

### $^{31}\text{P}$ and $^{23}\text{Na}$ NMR Lanthanide Induced Shifts in Axially Symmetric Macrocyclic Phosphonate Complexes\*

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A number of cyclic polyoxa and substituted cyclic polyaza macrocycles form complexes with the trivalent lanthanide cations displaying a wide range of stability constants. The unusual stability and rigidity of the lanthanide tetraazacyclododecane,  $\text{Ln}(\text{DOTA})^-$ , complexes appear to be a function of the favorable [3333] conformation of the cyclododecane ring and the fit of the lanthanide cations into the capped square antiprism structure [1, 2]. Increasing the size of the tetraaza ring from 12 (DOTA) to 14 (TETA) members decreases the stability [3] and the stereochemical rigidity [4] of the resulting  $\text{Ln}^{3+}$  complexes. Changing from a tetraazacyclododecane structure (DOTA) to a triazacyclononane structure (NOTA) results in substantially lower stability constants [5] (similar to the TETA complexes) and less rigidity in their  $\text{Ln}^{3+}$  complexes [6, 7]. Thus, the cavity size and the number and identity of the donor atoms in the tetraazacyclododecane tetraacetate chelate appear optimal for the most stable  $\text{Ln}^{3+}$  complexes.

We have prepared an analog of DOTA which contains four methylene phosphonate arms substituted for the acetates. This new chelate, tetraazacyclododecane- $N,N',N'',N'''$ -tetramethylenephosphonate (DOTP), forms complexes with the  $\text{Ln}^{3+}$  cations showing higher stability constants and even more stereochemical rigidity than the corresponding  $\text{Ln}(\text{DOTA})^-$  complexes at room temperature [8]. We report here  $^{31}\text{P}$  and  $^{23}\text{Na}$  lanthanide induced NMR shifts (LIS) for the resulting  $\text{Ln}(\text{DOTP})^{5-}$  complexes and some preliminary  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra which verify the rigidity of the complexes.

#### Experimental

DOTP was synthesized and characterized as described elsewhere [9]. The  $\text{Ln}^{3+}$  complexes were

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prepared by mixing a 10 mM solution of DOTP adjusted to pH 8–9 with one equivalent of lanthanide chloride while maintaining the temperature near to 80 °C. The final pH was adjusted with NaOH and the  $[\text{Na}^+]_{\text{T}}$  adjusted as necessary to 140 mM. NMR spectra were recorded either on a JEOL FX-200 or a Bruker MSL-200 spectrometer at  $25 \pm 1$  °C.

#### Results and Discussion

The  $^1\text{H}$  spectrum of  $\text{Yb}(\text{DOTP})^{5-}$  presented in Fig. 1 is representative of the remaining complexes. Each complex shows six resonances indicating that: (a) the ethylenediamine moiety is locked into a rigid conformation such that each proton is magnetically non-equivalent; and (b) the methylene phosphonates are bound sufficiently long to make the methylene protons non-equivalent. Clearly, the complex has a 4-fold axis of symmetry. The  $^{13}\text{C}$  spectrum of  $\text{Eu}(\text{DOTP})^{5-}$  illustrates that the ethylenediamine carbons are also non-equivalent, as expected for a five-membered chelate ring held in a single conformation. In each case, one of the ethylenediamine carbon resonances is broader than the other, indicating that one carbon is substantially closer to the paramagnetic cation in this rigid complex.

The  $^{23}\text{Na}$  and  $^{31}\text{P}$  LISs for the entire series of  $\text{Ln}(\text{DOTP})^{5-}$  complexes are presented in Table I. The  $^{31}\text{P}$  shifts represent fully bound LIS values referenced to the averaged  $^{31}\text{P}$  chemical shift of  $\text{La}(\text{DOTP})^{5-}$  (20.6 ppm) and  $\text{Lu}(\text{DOTP})^{5-}$  (21.3 ppm). The  $^{23}\text{Na}$  shifts were found to be quite sensitive to the concentrations of  $\text{Na}^+$  and  $\text{Ln}(\text{DOTP})^{5-}$ , other competing cations such as  $\text{K}^+$  or  $\text{Ca}^{2+}$ , and pH. The values reported in the Table have been normalized to 10 mM  $\text{Ln}(\text{DOTP})^{5-}$ , 140 mM  $\text{Na}^+$ , pH 10, and for small differences in bulk susceptibility. The  $^{23}\text{Na}$  LIS values parallel theoretical pseudocontact shift values for the  $\text{Ln}^{3+}$  cations. The direction of the  $^{23}\text{Na}^+$  shifts is identical to those reported for the  $\text{Ln}(\text{DOTA})^-$  complexes although the magnitude of the LISs is substantially greater in the phosphonate complexes (at equivalent concentrations). The larger shifts induced by the  $\text{Ln}(\text{DOTP})^{5-}$  complexes may be due to minor changes in structure or result from larger  $\text{Na}^+$  binding constants to the phosphonate complexes.

The  $^{23}\text{Na}^+$  shifts are presumed to be entirely pseudocontact in origin. A plot of  $\text{LIS}/\langle S_z \rangle$  versus  $D/\langle S_z \rangle$  shows a clear break in the data between the light (Ce → Eu) and heavy (Tb → Yb) complexes. The slope of this plot yields the geometric factor,  $G$ , and the intercept gives the hyperfine coupling constant,  $A$  [10]. Both lines (light and heavy series) display intercepts near zero, as expected, but the slope for the heavy complexes is about 5 times greater than

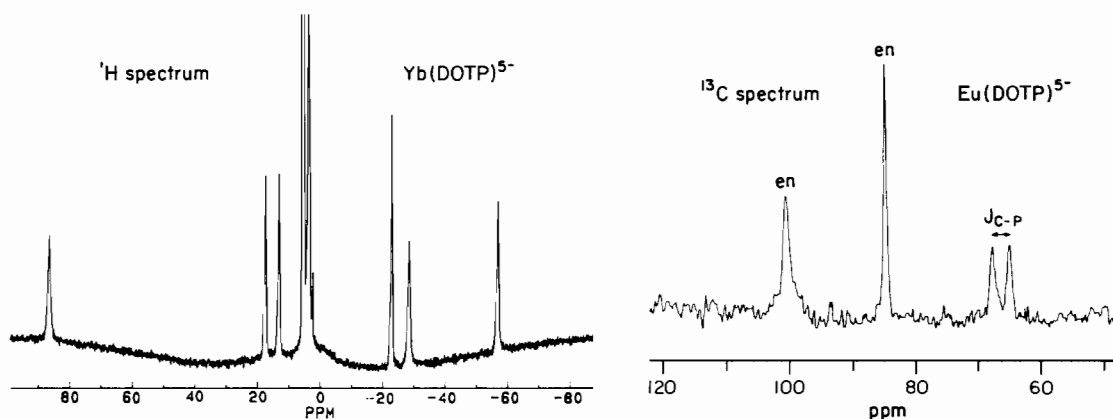


Fig. 1. High resolution  $^1\text{H}$  spectrum of  $\text{Yb}(\text{DOTP})^{5-}$  (left) and  $^{13}\text{C}$  spectrum of  $\text{Eu}(\text{DOTP})^{5-}$  (right). Both spectra were collected on 10 mM samples at pH 7 and 25  $^\circ\text{C}$ .

that for the lighter complexes. The breaks we observe in this data do not result from cation size contraction [11] since presentation of the same data as LIS/ $D$  versus  $\langle S_z \rangle / D$  shows similar breaks. Thus, there appears to be a structural change between  $\text{Eu}(\text{DOTP})^{5-}$  and  $\text{Tb}(\text{DOTP})^{5-}$  which results in larger  $^{23}\text{Na}^+$  shifts for heavier complexes. The  $^{23}\text{Na}^+$  pseudocontact shifts for each complex calculated from the slope of the respective lines are shown in parentheses for comparison.

TABLE I.  $^{23}\text{Na}$  and  $^{31}\text{P}$  Lanthanide Induced Shifts for the  $\text{Ln}(\text{DOTP})^{5-}$  Complexes<sup>a</sup>

$\text{Ln}^{3+}$	$^{31}\text{P}$ (ppm)	$^{23}\text{Na}$ (ppm)
Ce	-1.35 (3.7)	-0.8 (-0.7)
Pr	-2.82 (6.4)	-1.4 (-1.2)
Nd	-27.3 (2.4)	-0.6 (-0.4)
Sm	12.4 (0.4)	-0.2 (-0.1)
Eu	33.9 (-2.3)	2.8 (2.2)
Tb	453.0 (395.9)	-40.8 (-46.4)
Dy	353.5 (460.4)	-43.8 (-53.9)
Ho	152.1 (179.5)	-17.2 (-21.0)
Er	-176.8 (-151.9)	21.6 (17.8)
Tm	-341.0 (-244.0)	41.7 (28.6)
Yb	-68.5 (-101.3)	6.1 (11.9)

<sup>a</sup>The spectra were collected on 10 mM  $\text{Ln}(\text{DOTP})^{5-}$  samples containing 140 mM  $\text{Na}^+$  (pH = 7 for  $^{31}\text{P}$  spectra and pH = 10 for  $^{23}\text{Na}$  spectra). Positive LIS values are to low field. Values in parentheses are the calculated pseudocontact shifts (see text).

Plots of LIS/ $\langle S_z \rangle$  versus  $D/\langle S_z \rangle$  for the  $^{31}\text{P}$  data show the same breaks as the  $^{23}\text{Na}$  data. The slopes derived from these plots were used to estimate the pseudocontact shift contributions and these values are also presented in Table I. The  $^{31}\text{P}$  shifts for the heavy lanthanide complexes (Tb  $\rightarrow$  Yb) are dominated by pseudocontact contributions although the contact term is clearly non-zero, as expected for phosphorus shifts. Interestingly, the  $^{31}\text{P}$  shifts for the light lanthanide complexes appear to be heavily dominated by contact contributions.

The origin of the structural change which occurs between  $\text{Eu}(\text{DOTP})^{5-}$  and  $\text{Tb}(\text{DOTP})^{5-}$  cannot be determined from this data. However, previous stability constant measurements for the entire series of  $\text{Ln}(\text{DOTA})^-$  complexes [5] indicate there is about a 30-fold increase in  $\log K$  between the  $\text{Eu}^{3+}$  and  $\text{Tb}^{3+}$  complexes, which reflects the rather strict size requirements of the tetraazatetraacetate cavity. The data presented here suggest that the  $\text{Ln}(\text{DOTP})^{5-}$  complexes parallel this trend, although a more quantitative analysis of the structural change which occurs between  $\text{Eu}(\text{DOTP})^{5-}$  and  $\text{Tb}(\text{DOTP})^{5-}$  must await a more complete analysis of the  $^1\text{H}$  and  $^{13}\text{C}$  LIS values.

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