Table II. Minimum Proton R Factors and Lanthanide Nitrogen Distances

	R_H	d, A	$R_{C \text{ and } H}$
Eu	3.0	3.2	47.7
Nd	4.8	3.3	46.8
Er	1.1	3.0	17.6
Tb	1.5	2.6	26.9
Ho	1.3	2.6	33.3
Pr	2.0	2.5	11.6
Dy	1.8	2.7	30.0
Yb	1.4	3.1	4.0

gen heterocycles, with the least contact shift perturbation, Yb(DPM)$_3$ is the chelate of choice. In fact, applying the R factor method to simultaneously fit *both* carbon-13 and proton shift data for isoquinoline Yb(DPM)$_3$ solutions results in a minimum R factor of 4.0%, well within the accuracy of the two sets of experimental data.[10] Neglecting the C-1, C-3 resonances (those most affected by contact shifts) produced a carbon-13 difference map indistinguishable from the experimental data scatter.

We list the following positive features concerning Yb(DPM)$_3$.[11] (i) The induced shifts are downfield, facilitating interpretation of spectra. (ii) Little line broadening of either the carbon or proton resonances is observed. (iii) The proton shifts detected are *ca.* 300% larger than for Eu(DPM)$_3$ at equal chelate concentrations. (iv) Yb(DPM)$_3$ is suitable for use to determine structural features from dispersed carbon-13 spectra, Eu(DPM)$_3$ is just as certainly not useful. Further experiments exploring the utility of correlated, dispersed carbon-13 and proton spectra are in progress.

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(10) For even Pr(DPM)$_3$ or Er(DPM)$_3$, R factors of 11.6 and 17.6% are observed using both carbon and proton shift data (see $R_{C \text{ and } H}$ values in Table II).

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(12) John Simon Guggenheim Fellow, 1972–1973.

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Evidence for Europium-Induced Fermi Contact Shifts in Carbon-13 Nuclear Magnetic Resonance Spectra

Sir:

Notwithstanding the caution voiced by Weissman that both contact and pseudocontact shifts are to be expected in molecules coordinated to europium shift reagents,[1] numerous workers have applied a simplified form of the McConnell–Robertson relationship for pseudocontact interaction[2] as the sole interpreter of lanthanide induced shifts in rigid organic molecules. In the iterative computational schemes employed, the pseudocontact model reproduces proton shift behavior to a high degree of precision,[3-7] but duplication of ^{13}C data by this model *seems* less satisfactory.[8,9] The following extension of our computational procedure[6] to ^{13}C and ^{1}H spectra of pyridine bases coordinated to Eu(DPM)$_3$ includes a general method for obtaining the ratio of pseudocontact to measured ^{13}C nmr shifts, as well as a direct comparison between the applicability of a simplified pseudocontact model to both ^{13}C and ^{1}H Eu(DPM)$_3$ shifted spectra.

The rationale for this approach requires matching ^{13}C and ^{1}H spectral behavior. Correlation of the 100-MHz ^{1}H data (Varian HA-100) and 22.265-MHz ^{13}C data (Bruker HFX-90) was achieved by using the same sample for both measurements. The data were reduced using linear plots of shift perturbation *vs.* Eu(DPM)$_3$ extrapolated to 1:1 Eu(DPM)$_3$:substrate ratio. All chemical shifts were expressed in ppm from internal $(CH_3)_4Si$ (^{13}C, ^{1}H). The samples were 0.5 M in substrate with Eu(DPM)$_3$ varying from 0.0 to 0.3 M. These extrapolated values, for three different nitrogen heterocyclic compounds, are recorded in Table I.

The correlated ^{13}C and ^{1}H isotropic shifts were treated in the following way: (i) the europium location was mapped *vs.* the agreement factor, R, for the ^{1}H data;[6] (ii) the scale factor, K, used to match experimental to calculated ^{1}H shifts, was recorded; (iii) the carbon pseudocontact shift values for each europium location were computed using this scale factor; and (iv) a difference spectrum ($^{13}C_{obsd} - {}^{13}C_{calcd} = {}^{13}C_{diff}$) was generated for the carbon spectrum. Pyridine can be used to illustrate this procedure. Systematic variation of the europium location over the surface of spheres of radius 2.0–5.0 Å centered on the pyridine nitrogen in 0.1 Å steps showed a decrease in the R factor from 18.8% (2.25 Å) to 0.9% (2.7 Å), followed by an increase to 5.0% (4.0 Å). Over the range 2.6–3.0 Å, numerous regions were found for the lanthanide which gave R factors of less than 2%. The best agreement, R = 0.9% was noted at 2.7 Å.[10] At this location, a difference spectrum ($^{13}C_{obsd} - {}^{13}C_{calcd} = {}^{13}C_{diff}$) was obtained; it is included in Table I. Corresponding

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(10) We anticipated the europium would lie along the C_2 axis through the nitrogen atom of pyridine. However, the minimum R factors were obtained when the Eu atom was displaced *ca.* 20° from the C_2 axis and *ca.* 10° from the plane of the ring. This unexpected result may be an artifact of our computational approach, or it may be due to experimental error or a combination of both factors. In any event, the europium angular location was found to influence the R factor much less than the Eu–N distance.

Table I. Experimental 1:1 $Eu(DPM)_3$:Substrate Chemical Shifts of Some Pyridine Bases

	R (^1H)	Distance, Å (Eu–N)		$^1H_{obsd}$	$^1H_{calcd}$	$^{13}C_{obsd}$	$^{13}C_{calcd}$	$^{13}C_{diff}$	Rel $^{13}C_{diff}$
Pyridine	0.9%	2.7	α	−31.02	−31.11	−90.00	−67.78	−22.22	−1.00
			β	−10.68	−10.59	+0.88	−24.33	+25.21	+1.13
			γ	−9.71	−9.33	−30.22	−18.73	−11.49	−0.52
3,5-Lutidine	0.6%	2.8	α	26.7	26.66	67.80	51.66	16.14	−1.00
			β			−3.10	19.44	−22.54	+1.40
			γ	7.50	7.55	22.70	14.95	7.75	−0.48
			β-CH_3	4.91	5.08	6.00	6.24	0.24	−0.01
Isoquinoline	3.0%	3.2	1	23.7	23.6	70.2	34.2	36.0	−1.00
			3	25.7	25.7	64.0	37.5	26.5	−0.74
			4	9.11	9.3	0.17	16.3	−16.0	+0.44
			5	6.06	5.3	8.9	6.9	2.0	−0.06
			6	3.44	3.4	2.8	5.0	−2.2	−0.06
			7	3.44	3.5	2.1	5.2	−3.2	−0.09
			8	5.77	6.6	10.1	8.4	1.8	−0.05
			9			3.64	16.1	−12.5	+0.35
			10			21.6	13.0	8.6	−0.24

difference spectra were obtained for all europium locations with $R < 2.0\%$ and a considerable range of absolute values of $^{13}C_{diff}$ was noted. However, the difference spectra can be expressed as relative spectra, obtained by setting any desired $^{13}C_{diff}$ (say C-α) at −1.0 and scaling the other shifts to it. Even though the absolute values of the carbon discrepancies differ by as much as 30%, the relative values of $^{13}C_{diff}$ remain nearly constant.

Analogous ^{13}C difference spectra were obtained for two additional pyridine bases. The table lists the N–Eu distance for the minimum R obtained from the ^1H data. The set of magnitudes of the calculated carbon difference shifts obtained for the minimum R position, as well as the relative shifts, can be found in Table I.

The most striking aspect of the ^{13}C difference spectra is the regular alternation of signs of the difference shifts in the heterocyclic ring, *viz.*, −, +, − at C-α,β,γ. Similar alternation of precisely reversed sign order has been noted by Doddrell and Roberts[11] as well as Morashima, *et al.*,[12] for pyridine base adducts of bis(acetylacetonato)nickel(II). Polarization leaving β spin in the ring has been predicted[13] to occur for the lanthanides and could provide a ready explanation for this sign reversal if the Ni spin is α. The sign alternation has been examined theoretically and was attributed to spin delocalization in the σ-bond molecular framework, with the further assumption of excess α spin for Ni(II) complexes.[14] Furthermore, large upfield shifts have been measured for heterocyclic, europium bonded nitrogens as might have been anticipated from the above discussion.[15,16]

Though the precise relationships among the magnitudes of the carbon shifts calculated are suspect due to inadequacies in the theory, we nevertheless feel compelled to compare our ^{13}C difference spectra with some quantitative predictions from INDO calculations. The calculated shift ratios for pyridine (assuming β spin) are −1:+0.58:−0.34 for the α, β, and γ carbons which compares to our difference shift ratios of −1:+1.13:−0.52.[14,17] While this reasonable agreement may in some part be coincidental, resulting from experimental or theoretical errors, we argue for and will make use of ^{13}C difference maps as measures of the Fermi contact shift.[18]

Are the proton data then properly treated as pseudocontact? The answer certainly is *not precisely.*[19] We have observed that if small changes in the values for the proton chemical shifts are introduced into the R factor calculations, this does not effect a drastic alteration of the europium position (*i.e.*, less than 10%). Moreover, shift ratios in the carbon difference spectra are not changed significantly. Attempts to improve the pseudocontact description of the proton data based on the ^{13}C contact shift have failed because we cannot determine a constant scaling factor between ^{13}C and ^1H shifts for the various CH bonds.

In summary, we are confident that $Eu(DPM)_3$ interacts with pyridine-type bases to produce both Fermi contact and pseudocontact shifts. The ^{13}C nmr data *cannot* be explained without specific inclusion of a large amount of contact shift. Indeed, we suggest that considerable confusion may result if the assignment of ^{13}C resonances is attempted from europium shifts alone,[20,21] especially when easily polarized molecules like pyridine are examined. On the other hand, the proton data even for the nitrogen heterocyclics can be satisfactorily treated by the pseudocontact model. For now, ^{13}C difference spectra may be viewed as indicative of the contact shift and are therefore useful probes to

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(18) Ratios of the α, β, and γ shifts were calculated using crystallographically determined pyridine bond distances. Small changes in these values cause large variations in shift ratios. See ref 14.

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examine the relative contact and pseudocontact shifts induced by the different lanthanides.

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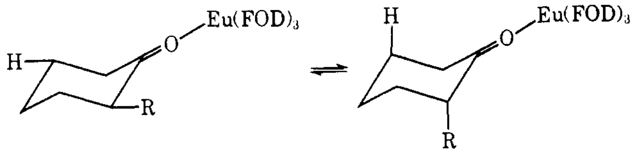
Conformational Analysis of 2-Alkylcyclohexanone–Lanthanide Chelate Complexes

Sir:

Induced shifts in nmr spectra which result from complexation of a substrate with lanthanide chelates[1] have found widespread use in structural[2] and stereochemical[3] analyses. In many cases, large differential shifts permit analysis of the nmr spectrum from which a structural assignment can be deduced.[4] For conformational analysis, quantitative values for the induced shifts are usually sought.[3a,3b] Several methods have been presented for obtaining intrinsic induced shifts but all seem to have limitations.[5] We now report on the conformational equilibria of alkylcyclohexanone–lanthanide chelate complexes obtained from induced shift ratios.

The complexity of the nmr spectra of 2-alkylcyclohexanones prevents a direct analysis of the spectra to obtain chemical shifts for use in conformational analysis.[6] Addition of Eu(FOD)$_3$ produces large differential downfield shifts which greatly simplify the spectra and allow assignments to be made.[7] In the limit of complete complexation, the induced shift, $\Delta_B{}^{av}$, for a ring proton should be the conformational average of the induced shifts for the proton in the two conformations of the complex



$$\Delta_B{}^{av} = n_{eq}\Delta_B{}^{eq} + n_{ax}\Delta_B{}^{ax}$$

where n_{eq} and n_{ax} are the mole fractions of equatorial and axial conformers and $\Delta_B{}^{eq}$ and $\Delta_B{}^{ax}$ are the characteristic induced shifts for protons in the equatorial and axial positions.

In order to obtain characteristic induced shifts for the protons in the equatorial and axial positions of complexed cyclohexanones, 4-*tert*-butylcyclohexanone was chosen as a model compound and the effect of varying Eu(FOD)$_3$ concentration on its nmr spectrum determined. Rather than attempting to use graphical or numerical methods to determine absolute values for the induced shifts of each of the ring protons in the complex, the ratio of induced shift of a ring proton relative to the sum of the induced shifts for the two protons at that ring position was obtained as outlined below.

When exchange of substrate between the complexed and uncomplexed state is rapid, the observed chemical shift in the presence of chelating agent, δ_{obsd}, for any proton of the substrate will be an average value of its chemical shift in the uncomplexed ketone, δ_0, and its chemical shift in the substrate–lanthanide chelate complex, $\Delta_B + \delta_0$. Thus

$$\delta_{obsd} = \delta_0 + F\Delta_B$$

where F is the fraction of substrate present as complex. For any two protons, H_a and H_b, of the same substrate in one solution of any particular concentration of substrate and chelate the following relationship[8] can be derived

$$\delta_{obsd}{}^{H_a} = \delta_0{}^{H_a} + \left(\frac{\Delta_B{}^{H_a}}{\Delta_B{}^{H_a} + \Delta_B{}^{H_b}}\right)(\delta_{obsd}{}^{H_a} + \delta_{obsd}{}^{H_b}) - \left(\frac{\Delta_B{}^{H_a}}{\Delta_B{}^{H_a} + \Delta_B{}^{H_b}}\right)(\delta_0{}^{H_a} + \delta_0{}^{H_b})$$

For a different concentration of substrate or chelate, different chemical shifts, $\delta_{obsd}{}^{H_a}$ and $\delta_{obsd}{}^{H_b}$, will be observed. However, a plot of $\delta_{obsd}{}^{H_a}$ *vs.* $(\delta_{obsd}{}^{H_a} + \delta_{obsd}{}^{H_b})$ for each of the different solutions should be linear with a slope equal to the relative induced chemical shifts, $\Delta_B{}^{H_a}/(\Delta_B{}^{H_a} + \Delta_B{}^{H_b})$.

The principal advantage of this procedure is that substrate and reagent concentrations need not be known and that no special precautions to exclude competitive scavengers need be taken. In addition, the often difficult task of determining chemical shifts of the uncomplexed substrate, δ_0, is avoided.[9,10] Such a plot

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(7) See Figure 4 of ref 4b.

(8) To derive this relationship, the separate equations for $\delta_{obsd}{}^{H_a}$ and $\delta_{obsd}{}^{H_b}$ are written and then summed. By substituting the solution for F from the $\delta_{obsd}{}^{H_a} + \delta_{obsd}{}^{H_b}$ equation into the $\delta_{obsd}{}^{H_a}$ equation, the relationship is obtained directly.

(9) The previous procedure employing internal protons as standards[5h] required chemical shift assignments for the uncomplexed substrate.

(10) The condition that the substrate concentration be much larger than the lanthanide chelate concentration must be maintained. Shapiro and Johnston have shown that under these conditions the major complex is the LS$_2$ species.[11] Our relative shifts then would apply to this species.

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