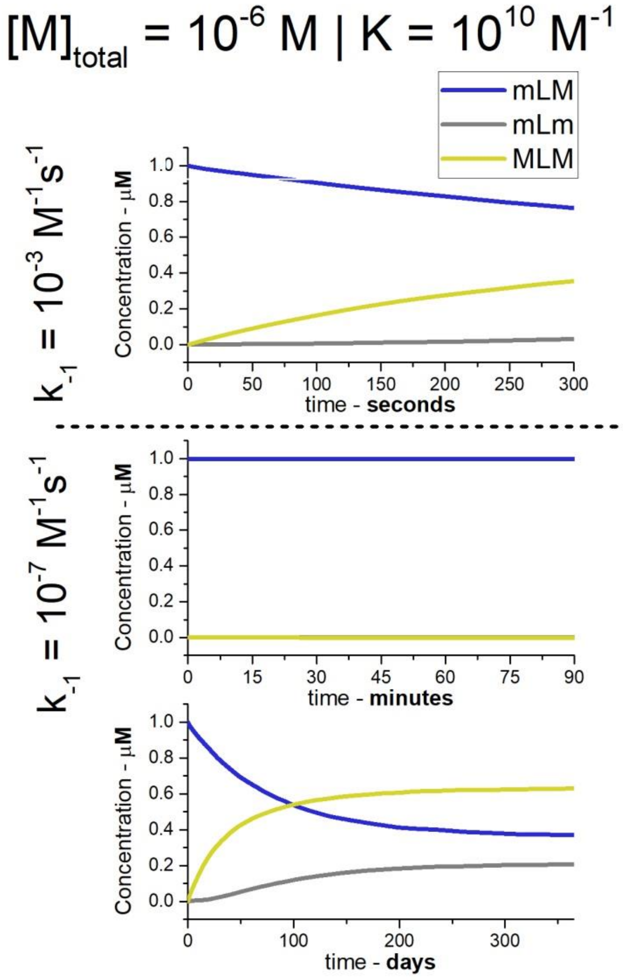


Figure 3. Modelled changes in the concentration of two lanthanide complexes as a function of time and K in a solution containing an irreversible metal ion scavenger binding and precipitating the lanthanide ion at the rate of diffusion. The modelling uses apparent rates of dissociation in a system where there is diffusion limited precipitation of the lanthanide upon decomplexation, with the values of k_{-1} and K indicated on the graphs.

Chemistry with Kinetically inert systems

Kinetically inert complexes will have an unchanged constitution over extended time periods. Ions will not be released or exchanged when the complexes are dissolved. Ions will not be scrambled between binding sites, and there will not be free ions in solution. Thus, kinetically inert complexes can be treated in the same way as organic molecules, and used as molecular building blocks. Considering the preparation of a heterobimetallic complex where two metal ions are coordinated in two identical binding pockets, the problem is defined in Figure 4. Without kinetic control the metal ions are immediately scrambled, while the targeted heterobimetallic complex is the only one formed from the kinetically inert complexes.



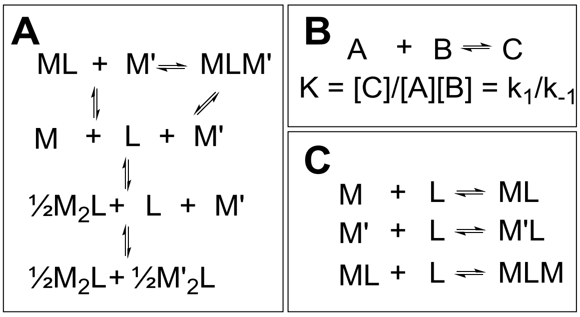
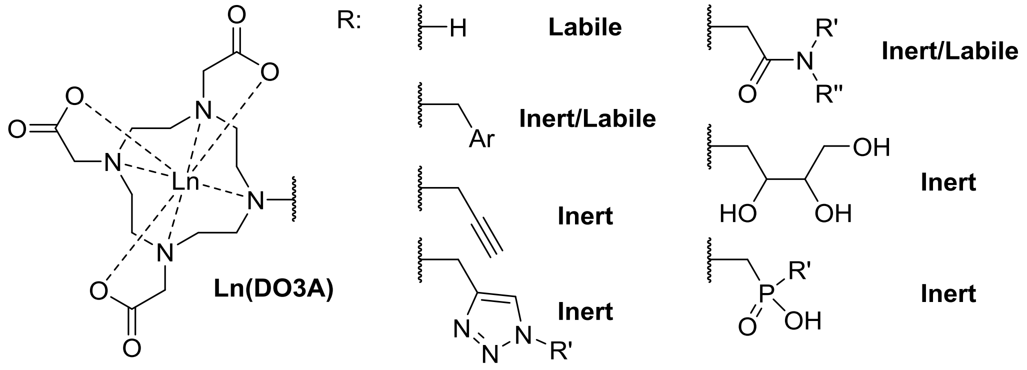


Figure 4. Top: The influence of the magnitude of the dissociative rate constant (k_{-1}) on the formation of and speciation multimetallic lanthanide complexes. Bottom the model used in the modelling: A, equilibria between a ligand with two identical binding sites and two different metal ions. B, association and rate constants defined for the 1:1:0 complex. C, the equilibria used in the modelling. Note that the constants described in B are identical for the three equilibria in C. In these systems K defines the end point (when equilibrium is achieved).

Molecular building blocks

Kinetically inert building blocks must have rate constants for dissociation lower than ~10^{-6} s^{-1} *under the actual experimental conditions*. For lanthanide(III) complexes, this restricts possible ligands to macrocyclic frameworks with at least seven donor atoms, and for prolonged stability eight donors are needed.

Although complexes of DO3A derivatives with bulky or lipophilic substituents on the fourth nitrogen (see Scheme 2) have been shown to be kinetically inert,[29-31] less bulky substituents can give rise to kinetically unstable complexes.[32] Similarly, DO3A-monoamide derivatives are generally kinetically labile but can be rendered inert by the use of bulky R' substituents.[33] Taken together, these observations reveal that dissociative demetallation is unlikely to occur from the most stable conformation of a multi-dentate ligand: instead, structural distortions to high energy conformations of the complexes are likely to be key to metal ion release. If this activation energy barrier can be maximized, synthetic chemistry with lanthanide complexes under kinetic control becomes possible.[29,30,34-44]

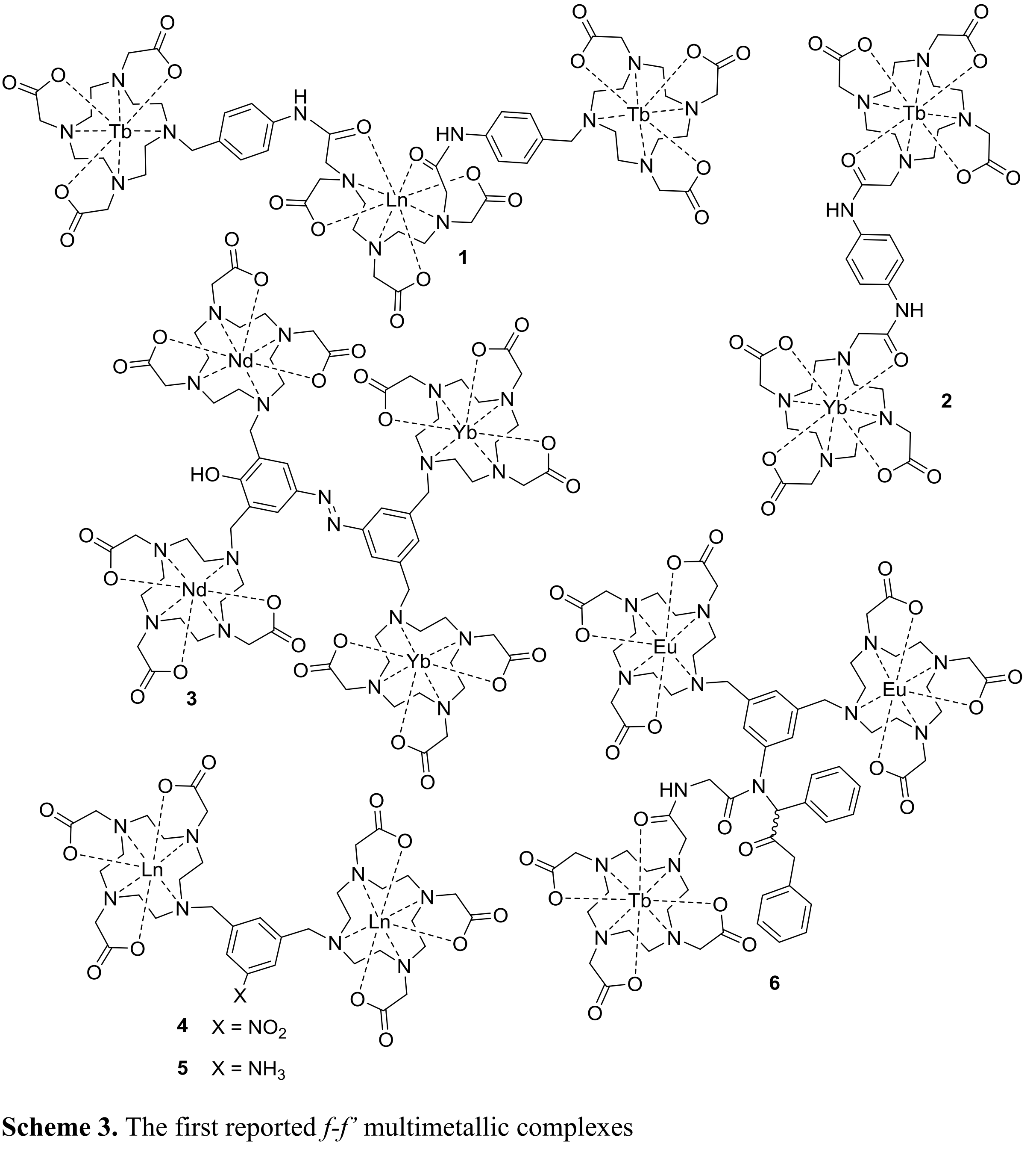


Scheme 2. Kinetically inert and labile [Ln(DO3A)] derivatives generalized by the structure of the fourth pendant arm.

f-f' multimetallic complexes

Creating discrete *d-f* multimetallic complexes in solution, or indeed *d-d'* multimetallic complexes in solution, can exploit the different chemistry of the two metal ions. This is not possible in the *f*-block, where the chemistry of the trivalent ions is too similar.[2,7] Earlier attempts exploited selectivity on the basis of size and coordination number to distinguish between early and late lanthanides,[45,46] but the lanthanide contraction means that such an approach cannot offer site specificity: indeed mixtures must result from thermodynamic control. Well-defined multimetallic complexes can only be achieved by using kinetically inert complexes as building blocks.

In our earliest studies,[47] we exploited the kinetic stability of lanthanide complexes with 4-aminobenzyl-DO3A, and used the formation of a secondary binding site to confirm that such systems were indeed kinetically stable. In the synthesis of **1** (Scheme 3) such complexes are reacted with DTPA bis anhydride: we observed no migration of terbium between the macrocyclic and DTPA-derived binding sites.[47] Having done so, we incorporated an ytterbium ion into the DTPA-derived site, creating a well-defined heterometallic *f-f'* system for the first time. Tremblay and Sames modified this approach using a ligand containing both cyclen-derived and DTPA-derived domains, then exploited the kinetic inertness of lanthanide ions bound in the cyclen-derived site while removing excess lanthanide from the DTPA-derived site.[48]



Scheme 3. The first reported *f-f'* multimetallic complexes

In the intervening years, we have extended and tested a variety of approaches to heterometallic *f,f'* and *f,f',f''* complexes. For instance, kinetic stability can be combined with orthogonal protection strategies to obtain quasi-symmetric heterometallic complexes like **2** (Scheme 3) via the orthogonally protected pro-ligand, before sequential deprotection and complexation to access first a mononuclear complex, and then a bimetallic one.[49]

The effectiveness of kinetic control can be seen in the bimetallic tetranuclear complex **3**, which we prepared by diazotization of **5** and subsequent reaction with the lanthanide complexes of α,α'-bis(DO3A)-2-hydroxy-*m*-xylene (not shown).[50] This reaction sequence is performed under particularly challenging highly acidic conditions in the diazotization step. Even here, the complexes remain intact, with no migration of lanthanides between sites.

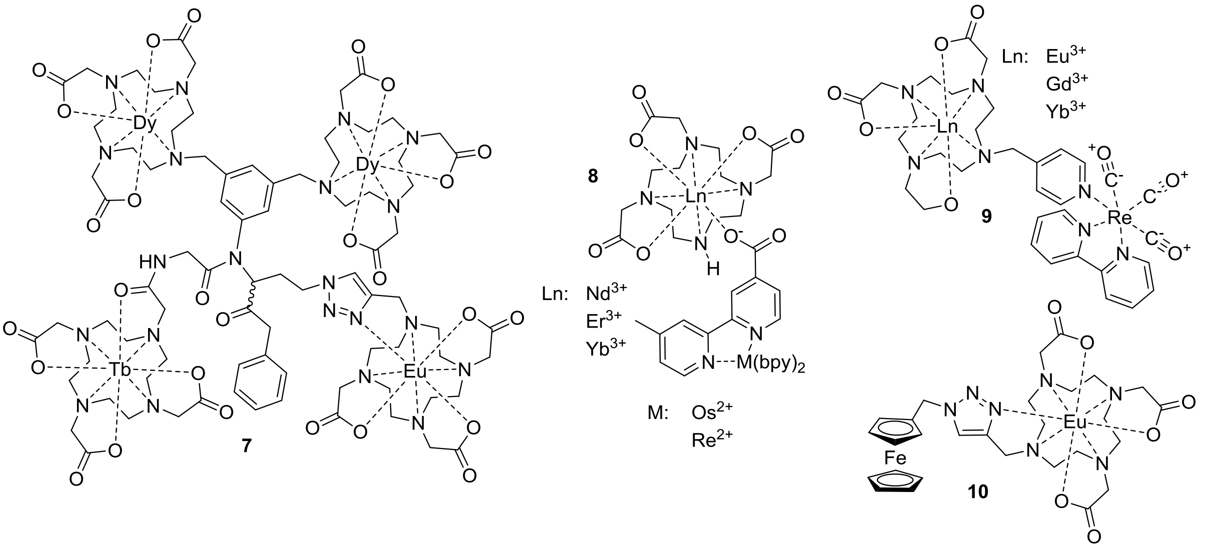
A wide range of reactions can now be used to link kinetically stable complexes. Of these, we have made considerable use of click chemistry,[29,30,35-38] peptide coupling and Ugi reactions in the preparation of heterometallic arrays.[39-44] All these routes offer effective pathways to linking complexes together. Ugi chemistry is currently the most appealing route owing to the structural diversity that can be generated from four components (an aldehyde, an amine, an isonitrile and a carboxylic acid). In principle, all four components can be appended to a lanthanide complex, though we have not made use of isonitrile appended lanthanide complexes. In this way, we have prepared bimetallic lanthanide complexes such as **6**, which offers an interesting case in being structurally related to **4**. **4** and **6** exhibit dramatically different affinities for isophthalate, revealing that it is possible to control the binding domain in a complex without direct modification to the binding site.[39,40] This reveals the importance of conformational space in determining affinity for a guest. The same building blocks were also used to prepare the trimetallic complex **7** (scheme 4), in which three different lanthanide ions were incorporated into a single molecule for the first time.[39]

d-f multimetallic complexes

Kinetic stability is common in *d*-block coordination chemistry, particularly for d6 transition metal complexes with low spin configurations.[2] Such complexes (e.g. $[Ru(Bpy)_3]^{2+}$) have have been in widespread use as luminescent tags and labels for more than 20 years.[51,52] Heterometallic complexes containing such ions were first prepared using *d*-block complexes as building blocks. Van Veggel showed that ruthenium complexes could be elaborated to form systems containing a second binding site suitable for a lanthanide ion.[53] In such systems, the lanthanide itself is labile, but as the transition metal complex is kinetically inert, no scrambling between sites can occur.

Kinetically stable lanthanide complexes extend the range of possibilities. For instance, mixing lanthanide DO3A complexes with carboxylate appended complexes of Re(I), Ru(II) and Os(II) results in the formation of self-assembled heterometallic complexes where the carboxylate displaces solvent from the lanthanide centre.[47,54-56] The simplicity of this approach allows rapid screening of pairs of ions. However, the affinity of mono-dentate carboxylate ligands for [Ln(DO3A)] is low (logK ~3), meaning that these systems exist at or close to equilibrium. By contrast, the alternative approach of using a kinetically inert lanthanide complex to displace a labile ligand from a rhenium (I) centre yields a wholly robust and kinetically inert bimetallic system such as **8** and **9** (Scheme 4).[57] In such species, the ^{3}MLCT state of the rhenium complex acts to sensitize lanthanide excited state formation.[58]

As for *f-f'* complexes, kinetically inert complexes can also be prepared by covalently linking two kinetically inert complexes from the *d*- and *f*-block. This variety of available routes creates options for the synthetic chemist to prepare a kinetically inert, and elaborate it further- either by extending the ligand structure to incorporate another binding site, or by linking two or more inert complexes together.[58-62]



Scheme 4. Examples of heterometallic complexes

d-*f* hybrid complexes also allowed us to exploit the variable oxidation states of transition metal complexes. For instance, the click reaction of azidomethylferrocene with lanthanide complexes of DO3A-propargyl, yields compound **10** (Scheme 4).[37] Electrochemical oxidation and reduction of the ferrocene centre can then be used to reversibly modulate the intensity of the lanthanide luminescence.

Provided the lanthanide ion is bound in a kinetically inert binding site, there are potentially no limits on the formation of heterometallic complexes containing ions from other parts of the periodic table, e.g. by incorporating crown ethers that can select for *s*-block ions such as potassium.[36]

Applications of multimetallic lanthanide complexes

By incorporating binding sites for several metal ions the unique properties of each can be exploited. Luminescent lanthanide complexes have been prepared that exhibit modulation by redox potential (Fe/Eu),[37] dissolved oxygen concentration (Eu/Tb),[41] and by the presence of specific simple ions.

Furthermore, the presence of multiple ions can be used to create a ratiometric response that enables quantification, a response that is governed by the relative position of the two kinetically inert complexes in the molecular architecture.[40-42,63] Thus the response to dissolved oxygen concentration can be changed by exchanging the position of the individual lanthanide ions in complexes like **6**;[41] a feat that is only possible using kinetically inert complexes. Compound **6** and compound **7** are made from **4**. Compound **4** and its analogues have proved very useful in their own right.[64] The existence of two heptadentate binding sites allows bidentate anions to act as bridging ligands between the two lanthanide centres through displacement of solvent from both coordination spheres.[65] Fortuitously, we discovered that these systems exhibit very high selectivity for 3,5-diarylcarboxylic acids such as isophthalate and dinicotinate.[40,66-68] Thus a kinetically stable [Ln(DO3A)] complex bearing an isophthalate group on the fourth pendant arm will self-assemble with derivatives of **4** to give rise to heterometallic lanthanide complexes with two different lanthanide binding domains.[65] As with self-assembled *d-f* complexes, these are formed through assembly of kinetically inert molecular building blocks, assembled under thermodynamic control.[40]

Generalising from the systems studied here, the molecular building block approach enables the design of architectures where the unique properties of the trivalent lanthanide ions are used in combination with standard methodologies from other fields.[34-36,40,69]

Access to multimetallic systems provides the ability to address metal ions singly or in concert. Beyond the approaches that have already been explored, others suggest themselves: notably the prospect of using both lanthanide ions to convey information. Given a single sensitizing chromophore, it should be possible to establish and control energy transfer by controlling superexchange by adding or removing bridging ligands, or by utilizing induced molecular motion to bring two centres into proximity. Furthermore, excited state manifolds in which multiple metastable excited states isolated on ions in different parts of a complex could allow information processing by by design.

Summary and perspective

Defining kinetically stable lanthanide complexes that can react through their periphery has opened up a new world of polymetallic lanthanide containing systems. These bagan as synthetic curiosities, but are becoming potentially important tools for quantitative imaging.

Our approach to heterometallic systems is founded on the idea that that complexes can be considered kinetically inert with the rate of decomplexation is below 10^{-6} s^{-1} in the conditions where the complex is investigated or used. Typically, this corresponds to a pseudo first order rate constant of decomplexation k_{obs} at pH = 1 that is below 10^{-5} s^{-1}. Lessons can be drawn on kinetic stability with much wider resonance beyond the preparation of heterometallic systems. In particular, they are valid for any system used *in vivo* – and it is clear that an understanding of the metal binding constant for any inorganic system is not sufficient to understanding its usefulness or safety.

While the kinetically inert lanthanide complexes that we and others have employed exhibit a rich chemistry, there are still challenges. At the most fundamental level, these involve structural characterization. Though NMR and luminescence spectroscopy always give rise to data that may provide key insights into structure in solution, crystallographic characterization requires samples to crystallise. Kinetically inert lanthanide complexes frequently oblige in this regard when symmetric or highly charged, but unsymmetrical and neutral complexes tend to form plastic solids rather than crystals, and even when crystals are obtained their analysis tend to be challenging.[70] This makes it more important to use other techniques that can provide structural information. It is certain that more can be achieved by measuring solution structures with NMR in the presence of paramagnetic ions, though we should note that reliable structures will be contingent on a better understanding of magnetic anisotropy in open shell lanthanides.[71] In the context of doing this in heterometallic systems, it is also necessary to define the effect of two different paramagnetic centres on each nucleus under study.

The ability to prepare systems that contain two different paramagnetic lanthanide ions facilitates addressing them separately or in concert – allowing the relative behavior of two different signals to be exploited in the development of diagnostic probes for quantitative imaging. We have already begun to exploit this in a variety of way: exploiting changes to the available quenching pathways in the excited state manifold to sense species such as oxygen, or defining systems in which an analyte binds to one type of lanthanide ion in a certain cavity, while leaving a different lanthanide in a different binding site untouched. The bulk of our work to date has focused on the development of luminescence methods to address heterometallic species and interrogate their environment in solution and on surfaces. Moreover, the NMR behaviour of the same systems reveals potential that is yet to be exploited: the differences in paramagnetic shift induced by two different centres offer the potential for straightforward extension to MR imaging using methods such as paraCEST or paraSHIFT. Using a single toolkit, it is thus possible to envisage developing probes that function over a variety of length scales from the microscopic to the whole organism.

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Professor Stephen Faulkner obtained his DPhil from the University of Oxford, and from there went to take an Addison Wheeler Fellowship at the University of Durham. From Durham, Steve moved first to the University of Surrey and thence to the University of Manchester - where he became Professor of Inorganic Chemistry in 2005. Steve returned to Oxford in 2008. Throughout, Steve's interests have focused on the coordination chemistry and spectroscopy of the *f*-block elements, including contributions to understanding near-IR luminescence, energy transfer, magnetic anisotropy and synthetic coordination chemistry in f-element complexes.

Associate Professor Thomas Just Sørensen obtained his PhD from the University of Copenhagen in 2010. After working with Prof Stephen Faulkner at Oxford, Sir J. Fraser Stoddard at UCLA, Prof Jerome Lacour in Geneva, and Profs Ignacy and Karol Gryczynski at UNT Thomas returned to take a permanent position at the University of Copenhagen in 2014. Thomas is an entrepreneurial scientist and with three spin-out companies under his belt, his research focuses on both fundamental and applied aspects of lanthanide chemistry in solution.

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