Use of Lanthanide Nuclear Magnetic Resonance Shift Reagents in Determination of Molecular Configuration[1]

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Abstract: Previous determinations of molecular geometry by use of lanthanide shift reagents have been based on the (tacit) assumption that the complex is rigid. However, whenever rapid internal rotations are present it is necessary to average the *entire quantity*, $[(3 \cos^2 \theta_i - 1)/r_i^3]$, *before* comparing observed and calculated shift ratios. This paper presents several models for free or hindered internal rotation and tests the models on three organic substrates which are rigid except at the point of attachment to the lanthanide. While diacetoneglucose appears to be rigid at the point of attachment (so that the configuration of the complex can be established with confidence), both aniline and a rigid bicyclic alcohol (**1**) exhibit considerable internal rotation. In fact, the shift ratios for aniline cannot be accounted for by any "static" model for the complex. Moreover, examples are provided which show that "good" fits between observed and calculated shift ratios are not in themselves evidence for the existence of that conformation (for both aniline and **1**, some of the best "fits" occur at chemically unreasonable values for the lanthanide–donor atom separation). However, the use of several models for internal rotation, interpreted by means of contour plots of "fits" as a function of geometry of the complex, can provide a means for sorting out the correct from the spurious calculated configurations.

There are two distinct aspects to the determination of molecular geometry from the pseudo-contact-type contribution to lanthanide-induced nmr chemical shifts: (1) experimental determination of reliable values for the bound chemical shifts, Δ_i, for each proton involved, and (2) proper use of the $[(3 \cos^2 \theta - 1)/r^3]$ dependence in Δ_i to obtain molecular geometry (see Theory). Each of these steps entails a compromise between rigor and practical utility, and the optimal procedure is dictated by the information desired.

When (as in the present instance) the ultimate object is molecular configuration, the experiment should be designed to yield Δ_i and stoichiometry while suppressing the complication of intermediate steps in formation of the complex. For the molecular association of lanthanide shift reagent (L) with organic substrate (S), restriction of measurements to the concentration range, $[S]_0 \gg [L]_0$, ensures that the predominant species of complex will be LS_n, so that the parameters to be determined reduce to K_B, Δ_i, and n. In any concentration range, the effect of intermediate equilibria in eq 1 will be

$$L + nS \underset{}{\overset{K_B}{\rightleftharpoons}} LS_n \qquad (1)$$

to add *at least two more* parameters (chemical shift and binding constant) for each intermediate complex, while the number of experimental variables is the *same* as before; under these conditions a much greater range of concentration must be employed in order to reach any degree of reliability in the results.[5] However, the limit, $[S]_0 \gg [L]_0$ constrains the system to behave as if it were a simple one-step binding process, and a convenient, precise, and accurate method for obtaining both stoichiometry and Δ_i is simply to plot $[S]_0$ *vs.* $(1/\delta)$, where δ is the induced shift for a particular $[S]_0$ and constant

$[L]_0$.[6] Accumulating experimental evidence supports the consistency of this method in determinations of K_B and Δ_i,[6–8] stoichiometry,[9] and geometry[10] of the bound substrate.

In the Theory, it is shown that all previous determinations of molecular geometry by use of lanthanide shift reagents have been based on a single (and in general not even the best) model for internal motion in the complex. A variety of new models are proposed and tested on selected substrate molecules described in the Results and Discussion. While present treatments in this paper were successful in arriving at well-defined and chemically reasonable substrate configurations, the interpretation rests on a number of assumptions, and these are listed in the Theory for future reference.

Theory

The determination of molecular configuration from experimentally derived bound chemical shifts (Δ_i) is a highly underdetermined problem. The analysis becomes tractable only when a number of preliminary conditions are satisfied.

(1) The Δ_i values themselves are obtained in the most direct and reliable way (see the introductory section).

(2) Δ_i is wholly pseudo-contact in origin, as seems to be the case for proton shifts induced by Eu or Pr shift reagents.[11] This assumption does not appear to be valid for ^{13}C shifts from any shift reagent.[12]

(3) The geometry of the substrate bound in the complex is the same as that of free substrate in solution.

(4) The effective electronic g tensor is axially symmetric, with principal axis along the Eu–donor atom

(6) I. M. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Can. J. Chem.*, **50**, 2119 (1972).
(7) I. M. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Chem. Commun.*, 1281 (1971).
(8) D. R. Kelsey, *J. Amer. Chem. Soc.*, **94**, 1764 (1972).
(9) V. G. Gibb, I. M. Armitage, L. D. Hall, and A. G. Marshall, *ibid.*, **94**, 8919 (1972).
(10) I. M. Armitage, L. D. Hall, A. G. Marshall, and L. G. Werbelow, *Chem. Technol.*, in press.
(11) W. D. Horrocks, Jr., and J. P. Sipe, III, *J. Amer. Chem. Soc.*, **93**, 6800 (1971).
(12) J. D. Roberts, private communication.

bond; without this assumption, the problem is too underdetermined to solve. Determination of stoichiometry for the complex thus becomes important, since the g tensor principal axis will most easily be located in a 1:1 adduct. Since the g tensor in the solid can deviate markedly from axial symmetry,[13] we require sufficient internal rotational motion about the Eu–donor atom bond to ensure effectively axial symmetry for the complex in solution.[14] This motion need merely be fast compared with Δ_i, which seems highly likely in view of the rather long Eu–donor bond distances observed by X-ray diffraction.[15]

With these assumptions, Figure 1 defines the starting point for determination of molecular geometry. This right-handed coordinate system has been designed to facilitate computer fits of shift data: the donor atom (atom 1) defines the origin; proceeding from atom 1 to 2 defines the positive x direction; atom 3 is then assigned a positive y value in the x–y plane. Ω, ϕ, and $\mathbf{R}$ unambiguously fix the position of the lanthanide atom relative to the molecular frame.

Since the molecules of present interest are rigid except at the point of attachment to the lanthanide, a "determination" of the configuration of the complex consists of finding the "best" values of $\mathbf{R}$, Ω, and ϕ, given the configuration of the substrate molecule itself. The Appendix gives a rapid method for obtaining the desired parameters, $\mathbf{r}_i$ and θ_i for the ith proton, from (guessed) values of the Eu–donor atom bond distance $\mathbf{R}$, the polar (Ω) and azimuthal (ϕ) angles which locate the Eu–donor bond axis relative to the molecular frame, and the coordinates of all atoms in the substrate. Assuming a perfectly rigid complex, one could proceed as follows. First guess a location for the lanthanide atom (i.e., choose values for $\mathbf{R}$, Ω, and ϕ) and compute [(3 cos² θ_i − 1)/$\mathbf{r}_i^3$] for each proton of the substrate; then calculate the normalized variance (the "R" value)[16] between ratios of this quantity and observed shift ratios for all possible independent pairs of protons. Repeat the procedure many times for different values of $\mathbf{R}$, Ω, and ϕ and then choose the most probable conformation as that which gives the best "fit" (smallest normalized variance, smallest "R" value) to the observed shift ratios. The difficulty with this treatment is that it is quite possible to obtain correct shift *ratios* from incorrect *absolute* shifts, so that sometimes the best "fits" are obtained at chemically unreasonable values of $\mathbf{R}$ and Ω (see Results).[17]

The source of the difficulty lies in attempting to fit the observed shifts to those computed for *individual* conformations (this procedure will at best indicate the average values of $\mathbf{r}_i$ and θ_i). However, the observed quantity is Δ_i

$$\Delta_i \propto \left\langle \frac{3 \cos^2 \theta_i - 1}{\mathbf{r}_i^3} \right\rangle \neq \frac{3 \cos^2 \langle \theta_i \rangle - 1}{\langle \mathbf{r}_i \rangle^3} \quad (2)$$

(13) W. D. Horrocks, Jr., J. P. Sipe, III, and J. R. Luber, *J. Amer. Chem. Soc.*, **93**, 5258 (1971).

(14) For nonaxial magnetic symmetry, the induced shift is of the form (W. DeW. Horrocks, Jr., and E. S. Greenberg, *Inorg. Chem.*, **10**, 2190 (1971)), $\Delta_B = \text{const}[3 \cos^2 \theta - 1)/r^3] + \text{const}'[\sin^2 \theta \cos 2\Phi/r^3]$. For fast internal rotation, averaging of cos 2Φ over 2π makes the second term go to zero, leaving the desired eq 2.

(15) R. E. Cramer and K. Seff, *Chem. Commun.*, 400 (1972).

(16) M. R. Willcott, III, R. E. Lenkinski, and R. E. Davis, *J. Amer. Chem. Soc.*, **94**, 1742 (1972); R. E. Davis and M. R. Willcott, III, *ibid.*, **94**, 1744 (1972).

(17) An "R" value of 0.04 or less for the present calculations corresponds to agreement well within experimental error for each of the experimental "bound" shift ratios.

where the brackets denote an average over all possible bound conformations during the residence of a substrate at a shift reagent. Whenever rapid internal rotations are present, it is necessary to average the *entire quantity* [(3 cos² θ_i − 1)/$\mathbf{r}_i^3$] on account of the inequality just written, and any analysis based on a best single conformation should not be expected to succeed. The three simplest models for internal rotation are free rotation, no rotation, and jumps between the minima of an n-fold potential (the remainder of this paper concerns applications of these three models to the internal motions in selected molecules which are expected to fall into these categories).

Free rotation about the atom 1–atom 2 axis is readily simulated by multiplying the quantity [(3 cos² θ_i − 1)/$\mathbf{r}_i^3$] by a normalized unit weight factor

$$P(\phi) \, d\phi = (^1/_2\pi) \, d\phi \quad (3)$$

followed by integration over all ϕ from 0 to 2π, where this operation is carried out *before* comparing observed with calculated shift ratios. The same procedure may be used for the opposite limit of a rigidly locked complex by use of the weight factor

$$P(\phi) \, d\phi = \delta(\phi - \phi_0) \, d\phi \quad (4)$$

where ϕ_0 is the (fixed) azimuthal angle in the Dirac δ function. Since no real molecule will be perfectly rigid, it is desirable to relax the distribution (4), to span some specified angular range in ϕ in the vicinity of ϕ_0—we have for convenience chosen a Gaussian weight factor[18]

$$P(\phi) \, d\phi = (A/\sqrt{\pi}) \exp[-A^2(\phi - \phi_0)^2] \, d\phi \quad (5)$$

In eq 5, a large value of A corresponds to a narrow distribution of possible angles; the values of $A = 8^{1/2}$ or $A = 1$ in the next section correspond to rms widths of about 14 or 40° about ϕ_0, respectively. Finally, the possibility of rapid random jumps between n equally likely values of ϕ may be simulated by use of the periodic weight function

$$P(\phi) \, d\phi = (1/\pi) \cos^2 [(n/2)(\phi - \gamma)] \, d\phi \quad (6)$$

where γ is the ϕ distance between $\phi = 0$ and the nearest potential minimum in ϕ. Random jumps may also be simulated by δ-function distributions

$$P(\phi) \, d\phi = a\delta(\phi - \phi_1) + b\delta(\phi - \phi_2) + \ldots + f\delta(\phi - \phi_n) \, d\phi \quad (7)$$

where $a, b, \ldots, f$ represent the probability of finding the complex with ϕ value $\phi_1, \phi_2, \ldots, \phi_n$, respectively. Numerical integration (when necessary) was carried out by low-order Gauss–Legendre quadrature (*i.e.*, 6, 8, or 10 point) and in most cases checked against higher order formulas to verify its validity.

Experimental Section

Solvents used in this study were CDCl₃ and CCl₄. CDCl₃ (99.8%) from Merck, Sharp, and Dohme, Montreal, was stored over Linde molecular sieve (4A) which was preheated to 100° for 24 hr prior to use. CCl₄ (reagent grade) from Fisher Scientific Co. was distilled and stored over NaOH pellets prior to use.

Aniline (reagent grade) from British Drug Houses Ltd. was puri-

(18) The actual domain of integration is from $\phi = \phi_0 + \pi$ to $\phi = \phi_0 - \pi$. Thus it is correct to compute induced shift *ratios* for any given A, but one should not compare *absolute* shifts computed from different choices for A.

Table I. Induced Chemical Shift Data for Association of Three Substrates with Lanthanide Nmr Shift Reagents

Substrate		$\Delta_B{}^a$	Δ_B ratios	$K_B{}^a$	Reagent	Solvent
Aniline	o	14.90 ppm		19 l. mol^{-1}	Eu(DPM)$_3$	CDCl$_3$
	m	3.11	o/m = 4.79	22		
	p	3.72	o/p = 4.00	20		
DAG[20]	H$_1$	4.46	H$_3$/H$_2$ = 2.59	33	Eu(DPM)$_3$	CDCl$_3$
	H$_2$	6.06	H$_3$/H$_1$ = 3.52	31		
	H$_3$	15.70	H$_3$/H$_4$ = 1.82	29		
	H$_4$	8.61		30		
	H$_5$	22.14^c		30		
1[20]	H$_5$	55.0 Hz^b	H$_5$/H$_6$(exo) = 1.40	≥100	Eu(FOD)$_3$	CCl$_4$
	H$_6$(exo)	39.4 Hz	H$_5$/H$_6$(endo) = 2.90			
	H$_6$(endo)	19.0 Hz				

^{a} Values for Δ_B and K_B were obtained from plots of [S]$_0$ vs. (1/δ), as explained in ref 6. For aniline and DAG, binding was unequivocally shown to be 1:1.[6] ^{b} For binding of **1** to Eu(FOD)$_3$, the binding was too strong to measure, and the listed shifts correspond to the induced shifts for an [L]$_0$/[S]$_0$ ratio of 0.3. The shift ratios for **1** are in good agreement with those in ref 15 for the unsubstituted alcohol. ^{c} The H$_5$ proton was not used in the analysis because of the possibility of internal rotation about the C(4)–C(5) bond which would complicate the analysis.
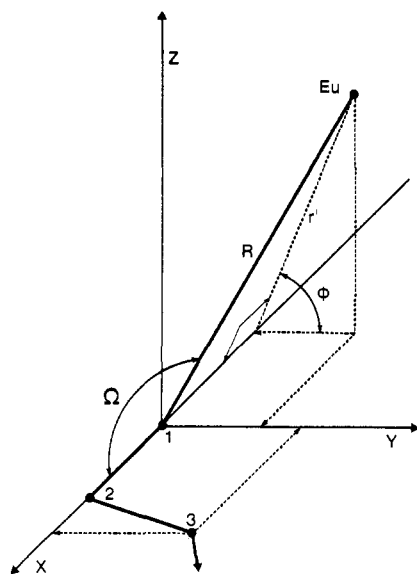

Figure 1. Coordinate system for substrate–shift reagent complex. R is the lanthanide–donor atom bond direction vector; |R'$_i$| = |R| sin Ω. Origin is at atom 1; proceeding at atom 2 then defines the positive x axis; atom 3 is then assigned a positive y value in the x–y plane; z direction then follows from right-hand convention. Ω, ϕ, and R unambiguously define the position of the lanthanide relative to the donor atom.

fied as follows.[19] A 10-ml sample was distilled from a small amount of zinc dust and a 4-ml fraction collected from the middle: bp 183°. *exo*-5-Hydroxy-1,2,3,4,7,7-hexachloronorborn-2-ene[10] was sublimed immediately prior to use (mp 154.5°). Diacetoneglucose [1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose] was purified by recrystallization from chloroform–*n*-hexane (1:2 v/v), giving mp 104–105°, and was then dried *in vacuo* at 60° for about 12 hr before use.

Eu(DPM)$_3$[20] was prepared from europium oxide (99.99%) by the method of Eisentraut and Sievers.[21] It was sublimed immediately prior to use and handled thereafter in a glove bag which had been flushed many times with dry nitrogen, and a nitrogen atmosphere was maintained throughout. Eu(FOD)$_3$[20] was also prepared from europium oxide, by the method of Springer, Meek, and Sievers.[22]

(19) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1957, p 564.

(20) Abbreviations used: Eu(DPM)$_3$ for tris(dipivalomethanato)-europium(III); Eu(FOD)$_3$ for tris(2,2-dimethyl-6,6,7,7,8,8-hepta-fluoro-3,5-octanedionato)europium(III); DAG for diacetoneglucose, proper name 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose; **1** for *exo*-5-hydroxy-1,2,3,4,7,7-hexachloronorborn-2-ene.

(21) K. J. Eisentraut and R. E. Sievers, *J. Amer. Chem. Soc.*, **87**, 5254 (1965).

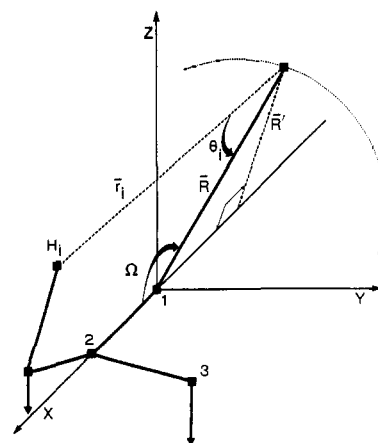(22) L. S. Springer, Jr., D. W. Meek, and R. E. Sievers, *Inorg. Chem.*, **6**, 1105 (1967).

Figure 2. Coordinate system for substrate–shift reagent complex. r$_i$ is the distance vector from the lanthanide atom to the ith proton of the substrate; θ_i is the angle between R and r$_i$. Internal rotation of R about the x axis consists of permitting a range of ϕ values, shown as the circle in the figure.

The product was recrystallized twice from methylene chloride and then stored in a vacuum desiccator over P$_2$O$_5$ until use.

All sample preparations were carried out in a glove bag which had been flushed several times with dry nitrogen and then maintained in a nitrogen atmosphere. Samples were prepared such that [L]$_0$ remained constant (*ca.* 0.006 *M*) while [S]$_0$ varied (*ca.* 0.02–0.1 *M*). All nmr measurements were performed on a Varian XL-100 spectrometer in the frequency-swept mode, using internal tetramethylsilane[6] at a probe temperature of approximately 40°.

Shift reagents used were Eu(DPM)$_3$ with aniline and DAG,[20] and Eu(FOD)$_3$ with **1**.[20] All experimental shift ratios are listed in Table I.

Results and Discussion

Determinations of molecular geometry from chemical shift ratios are best illustrated by contour plots of the type shown in Figures 3–7. The contours are simply paths of constant normalized variance ("R" value,[16] agreement factor) between observed and calculated shift ratios, as a function of possible positions of the lanthanide–donor atom distance (R), the angle (Ω) between the europium donor bond and the bond between atom 2 and the donor atom, and the azimuthal angle (ϕ) shown in Figures 1 and 2. A small normalized variance thus connotes very good agreement between observed and calculated shift ratios.

The first substrate considered is the monofunctional donor, diacetoneglucose, or DAG.[20] Figure 3 shows the contours which are obtained, under the assumption
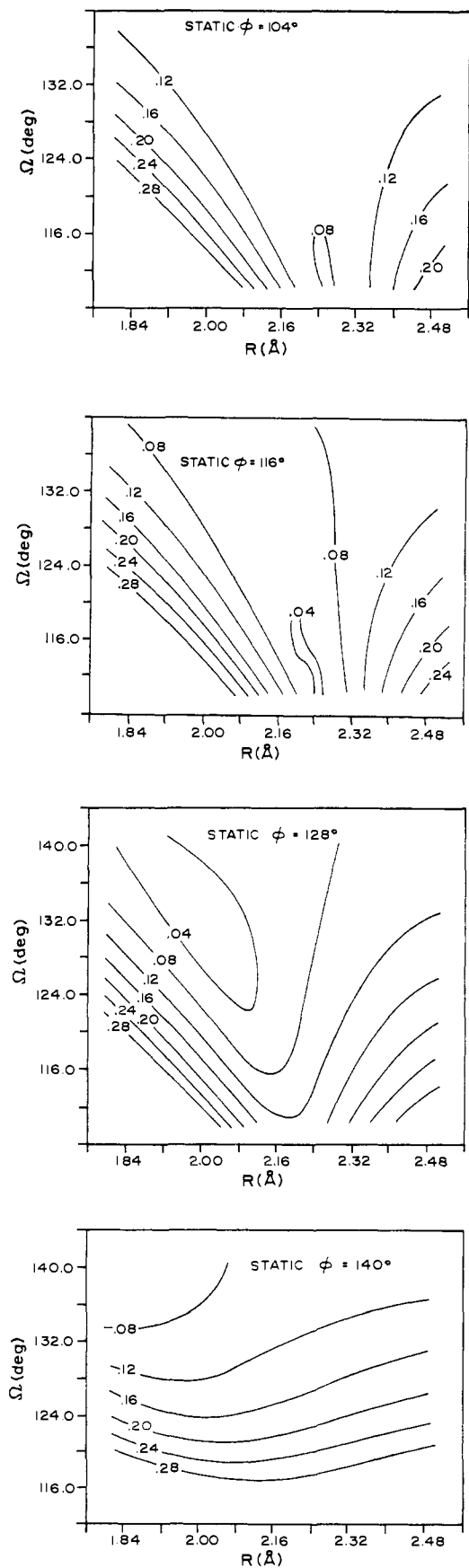
Figure 3. Contours of normalized variance (between observed and calculated induced chemical shift ratios) as a function of possible positions of the lanthanide atom relative to the donor atom of the substrate for DAG.[20] It has been assumed that there is no internal rotation about the bond from carbon to donor oxygen. **R**, Ω, and φ are as in Figure 1.
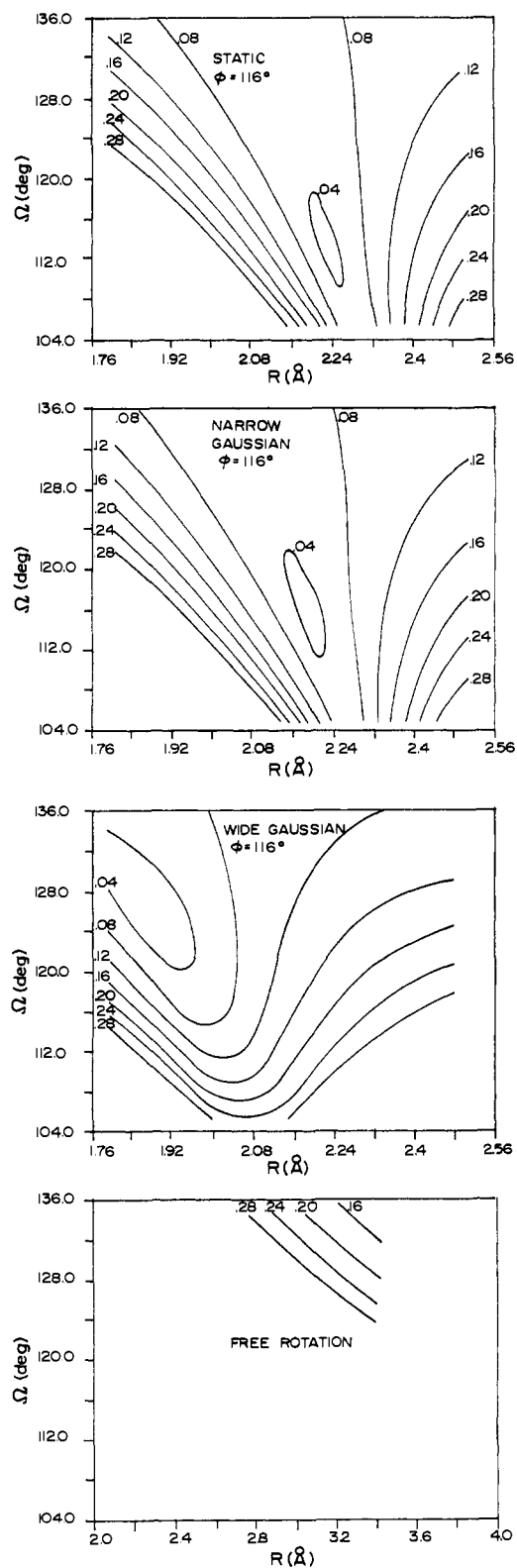

Figure 4. Contours of normalized variance as a function of lanthanide position for DAG.[20] For the "static" plot, there is no internal rotation about the carbon–donor bond. For the "narrow" and "wide Gaussian," φ values are first weighted by the factor, $(A/\sqrt{\pi})\exp[-A^2(\phi - \phi_0)^2]$ dφ, and then integrated over all φ (with $A = \sqrt{8}$ or 1, respectively) before comparing observed with calculated shift ratios (see Theory). For the "free rotation" plot, φ values are averaged over all φ from 0 to 2π using unit weight factor.

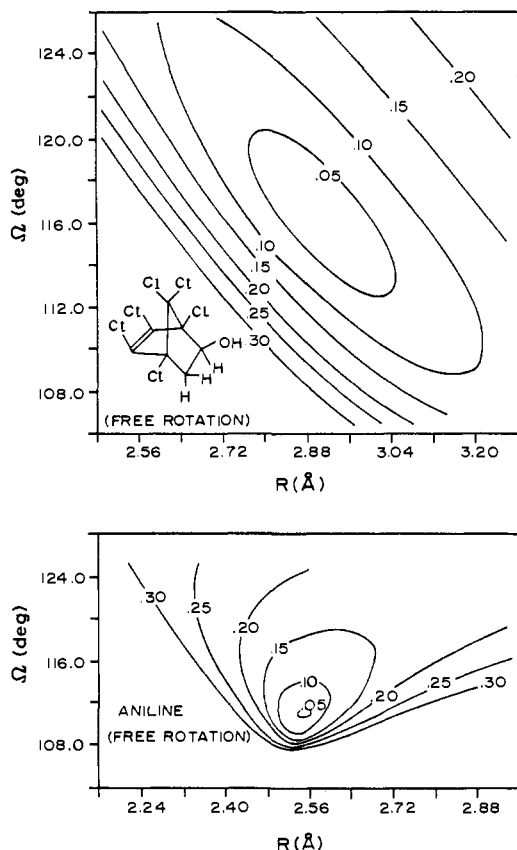that there is no internal rotation about the carbon–donor bond. Two features are evident. First, for
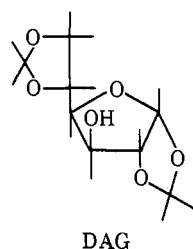
Figure 5. Contours of normalized variance as a function of lanthanide position for aniline or **1**.[20] Internal rotation about the C–N (or C–O) bond is assumed to be completely free (unhindered).

DAG

some choices of ϕ, there are no "good" fits (*i.e.*, having normalized variance smaller than 0.04). Second, among the range of ϕ values for which good fits are obtained, some ϕ values lead to unreasonably short europium–oxygen bond distances.[15] Based on these results, if DAG is rigid with respect to internal rotation about the carbon–donor bond, then the most likely position of the europium is $R = 2.2$ Å, $\Omega = 114°$, and $\phi = 116°$.

Figure 4 shows the effect of varying degrees of internal motion on the agreement between observed and calculated shift ratios for DAG. Beginning (as in Figure 3) with a static molecular frame, we now allow for a Gaussian distribution of ϕ values, centered at the most likely ϕ value of 116°, with a root-mean-square width of either 14° ("narrow Gaussian" in Figure 4) or 40° ("wide Gaussian"). It is clear that this greater latitude in internal rotational position produces less reasonable fits, with respect both to agreement with experiment (normalized variance) and also intuition (too-short values for Eu–O bond distance).[15] In fact, the contour plot for the assumption of completely free internal rotation about the carbon–donor bond (bottom right in
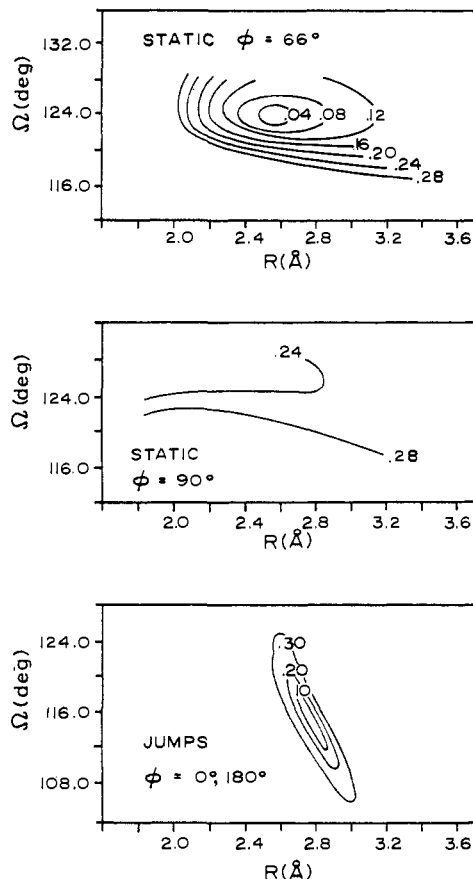

Figure 6. Contours of normalized variance as a function of lanthanide position for aniline. Top: fits based on experimental shifts for protons 2, 3, and 4, assuming no internal rotation about the C–N bond. Middle: fits based on experimental shifts for protons 2, 3, and 4, assuming no internal rotation about the C–N bond. Bottom: fits based on experimental shifts for protons 2, 3, and 4, assuming rapid jumps between fixed ϕ values of 0 and 180°.

Figure 4) shows that free rotation is simply not possible in this complex.

It is thus demonstrated that the DAG:Eu(DPM)₃ complex is relatively rigid, so that the geometry of the complex may be determined with confidence. The situation is considerably altered for the binding of either aniline or **1** to lanthanide shift reagents. Figure 5 shows

1
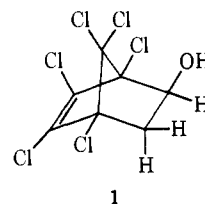
the contours which are obtained for these substrates under the assumption of completely free internal rotation about the C–N or C–O bond, respectively; for both substrates "good" fits are obtained. For aniline, the value of 2.55 Å for the Eu–N bond distance compares with typical X-ray values of about 2.65 Å, while the value of 2.9 Å for the Eu–O bond distance in **1** is quite large in comparison with the X-ray range of 2.3–2.4 Å.[14] It is thus instructive to examine other models for internal motion in these substrates.

The aniline results shown in Figure 6 are a particularly incisive illustration of the danger of literal inter-
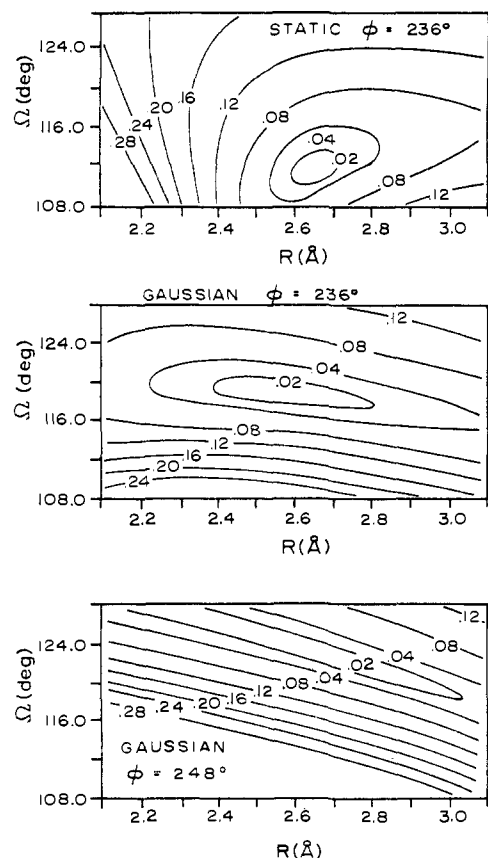
Figure 7. Contours of normalized variance as a function of lanthanide position foi 1.[20] Top: no internal rotation about C–O bond. Middle: Gaussian distribution in ϕ, $(A/\sqrt{\pi})\exp[-A^2(\phi - \phi_0)^2]$ with $A = 1$, centered at $\phi_0 = 236°$. Bottom: Gaussian of the same width, but centered at $\phi_0 = 248°$.

pretation of shift reagent results. In this case, protons 2, 3, and 4 formed the basis for the calculation, under the assumption that there was no internal rotation about the C–N bond. Excellent fits were obtained in the vicinity of $\phi = 66°$, and the fit at $\phi = 90°$ was very poor, leading to the conclusion that the complex is rigid, with $R = 2.55$ Å, $\Omega = 124°$, and $\phi = 66°$. The problem with this conclusion is that the experiment shows a single resonance for protons 2 and 6 (or 3 and 5) on opposite sides of the aromatic ring! Here then is a case where the agreement with experimental shift ratios for three protons is excellent, the Eu–N bond distance which results is reasonable, but the "determined" geometry is flat wrong.[23] Since the "static" fits at $\phi = 90°$ were poor, the remaining possibility (apart from free rotation) is that of random jumps between ϕ values of 0 and 180°; the contours from this model are shown as the bottom plot of Figure 6. The "fit" for this "jump" model is very sharply defined, with $R = 2.75$ Å and $\Omega = 115°$.[24] In conclusion for aniline no static conformation will fit the experimental data, and either free rotation of jumps between $\phi = 0$ and 180° give comparable

(23) When all five protons were included in a static model at the (only possible) ϕ value of 90°, a contour plot identical with that in the middle graph of Figure 6 was obtained, with even poorer agreement (higher "R" value contours).
(24) Attempts to fit the aniline data with the periodic model for angular position (see Theory) were erratic and generally unsuccessful, probably due to the use of Gauss–Legendre quadrature in the numerical integration. While rapid (and therefore cheap!), this form of numerical integration is not always suited to certain periodic functions.

results which bracket the X-ray value for the Eu–N bond distance.

Figure 7 illustrates another source of difficulty when internal rotation is present. The top plot gives the contours for a ϕ value giving a good "static" fit; the middle plot shows that this fit can be made to give even better agreement with experiment, if a Gaussian weight factor is applied to the ϕ values, with the Gaussian still centered at $\phi = 236$ with 14° rms width. However, the very best fits (smallest normalized variance) were obtained in the bottom plot, which is a Gaussian distribution in ϕ centered at $\phi = 248°$ with rms width of 14°. The embarrassing feature of this plot is the very wide range in values of R and Ω over which equally good fits could be obtained; so that virtually no information about R and Ω can be derived from the experiment. For substrate 1, the bound conformation probably exhibits some internal rotation, with the Eu more often opposed than adjacent to the apical chlorines.

Conclusions

The present paper provides a number of models for derivation of molecular configuration in the presence of internal rotational motion by use of lanthanide shift reagents. All three molecules studied were rigid except at the point of attachment to the lanthanide and so furnish the simplest type of problem for the analysis. The results show that determination of molecular geometry is straightforward only in cases (such as diacetoneglucose) where the entire complex is relatively rigid—the "fits" obtained in this case are not only "good" (in the sense of agreement with observed shift ratios) but also give chemically reasonable resuls. It thus appears that concern about anisotropy in the electronic g tensor[13,15] may not be warranted in solution, at least as far as geometry determination is concerned. However, when the presence of internal rotational motion, even when present only at the site of attachment to the lanthanide, can lead to either erroneous or undeterminative results for attempts to find the "best" single (static) conformation of the bound complex. Taken together, the present results demonstrate that determination of bound conformations of substrates bound to lanthanide shift reagents is fraught with difficulty even for rigid substrates, so that considerable caution (and a variety of motional models) should be invoked in any attempts to treat polyfunctional and/or nonrigid substrates.

Appendix

Calculation of r_i and θ_i from R, Ω, and ϕ. Referring to Figures 1 and 2, it is convenient to deal with the following quantities: r_i = distance vector from the lanthanide atom to the ith proton of substrate; R = lanthanide–donor atom distance vector; r_i' = distance vector from donor atom (origin) and ith proton (this vector is not shown in the figure); θ_i = angle between R and r_i; Ω = angle between R and the x axis; ϕ = angle between R' and y axis (a measure of the angle of internal rotation of the lanthanide–donor bond axis about the bond axis from the donor atom to atom 2).

It is expedient to compute $\cos^2 \theta_i$ from the dot product of R and r_i.

$$\cos^2 \theta_i = \{r_i \cdot R/|r_i||R|\}^2$$

One can now write

$$\frac{3\cos^2\theta_i - 1}{|\mathbf{r}_i|^3} = \frac{3(\mathbf{r}_i\cdot\mathbf{R})^2 - |\mathbf{R}|^2|\mathbf{r}_i|^2}{|\mathbf{R}|^2|\mathbf{r}_i|^5} \qquad (8)$$

but $\mathbf{r}_i = \mathbf{R} - \mathbf{r}_i'$, and $\mathbf{r}_i' = x_i\mathbf{i} + y_i\mathbf{j} + z_i\mathbf{k}$, where x_i, y_i, z_i are coordinates of the ith proton; $\mathbf{R} = |\mathbf{R}|\cdot\cos\Omega\mathbf{i} + |\mathbf{R}|\sin\Omega\cos\phi\mathbf{j} + |\mathbf{R}|\sin\Omega\sin\phi\mathbf{k}$. Sub-

stitution into eq 8 followed by some rearrangement gives the final result.

$$\frac{3\cos^2\theta_i - 1}{|\mathbf{r}_i|^3} = \frac{2|\mathbf{R}|^2 - 4|\mathbf{R}|Q + 3Q^2 - |\mathbf{r}_i'|^2}{(|\mathbf{r}_i'|^2 + |\mathbf{R}|^2 - 2|\mathbf{R}|Q)^{5/2}}$$

where $|\mathbf{r}_i'|^2 = x_i^2 + y_i^2 + z_i^2$, and $Q = x_i\cos\Omega + y_i\sin\Omega\cos\phi + z_i\sin\Omega\sin\phi$.

Macrocyclic Nuclear Magnetic Resonance Shift Reagents[1]

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Abstract: An account of work with macrocyclic nmr shift reagents is given. The reagents dealt with are dichlorogermanium tetraphenylporphine, dihydroxygermanium tetraphenylporphine, dichlorogermanium porphine, dihydroxygermanium porphine, dichlorogermanium phthalocyanine, and iron(II) phthalocyanine. The substrates dealt with are cis-4-*tert*-butylcyclohexanol, 4,4-dimethylcyclohexanol, trans-4-*tert*-butylcyclohexanol, 4-*tert*-butylphenol, 2,6-diisopropylphenol, 2,4-di-*tert*-butylphenol, 4-*tert*-butyl-2,6-dimethylphenol, 4-nitrophenol, acetic acid, methylmagnesium bromide, n-propylmagnesium bromide, n-octylmagnesium bromide, phenylmagnesium bromide, methylamine, n-butylamine, and n-hexylamine. Both the advantages and disadvantages possessed by the reagents and the ways in which they complement the familiar lanthanide reagents are discussed. The potential of certain additional macrocyclic reagents is also touched on.

The currently used group of β-diketone lanthanide shift reagents[2] is highly effective for many problems. However, none of these reagents are applicable to a number of important classes of compounds, and none of them show the degree of specificity sometimes desired.

A group of reagents, which are quite unlike these lanthanide reagents and which, as a consequence, are able to fill in some of the gaps left by them, is described in this paper.[3] These reagents are all metal porphines, metal tetraphenylporphines, or metal phthalocyanines.[6] All but one of them form the requisite reagent–substrate bonds by a reaction in which part or all of the functional group of the substrate is replaced by a portion of the reagent containing the porphyrin ring. The remaining reagent forms the requisite bond by a coordination reaction. The shifting ability of these reagents arises mainly from the ring currents of their macrocycles, although the substrate functional group alterations which they cause are sometimes also of importance.

These reagents, while unlike the β-diketone lan-

thanide reagents in mode of action and, to a considerable extent, in applicability, do resemble them in ease of use and effectiveness.

Experimental Section

Synthesis of Reagents. A. Dichlorogermanium Tetraphenylporphine. A mixture of tetraphenylporphine[11] (4.32 g), germanium tetrachloride (7.7 g), and quinoline (50 ml) was heated at 220° under nitrogen with stirring for 50 min and then was cooled and filtered. The resultant purple crystalline product was washed with quinoline and benzene and dried (5.33 g).

A portion of this product was recrystallized from benzene and vacuum dried at 80°. *Anal.* Calcd for $C_{44}H_{28}N_4GeCl_2$: C, 69.88; H, 3.73; Cl, 9.38. Found: C, 69.62; H, 3.69; Cl, 9.42.

The nmr spectrum of this tetraphenylporphine showed a singlet at τ 0.93 (β protons) and complex multiplets at τ 1.76 and 2.23 (ortho and meta–para protons).[12]

B. Dihydroxygermanium Tetraphenylporphine. A mixture formed by adding alumina (Woelm V, 5 g) to a suspension of dichlorogermanium tetraphenylporphine (200 mg) in chloroform (100 ml) was shaken for 10 min and evaporated to dryness under vacuum. The residue was placed on the top of a small column of alumina (Woelm V, 10 g) and the resultant was eluted with benzene and then with chloroform. Evaporation of the chloroform eluate gave the product as a purple solid (185 mg).

This solid was extractively recrystallized from benzene with a Soxhlet extractor and vacuum dried at 110°. *Anal.* Calcd for $C_{44}H_{30}N_4GeO_2$: C, 73.46; H, 4.18; Ge, 10.14. Found: C, 73.12; H, 4.38; Ge 9.74; O, 0.01.

The nmr spectrum of this compound in very dry $CDCl_3$ showed a singlet at τ 0.97, multiplets at τ 1.72 and 2.23 (β, ortho, and meta–para protons, respectively[12]), and a singlet (which disappeared upon addition of CH_3OD) at τ 17.35 (hydroxyl protons).

C. Dichlorogermanium Porphine. In a preparation modeled after Kane's,[9] a mixture of porphine (400 mg), germanium tetrachloride (0.80 ml), and quinoline (5 ml) was heated at 210° under

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(3) Preliminary descriptions of this work have appeared.[4,5]

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