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Beyond Bleaney's Theory: Experimental and Theoretical Analysis of Periodic Trends in Lanthanide Induced Chemical Shift

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Abstract: A detailed analysis of paramagnetic NMR shifts in a series of isostructural lanthanide complexes relavant to PARASHIFT contrast agents reveals unexpected trends in the magnetic suscepti-bility anisotropy that cannot be explained by the commonly used Bleaney's theory. *Ab initio* calculations reveal that the primary as-sumption of Bleaney's theory – that thermal energy is larger than the ligand field splitting – does not hold for the lanthanide complexes in question, and likely for a large fraction of lanthanide complexes in general. This makes the orientation of the magnetic susceptibility ten-sor differ significantly between complexes of different lanthanides with the same ligand: one of the most popular assumptions about isostruc-tural lanthanide series is wrong.

Paramagnetic lanthanide(III) complexes are widely used as shift reagents in NMR, as contrast agents in MRI, and as spin labels in structural biology.[1] Quantitative theories of paramagnetic chemi-cal shift and paramagnetic relaxation are essential in these appli-cations. In particular, pseudocontact chemical shifts (PCS) in-duced by lanthanide complexes are commonly described by McConnell's long-range relation (SI units), [2]

$$\delta^{PCS} = \frac{1}{12\pi r^3}\Big[\chi_{ax}\big(3\cos^2\theta - 1\big) + 3\chi_{rh}\sin^2\theta\cos 2\varphi \Big] \quad (1)$$

where θ, φ, r are the polar coordinates of the nucleus relative to the lanthanide in the eigenframe of the molar magnetic suscepti-bility tensor, and χ_{ax} and χ_{rh} are axiality and rhombicity of the sus-ceptibility tensor. PCS interpretation and control often rely on Bleaney's theory[3] that connects axiality and rhombicity with the ligand field parameters and the lanthanide type,

$$\chi_{ax} = -\frac{\mu_0\mu_B^2 C_J B_2^0}{10(kT)^2}; \quad \chi_{rh} = -\frac{\mu_0\mu_B^2 C_J B_2^2}{30(kT)^2} \quad (2)$$

where C_J is Bleaney's constant, defined for each lanthanide (Tb -157.5, Dy -181, Ho -71.2, Er +58.8, Tm +95.3, and Yb +39.2), μ_B is Bohr's magneton, B_0^2 and B_2^2 are second order ligand field (LF) parameters. Eq.(2) is valid for a well-isolated ground state when the overall splitting of the ground *J*-multiplet due to the ligand field is smaller than *kT*.[3] It is often assumed that, for isostructural se-ries of lanthanide(III) complexes, LF parameters do not depend on the lanthanide. Under that assumption, the axiality/rhombicity

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ratio should be the same within the series, and the PCS should therefore vary only due to C_J. In reality, however, the LF splitting in many lanthanide(III) complexes is larger than *kT* even at room temperature.[4] It has been vividly demonstrated theoretically that none of the trends predicted by Eq.(2) are actually followed by the system in such cases,[5] but there are only a few experimental studies that have examined real isostructural lanthanide complex series of the kind that would challenge Bleaney's theory.[6]

Here, we present a systematic experimental and theoretical anal-ysis of paramagnetic shift trends in a series of lanthanide com-plexes (Scheme. 1) similar to those that are being used *in vivo* for dual (relaxation, temperature) and triple (relaxation, temperature, pH) imaging MRI studies.[7]
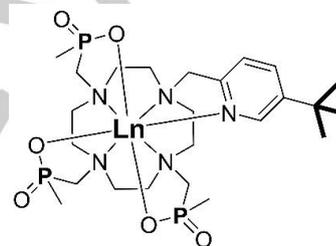
Scheme 1. Structure of the [Ln.L^1] complex, Ln = Tb, Dy, Ho, Er, Tm or Yb.

The ligand contains a *t*Bu reporter group located about 6.6 Å away from the lanthanide, resonating up to 85 ppm away from the usual proton chemical shift range, and relaxing sufficiently quickly to al-low rapid imaging. Recent studies have defined the structure and solution dynamics of [Ln.L^1] complexes, showing that they are 8-coordinate and exist in solution mostly as a twisted square an-tiprismatic Λ-λλλλ isomer both in the solid state and in solution.[8] Using crystallographic data for [Yb.L^1] as the initial guess, DFT geometry optimisations (M06-2X/cc-pVDZ/Stuttgart-ECP, see ESI) were performed to estimate the aqueous solution structures for the series of complexes shown in Scheme 1. A semi-auto-mated combinatorial assignment procedure (developed for *Spin-ach* library[9]) that simultaneously uses information on structure, pseudocontact shifts and relaxation rates to limit the combinato-rial space, has allowed us to assign all 31 individual proton NMR signals of the major conformer.

The traceless part of the magnetic susceptibility tensor for each complex was obtained by fitting Eq.(1) to the experimental data. Excellent fits were obtained, with the adjusted Pearson coefficient above 0.99 (details are given in the ESI). The contact contribution to proton paramagnetic shifts was found to be insignificant even for Ho, where the ratio of contact contribution to PCS is expected to be the largest, in contrast to many *d*-metal complexes, where other methods should be used.[10] The computed unpaired elec-tron spin populations on ligand protons are very small (ESI Table S3) even for equatorial protons where similar DFT studies predict the largest spin population.[11]

Susceptibility tensor fitting results (Figure 1) reveal a significant variation in the amplitude, shape and orientation of PCS fields in

the [Ln.L[1]] series, whereas Bleaney's theory suggests that only the amplitude and sign of the PCS field can change.
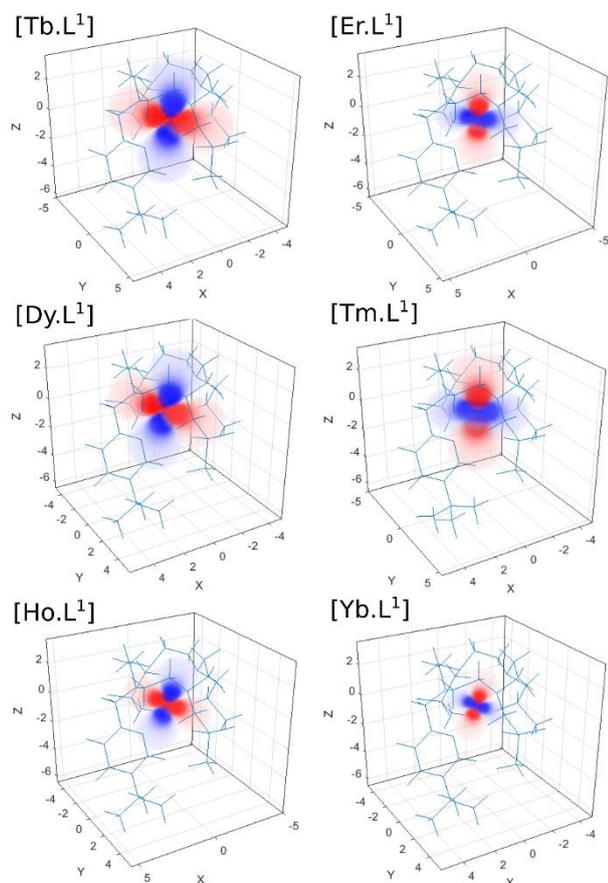

Figure 1. Pseudocontact shift fields for [Ln.L[1]] complexes reconstructed by *Spinach*[9] using the best-fit magnetic susceptibility tensor. Positive PCS is shown in red, negative - in blue, transparency indicates the absolute value normalized for all complexes (see the *ESI* for further information).

The magnetic susceptibility tensor changes from almost ideally axial for Tm^{3+} to almost fully rhombic for Dy^{3+} and Tb^{3+}. Moreover, the tilt of the main anisotropy axis (angle β in Table 1) also varies significantly. An attempt to fit axiality and rhombicity parameters given in Table 1 as a function of C_J using Eq.(2) resulted in a non-ideal fit (Pearson's coefficients of 0.97 and 0.95 respectively). The axiality of Tm and Dy deviates the most from the linear trend. The linear fit gives LF parameters $B_0^2 = -320(40)$ cm^{-1} and $B_2^2 = -210(30)$ cm^{-1}. These values, however, are close to those obtained by the analysis of [Eu.L[1]] emission spectrum. Indeed, the analysis of the splitting of the $^5D_0 \rightarrow ^7F_1$ transition gives $B_0^2 = -330$ and $B_2^2 = -150$ cm^{-1} (see Figure S9 in the ESI).

The current literature is dominated by highly symmetric complexes where the orientation of the susceptibility tensor is known *a priori* and only the magnitude is therefore discussed. Its anomalous variation in some studies is attributed to either changes in the ligand field, or to the additional terms proportional to T^{-3}, or explained – unreasonably – by adjusting C_J constants.[12]

Table 1. Magnetic susceptibility tensors (SI units) for the [Ln.L[1]] series, obtained by paramagnetic shift fitting and computed by CASSCF (in parentheses) expressed in terms of axiality (χ_{ax}), rhombicity (χ_{rh}) and Euler angles. See the ESI for the detailed description of the conventions used.

Ln	χ_{ax} /Å^3	χ_{rh}/ χ_{ax}	α /°	β /°	γ /°
Tb	−0.64	0.26	187	9	214
	(−0.49)	(0.24)	(200)	(18)	(29)
Dy	−0.57	0.30	189	20	201
	(−0.59)	(0.25)	(198)	(24)	(14)
Ho	−0.27	0.22	178	22	220
	(−0.25)	(0.14)	(195)	(27)	(224)
Er	0.28	0.14	217	8	359
	(0.23)	(0.17)	(215)	(23)	(24)
Tm	0.57	0.03	197	6	30
	(0.39)	(0.11)	(205)	(21)	(27)
Yb	0.11	0.13	185	23	211
	(0.14)	(0.11)	(204)	(30)	(21)

To find out the real causes of these discrepancies, we have analysed the electronic structure and magnetic anisotropy of the [Ln.L[1]] series using relativistic multi-reference *ab initio* calculations (SOC-CASSCF/ANO-RCC, see ESI for details), which are known to reproduce magnetic properties of lanthanide complexes exceptionally well.[13] In line with expectations, the LF splitting of the ground terms was found to be almost twice as large as kT at room temperature (**Error! Reference source not found.**). It would therefore be unreasonable to expect Eq.(2) to be valid.
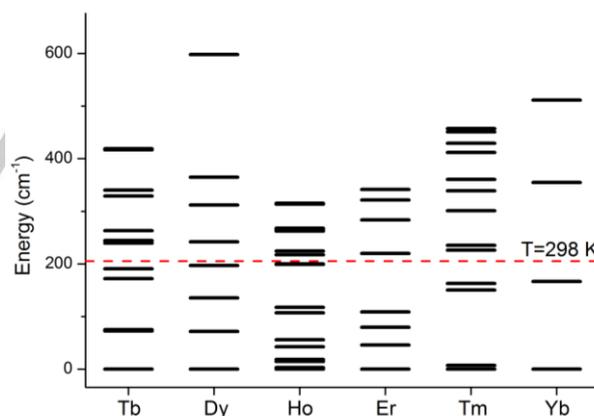

Figure 2. Energy splitting of the ground terms of [Ln.L[1]] due to the ligand field, computed by CASSCF/SOC-RASSI as implemented in MOLCAS 8.0. Calculations demonstrate that the LF splitting is larger than room temperature kT, indicating that Bleaney's approximation is not valid.

Axiality and rhombicity are reproduced quite well by the *ab initio* calculations (Table 1, values in parenthesis). The agreement is less good in the case of Tm^{3+} and Tb^{3+}, where the experimentally determined absolute value of the axiality is slightly higher than predicted by *ab initio* calculations. The tilt angle of the main magnetic axis is slightly overestimated in all calculations, but the trend is reproduced well. The ligand field parameters that fit the energies and the wavefunctions of the ground term (computed using

SINGLE_ANISO[14], see Table S7-S8) show a considerable variation of B_0^2, B_2^2 and other LF parameters within the series – the deviation from the average B_0^2 reaches ~100 cm^{-1}. Despite the obvious limitations of Bleaney's theory, the LF parameters computed by Eq.(2) agree reasonably well with the averaged *ab initio* results (B_0^2 =−440 cm^{-1} and B_2^2=−190 cm^{-1}, see Tables S7-S8), in accord with Eu emission spectral analysis.

The fact that not all the states of the ground multiplet are populated at room temperature also leads to deviations from other commonly used models. For example, PCS is often assumed to vary with temperature as $1/T^2$, because axiality and rhombicity have such a temperature dependence according to Eq.(2). However, calculations show that for some lanthanides, especially for Dy, the product of magnetic anisotropy with temperature squared may not quite reach a plateau at 300 K (ESI Figure S7). The variation in the observed shifts of the ^{t}Bu and methyl resonances with temperature from 290 to 316K in D_2O shows that there is small additional component to $1/T^2$ dependence (ESI Figure S10). The computed ratios of rhombicity over axiality and tilt angle β seem to have a common asymptote for all lanthanides at high temperature, as predicted by Bleaney's theory, but this limit is not reached at room temperature (ESI Figures S6-S8). Lowering the temperature reveals the differences in the electronic structures of different lanthanides. Below 40 K, the axiality of each complex becomes positive ("easy-axis" anisotropy), even for Tb, Dy and Ho, which have "easy-plane" anisotropy at higher temperatures. The orientation of the main magnetic axis at low temperature for Tb, Dy and Ho is closer to equatorial (β ~ 90°) but for Er, Tm and Yb it is closer to axial. A similar trend was reported for [Ln.DOTA(H$_2$O)]$^-$ complexes studied at 2 K by single crystal EPR. [15]

In summary, we have demonstrated the capability of novel simulation-assisted assignment tools to precisely map the pseudocontact shift field in a series of non-symmetric isostructural lanthanide complexes relevant to PARASHIFT agents. It turns out that the trends in the magnetic susceptibility anisotropy cannot be explained by Bleaney's theory. Relativistic CASSCF calculations suggest two reasons for this behaviour: first, the ligand field that is usually assumed to be constant does actually change within the series; second, the assumption in Bleaney's theory that the ligand field splitting of the ground term is smaller than *kT* does not hold for the systems in question.

The sensitivity of the pseudocontact shift field to the nature of the coordination environment, and the striking dependence of the PCS values on the orientation of the major component of the magnetic susceptibility tensor, [8] as one lanthanide ion is replaced by another, strongly suggests that the use of PCS data in structural analyses should be treated with much more caution than is usually taken at the moment.

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Assignment and fitting of paramagnetic proton NMR spectra of isostructural series of lanthanide(III) complexes reveal significant deviations from the commonly employed Bleaney's theory

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