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 relevant to PARASHIFT contrast agents reveals unexpected trends in the magnetic susceptibility anisotropy that cannot be explained by the commonly used Bleaney’s theory. Ab initio calculations reveal that the primary assumption 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 tensor differ significantly between complexes of different lanthanides with the same ligand: one of the most popular assumptions about isostructural 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 chemical shift and paramagnetic relaxation are essential in these applications. In particular, pseudocontact chemical shifts (PCS) induced by lanthanide complexes are commonly described by McConnell’s long-range relation (SI units),[2]

\[
\delta_{\text{PCS}} = \frac{1}{12\gamma_0^2} \left[ \chi_a (3\cos^2 \theta - 1) + 3\chi_n \sin^2 \theta \cos 2\varphi \right]
\]

where \(\theta\), \(\varphi\), \(r\) are the polar coordinates of the nucleus relative to the lanthanide in the eigenframe of the molar magnetic susceptibility tensor, and \(\chi_a\) and \(\chi_n\) are axiality and rhombicity of the susceptibility 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,

\[
\chi_a = -\frac{\mu_b \mu_C^2 B_0^2}{10(kT)}; \quad \chi_n = \frac{\mu_b \mu_C^2 B_2^2}{30(kT)}
\]

where \(C_b\) 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), \(\mu_b\) 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 \(kT\).[5] It is often assumed that, for isostructural series of lanthanide(III) complexes, LF parameters do not depend on the lanthanide. Under that assumption, the axiality/rhombicity ratio should be the same within the series, and the PCS should therefore vary only due to \(C_b\). In reality, however, the LF splitting in many lanthanide(III) complexes is larger than \(kT\) even at room temperature.[6] 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 analysis of paramagnetic shift trends in a series of lanthanide complexes (Scheme. 1) similar to those that are being used in vivo for dual (relaxation, temperature) and triple (relaxation, temperature, pH) imaging MRI studies.[7]

The lanugin contains a \(^1\)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 allow rapid imaging. Recent studies have defined the structure and solution dynamics of [Ln.L] complexes, showing that they are 8-coordinate and exist in solution mostly as a twisted square antiprismatic \(\Lambda\)-\(\Lambda\) isomer both in the solid state and in solution.[8]

Using crystallographic data for [Yb.L] 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-automated combinatorial assignment procedure (developed for Spinach library[9]) that simultaneously uses information on structure, pseudocontact shifts and relaxation rates to limit the combinatorial 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 electron spin populations on lanugin 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] series, whereas Bleaney’s theory suggests that only the amplitude and sign of the PCS field can change.

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Figure 1. Pseudocontact shift fields for \([\text{Ln}.L_1]\) 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).

Table 1. Magnetic susceptibility tensors (SI units) for the \([\text{Ln}.L_1]\) series, obtained by paramagnetic shift fitting and computed by CASSCF (in parentheses) expressed in terms of axiality \((\chi_{ax})\), rhombicity \((\chi_{rh})\) and Euler angles. See the ESI for the detailed description of the conventions used.

<table>
<thead>
<tr>
<th>Ln</th>
<th>(X_{ax}/\text{Å}^3)</th>
<th>(X_{rh}/X_{ax})</th>
<th>(\alpha^\circ)</th>
<th>(\beta^\circ)</th>
<th>(\gamma^\circ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tb</td>
<td>~0.64 (-0.49)</td>
<td>0.26 (0.24)</td>
<td>187 (200)</td>
<td>9 (18)</td>
<td>214 (29)</td>
</tr>
<tr>
<td>Dy</td>
<td>~0.57 (-0.59)</td>
<td>0.30 (0.25)</td>
<td>189 (198)</td>
<td>20 (24)</td>
<td>201 (14)</td>
</tr>
<tr>
<td>Ho</td>
<td>~0.27 (-0.25)</td>
<td>0.22 (0.14)</td>
<td>178 (195)</td>
<td>22 (27)</td>
<td>220 (24)</td>
</tr>
<tr>
<td>Er</td>
<td>0.28 (0.23)</td>
<td>0.14 (0.17)</td>
<td>217 (215)</td>
<td>8 (23)</td>
<td>359 (24)</td>
</tr>
<tr>
<td>Tm</td>
<td>0.57 (0.39)</td>
<td>0.03 (0.11)</td>
<td>197 (205)</td>
<td>6 (21)</td>
<td>30 (27)</td>
</tr>
<tr>
<td>Yb</td>
<td>0.11 (0.14)</td>
<td>0.13 (0.11)</td>
<td>185 (204)</td>
<td>23 (30)</td>
<td>211 (21)</td>
</tr>
</tbody>
</table>

To find out the real causes of these discrepancies, we have analysed the electronic structure and magnetic anisotropy of the \([\text{Ln}.L_1]\) series using relativistic multi-reference \textit{ab initio} calculations (SOC-CASSCF/ANO-RCC, see ESI for details), which are known to reproduce magnetic properties of lanthanide complexes exceptionally well.\(^{11,19}\) In line with expectations, the LF splitting of the ground terms was found to be almost twice as large as \(kT\) at room temperature (\textit{Error! Reference source not found.}). It would therefore be unreasonable to expect Eq.(2) to be valid.

Axiality and rhombicity are reproduced quite well by the \textit{ab initio} calculations (Table 1, values in parenthesis). The agreement is less good in the case of \(\text{Tm}^{3+}\) and \(\text{Tb}^{3+}\), where the experimentally determined absolute value of the axiality is slightly higher than predicted by \textit{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

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using SINGLE_ANISO\textsuperscript{[14]}), see Table S7-S8) show a considerable variation of $B_2^a$, $B_3^a$ and other LF parameters within the series – the deviation from the average $B_2^a$ reaches $\pm$100 cm\textsuperscript{-1}. Despite the obvious limitations of Steiner's theory, the LF parameters computed by Eq.(2) agree reasonably well with the averaged ab initio results ($B_2^a = -440$ cm\textsuperscript{-1} and $B_3^a = -190$ cm\textsuperscript{-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 S10). The computed ratios of rhombicity over axiality and $\beta$ tendency was reported for $[\text{Ln.DOTA(H}_2\text{O)}]$- complexes studied at 2 K by single crystal EPR.\textsuperscript{[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 artifacts. It turns out that the trends in the magnetic susceptibility anisotropy cannot be explained by Steiner'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 Steiner'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\textsuperscript{[9]} 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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Keywords: lanthanides • pseudocontact shift • paramagnetic NMR • ligand field • PARASHIFT


\textsuperscript{[13]} L. Ungur, L. F. Chibotaru, \textit{Lanthanides and Actinides in Molecular Magnetism} 2015, 6, 153-184.
