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Controlling the variation of axial water exchange rates in macrocyclic lanthanide(III) complexes†

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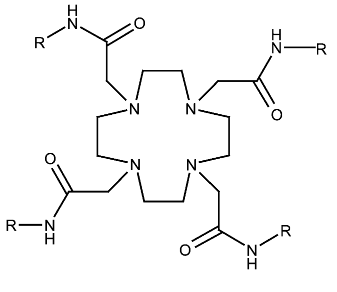
The rate of axial water exchange in well-defined series of lanthanide complexes depends on the extent of second sphere hydration which is determined by complex hydrophobicity and the nature of the lanthanide ion and its counter-ion.

In recent years the large number of studies on Ln(III) complexes aimed at assessing their potential role in the field of contrast agents for MRI applications, has improved our understanding of the factors determining the exchange rate of bound water molecules. It has been shown that such exchange rates cover several orders of magnitude, ranging from 1.25 ns for the Gd(III) aqua ion to 396 μs for the cationic complex [Eu.**1**]$^{3+}$. Moreover, it has been demonstrated that there are important structure-dependent factors that determine this exchange rate. For example, the two conformers of [Eu.DOTAM]$^{3+}$ (and their derivatives) display a 50-fold difference in rate at ambient temperatures.[1]



R =		
R =	H	**DOTAM**
R =	CH_2CO_2Et	**1**
R =	$CH_2COOtBu$	**2**
R =	CH_2Ph	**3**
R =	CH_2CO_2nBu	**4**
R =	$CH_2CO_2CH_2Ph$	**5**
R =	CH(Me)Ph	**6**

Although fast exchange rates are preferred in optimising the performance of MRI contrast agents based on the Gd(III) ion, recently it has been shown that slow-exchanging systems may also be exploited to induce a contrast in an MR image.[2] Indeed, the latter complexes may become the reference compounds for the class of CEST (or MT) contrast agents based on the transfer of saturated magnetisation on the solvent water resonance. To this end, a very slow water exchange rate and large shifts of the coordinated water signal are highly desirable. Therefore, it was deemed appropriate to gain a better understanding of the determinants of the slow rate of exchange of the coordinated water in such macrocyclic–lanthanide(III) complexes.

Different Ln(III) complexes of the same ligand were considered in order to assess the role of the lanthanide ion. Complexes of DOTAM, **1**[1,3] were selected because its Eu(III) complex is known to display a very slow exchange rate. For most of the paramagnetic [Ln.**1**]$^{3+}$ complexes considered in this work, it was possible to observe (if necessary at low temperatures†) the proton NMR signal of the coordinated water in the predominant square anti-prismatic isomer, well before the onset of exchange with the bulk water. The exchange rates of the triflate salts were evaluated through line-shape analysis (as a function of temperature) of the resonance of the coordinated water (for Eu and Nd) or of the resonance of the bulk water (for Ce, Pr and Yb). The results obtained indicate that only for the ions at the centre of the lanthanide series is the exchange lifetime, τ_M (= $1/k_{ex}$) relatively long (Nd = 79 ± 18 μs, Eu = 395 ± 60 μs, Gd = 159 ± 4 μs).[4] For either the earlier ions (Ce = 4.3 ± 0.2 μs, Pr = 4.9 ± 2.8 μs) or the later ones (Yb = 1.8 ± 1.0 μs) much shorter exchange lifetimes were measured. Having established that the solution structure does not change along the lanthanide series (as shown by analysis of the dipolar shift of the ligand ^{1}H resonances), the observed behaviour suggests that there may be a change in the position of the transition state for the dissociative[1] water exchange mechanism. Analysis of the water exchange rates for Yb, Eu and Pr complexes of **6**[5] had revealed a similar pattern: Yb, τ_M = 0.6 μs; Eu, 280 μs and Pr = 10 μs, in accord with the variation seen with DOTAM complexes.

Each of the complexes possesses a ground state coordination number of 9 and the water exchange process may occur either *via* an interchange process with an early transition state, resembling the structure of the ground state, or *via* a late transition state, resembling a structure in which the interchanging water molecule is closer to the Ln ion. Enhancements in rate are expected either if the ground state structure is destabilised or if the transition state structure is stabilised (*e.g.* by the presence of second-sphere waters in proximity). To elucidate structural changes across the lanthanide row, we determined X-ray crystal structures of eight [Ln.**6**]$^{3+}$ complexes of enantiopure *R,R,R,R*-**6**, *viz.* [Gd.**6**(H_2O)]$(NO_3)_3 \cdot 5H_2O$ (**7**) and two isomorphous series of triflate salts, differing by the content of the solvents of crystallisation.‡ Thus, [Ln.**6**(H_2O)]$(O_3SCF_3)_3 \cdot 3H_2O$ (**8**, Ln = Tb, Er, Lu) crystallise in the space group $P2_1$ and are also isomorphous with the Yb analog,[6] while [Ln.**6**(H_2O)]$(O_3SCF_3)_3 \cdot xH_2O \cdot y$EtOH (**9**, Ln = Ce, Pr, Gd, Er; *x* and *y* between 1 and 1.5) were solved in the space group *I*2. Phases **8** and **9** crystallise from water/ethanol solutions under similar conditions, even (for Er) in the same crystallisation. Crystals of **8** are moderately stable under atmospheric (but not dry!) air, while **9** quickly lose solvent. Variable-temperature X-ray measurements revealed no phase transitions in either **8** or **9** between 120 and 295 K. As we have observed earlier,[5,6] the Ln^{3+} ion invariably has a regular square-antiprismatic coordination with four macrocyclic N and four pendant-arm O atoms of **6**, the aqua-ligand capping the O_4 base of the antiprism. Lanthanide ions of different size are accommodated by changes in the ligand Ln–N and Ln–O distances (Fig. 1 and ESI†), which correlate closely with the ionic radius variation, irrespective of the outer-sphere composition. The

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† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b2/b202862j/

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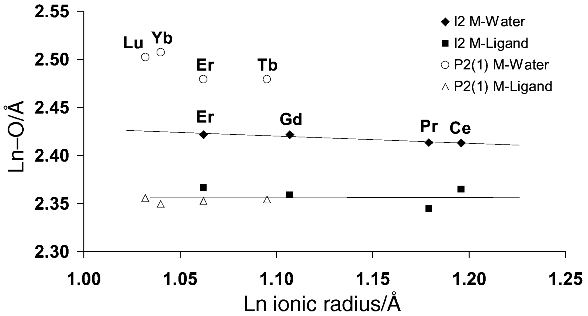

Fig. 1 Variation of Ln–OH_2 distances and Ln–ligand O distances, normalised to the ionic radius of Gd, in $[Ln.\mathbf{6}]^{3+}$ triflate salts.

latter, however, substantially affects the distance to the aqua-ligand, *viz.* the Er–OH_2 distances in phases **8** and **9** equal 2.432(2) and 2.377(3) Å, and the Gd–OH_2 distances in the nitrate (**7**), perchlorate and triflate (**9**) salts of $[Gd.\mathbf{6}(H_2O)]^{3+}$ are 2.351(3), 2.38 and 2.415(7) Å, respectively (the distances to the N and O atoms of ligand **6** remaining invariant). The differences can be attributed to different systems of hydrogen bonds. Thus, in **7** the aqua-ligand acts as a hydrogen-bond donor to two water molecules of crystallisation, locked in a unique stable cyclic array with two nitrate anions (Fig. 2). In triflate salts **8**, the aqua-ligand donates two hydrogen bonds to triflate anions and accepts one from a second-sphere water molecule. In the structures of phases **9**, the aqua-ligand is adjacent to a cavity, occupied by triflate anions and non-stoichiometric amounts of water and ethanol molecules, all intensely disordered (while there is only minor disorder in **8** and none in **7**).

Any substituents on the ligand which can aid the ingress of the exchanging water should lower the free energy of activation for water exchange, whilst the introduction of a more hydrophobic ligand surface should raise the free energy of the transition state leading to longer water exchange lifetimes. In order to get further support for this view, and to find a way to further elongate τ_M, a series of Eu(III) complexes based on the DOTAM structure has been prepared. They contain substituents above the coordination cage, which introduce a different accessible surface to the solvent water molecules, thus allowing variation of the ease of approach of the incoming water molecule. Europium complexes of **2**, **4** and **5** gave satisfactory spectral and analytical data. Their ^1H NMR spectral features indicate that they are present in solution as one dominant isomer (as previously reported for **1**, **3** and **6**), *i.e.* with the regular square anti-prismatic structure of the major isomer of the parent [Eu.DOTAM]. The coordinated water molecule resonates, at 298 K, *ca.* 50 ppm to higher frequency of the bulk water signals for each complex. The measured exchange lifetimes (at 298 K) of the series have been plotted against the accessible surface for the entering solvent molecules (Fig. 3), calculated by molecular modelling established on the structure of [Gd.DOTA]. The close correlation clearly indicates that the most hydrophobic substituents are more efficient in hindering the access of the entering water.

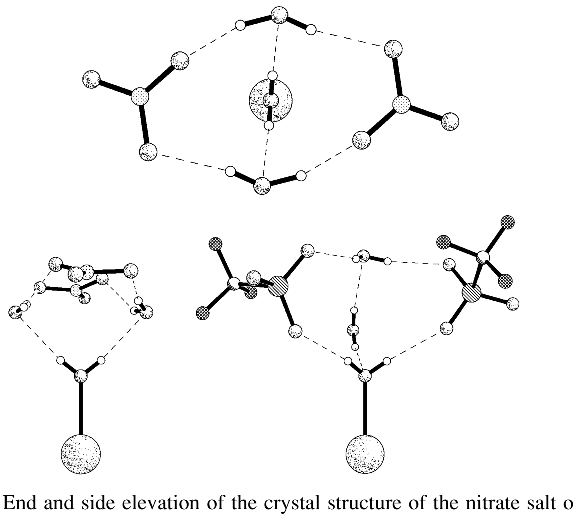

Fig. 2 End and side elevation of the crystal structure of the nitrate salt of $[Gd.\mathbf{6}]^{3+}$ (top and left), showing the strongly hydrogen bonded array capping the coordinated water molecule, compared to the network for $[Tb.\mathbf{6}]^{3+}(CF_3SO_3)_3$, in which the bound water serves as a hydrogen bond acceptor.

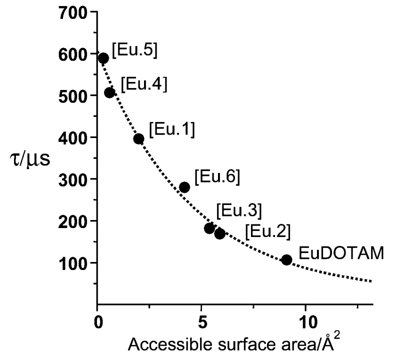

Fig. 3 Relationship between the lifetime of the coordinated water molecule in Eu–tetraamide complexes and the calculated solvent accessible surface, around the bound water.

In summary, the introduction of more hydrophobic substituents disfavours the presence of the second hydration sphere, whose hydrogen-bonded structure is critical in determining the facility of the water interchange process. The ongoing crystallographic study highlights the need to examine an extended series of complexes in a common crystal form.

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Notes and references

‡ *Crystal data*. **7**: monoclinic, space group *C*2 (no. 5), a = 23.290(6), b = 11.271(3), c = 22.244(6) Å, β = 104.13(1)°, Z = 4, R = 0.019 on 14112 unique reflections with $I \geqslant 2\sigma(I)$.

8: monoclinic, space group $P2_1$ (no. 4), Z = 2, T = 120 K, for Ln = Tb, Er, Lu, respectively a = 14.613(3), 14.473(1), 14.387(2), b = 11.728(2), 11.845(1), 11.931(1), c = 19.240(4), 19.217(1), 19.289(2) Å, β = 101.94(1), 102.35(1), 102.69(1)°, R = 0.032, 0.026, 0.029 on 13231, 21765, 15040 unique reflections with $I \geqslant 2\sigma(I)$.

9: monoclinic, space group *I*2 (no. 5, non-standard setting), Z = 8, for Ln = Ce, Pr, Gd, Er, respectively a = 32.176(8), 32.148(9), 32.018(4), 32.134(8), b = 12.754(4), 12.713(4), 12.654(2), 12.697(4), c = 33.047(8), 32.952(10), 32.715(5), 32.738(9) Å, β = 93.45(1), 93.70(1), 93.63(2), 93.54(1)°, R = 0.080, 0.057, 0.077, 0.042 on 27723, 22804, 21541, 30161 unique reflections with $I \geqslant 2\sigma(I)$.

CCDC reference numbers 182447–182454. See http://www.rsc.org/suppdata/cc/b2/b202862j for crystallographic data in CIF or other electronic format.

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