Calculation of Binding Constants and Bound Chemical Shifts for the Association of Lanthanide Shift Reagents with Organic Substrates

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Summary By varying the ligand concentration the bound chemical shift and the equilibrium constant for the binding of ligand to lanthanide may be determined; studies of tris(dipivalomethanato)europium(III) complexes show that n-propylamine is bound more strongly than is neopentanol.

LANTHANIDE 'shift reagents' have become standard in assignment of n.m.r. spectra of complex organic molecules.[1,2] For spectral assignments where the major objective is merely to obtain a first-order spectrum, it is possible to use the shift reagent empirically. However, it has been recognized[1] that the *magnitude* of the induced shift contains detailed information about the geometry of the complex, and hence of the organic substrate itself, and there have been a number of recent attempts[3] to extract this information. In such studies the 'bound' chemical shift, Δ_B, must be determined reliably. The method currently in use[4] is to plot the induced chemical shift, δ, *vs.* $[L_0]/[S_0]$, where $[L_0]$ and $[S_0]$ are the respective initial concentrations of lanthanide and substrate; the slope of this plot is assumed to be Δ_B, the bound chemical shift.

Unfortunately, the slope of such a plot may vary markedly with the *absolute* concentration of substrate,[5] as is shown in the Figure for the neopentanol–tris(dipivalomethanato)-europium(III) system. It can be shown that this concentration dependence is related to the strength of binding of

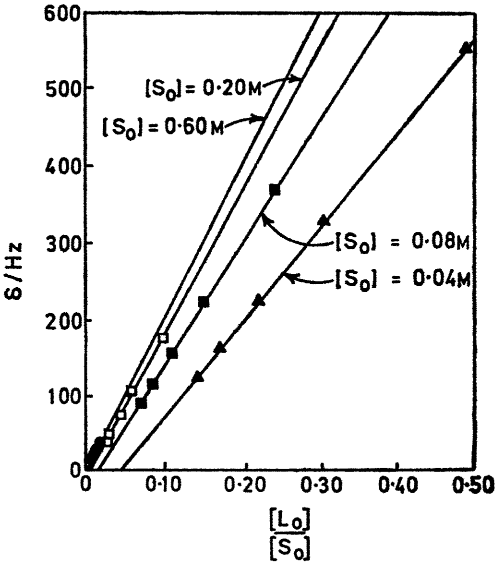

FIGURE. *Plot of induced chemical shift* (δ) versus *ratio of the initial concentrations of tris(dipivalomethanto)europium*(III), $[L_0]$, *to neopentanol*, $[S_0]$, *in deuteriochloroform solvent. Points on a given line represent experiments in which the concentration of lanthanide shift reagent was varied, keeping the neopentanol concentration fixed at the value listed for that line.*

substrate to lanthanide, and that the slope of a plot of δ *vs* $[L_0]/[S_0]$ will in fact approach Δ_B only at relatively high substrate concentration Since there is no *a priori* way of knowing how much substrate to use, determination of bound chemical shifts by this method must be regarded as questionable (*vide infra*) Furthermore, at the high concentrations of lanthanide which would be necessitated at high substrate concentrations, bulk susceptibility changes become substantial, and it is not clear that even an internal standard will properly compensate for them

On the other hand, if experiments can be performed in the concentration range $[S_0] \gg [L_0]$ then a plot of $[S_0]$ *versus* $(1/\delta)$ at constant $[L_0]$ will give a straight line whose slope is $[L_0]\Delta_B$ and whose *y*-intercept is $-\{(1/K_B) + [L_0]\}$, where K_B is the equilibrium binding constant for binding of substrate to lanthanide

Analysis of the chemical shifts induced by a constant concentration (*ca* 0·005M) of tris(dipivalomethanato)-europium(III) together with varying concentrations (*ca* 0 03—0·2M) of n-propylamine and of neopentanol are given in the Table As a critical test, it may be noted that the values of K_B calculated from induced shifts of different protons on the same molecule give identical results, within experimental error, even though the values for the bound chemical shift vary markedly with distance† of the respective proton from the lanthanide nucleus

The binding constants in the Table are the first reported for substrate–lanthanide complexes, and the bound chemical shifts in the Table represent the first reliable values of Δ_B

TABLE

Calculated values of bound chemical shifts (Δ_B) *and binding constants* (K_B) *for complexes of tris(dipivalomethanato)europium*(III)

Substrate		Δ_B/p p m [a]	K_B/l mol^{-1} [a]
n-Propylamine	H^1	38 7	12 3
	H^2	24 0	11 5
	H^3	13 2	12 9
Neopentanol	H^1	23 7	6 2
	H^3	9 5	6·5

[a] Values derived from the least-squares fit of a plot of $[S_0]$ *versus* $(1/\delta)$

It is of interest that the values of Δ_B determined from the data given in the Figure, using the literature procedure,[4] range from 12 6 to 20·5 p p m Thus, even the highest value is still *ca* 13% below the true value

The binding constant for n-propylamine is significantly higher than that for neopentanol This suggests that, for a given shift reagent, the characteristic induced shift magnitudes discussed by Sanders and Williams[6] may be correlated with changes in the binding constants for substrates with different functional groups

Analysis of the present data together with other unpublished results suggests that the errors for the Δ_B and K_B values obtained by the present graphical method are less than 10%

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† In this context it must be remembered that the pseudo contact contribution to the induced shift also contains a pronounced angular dependence

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