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Chemical Equilibria between a Lanthanide Shift Reagent and *n*-Hexylamine in Chloroform

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The $Eu(fod)_3$-induced ^1H NMR shifts of *n*-hexylamine were observed using two kinds of dilution methods. The results are analyzed in terms of the chemical equilibria among the shift reagent (L), substrate (S), 1: 1 (LS), and 1: 2 (LS_2) complexes. The association constants and the induced shifts intrinsic to the LS and LS_2 complexes are evaluated accurately by fitting the theoretical curves to the observed data. The values obtained are utilized to confirm the validity and usefulness of the extrapolation method proposed previously to determine the shift ratios for the LS complex.

It has been pointed out that, in order to determine the molecular structure in solution by means of the lanthanide-induced NMR shift (LIS), the ratios of shifts intrinsic to the lanthanide–substrate 1: 1 complex (LS complex) should be used.[1—4] In a previous paper[4] we proposed an experimental method to derive the shift ratios for the LS complex and applied it to the Eu(III)–L-azetidine-2-carboxylic acid system in D_2O solution. A lanthanide chelate compound such as $Eu(fod)_3$ (fod=1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) induces much larger shifts to a substrate dissolved in an organic solvent than a lanthanide ion does in aqueous solution. The stoichiometric analysis can therefore be made more precisely for the system of a lanthanide chelate and a substrate in an organic solvent. In the present paper we analyze the chemical equilibria of $Eu(fod)_3$ and *n*-hexylamine in chloroform, taking into account the formation of not only the LS complex but also the LS_2 (1: 2) complex. The results are utilized to show that the experimental method of obtaining the shift ratios for the LS complex[4] is an appropriate and useful one.

Experimental

All the NMR spectra were run on a Hitachi R-22 NMR spectrometer (90 MHz) in the frequency-sweep mode at a probe temperature of 37 °C. The shifts were measured using a frequency counter with estimated accuracy of ±1 Hz or less.

n-Hexylamine, $Eu(fod)_3$, and deuterated chloroform containing 1% tetramethylsilane were purchased, respectively, from Tokyo Chemical Industry Co., Dojin Chemicals, and E. Merck. As a trace amount of water in the reagents was found to have a serious effect on the results of LIS mesurements, it was eliminated with special caution. *n*-Hexylamine was distilled over sodium hydroxide in the dry nitrogen atmosphere and was stored with synthetic zeolite A-4. $Eu(fod)_3$, was dried over phosphorus pentoxide in an evacuated desiccator (10^{-3}—10^{-4} mmHg) for a week.[5,6] Deuterated chloroform was mixed with active alumina which was then removed by filtration. The samples for NMR measurements were prepared in a dry box flushed with nitrogen gas. The LIS values obtained in this way were reproducible and considerably larger than those obtained without these procedures.

The LIS's of *n*-hexylamine were observed for a series of solutions prepared by the following two methods.[4] In the successive dilution method an original solution containing approximately equimolar substrate and shift reagent was diluted stepwise with the solvent. The original concentrations of *n*-hexylamine and $Eu(fod)_3$ were 0.286 and 0.272 M, respectively. On the other hand, in the incremental dilution method an original solution was diluted stepwise with the substrate solution of the same concentration as in the original solution, so that only the $Eu(fod)_3$ concentration was lowered. The original concentrations of *n*-hexylamine and $Eu(fod)_3$ were 0.097 and 0.248 M, respectively.

Method of Analysis

Chemical equilibria among a lanthanide shift reagent (L), a substrate (S), and the complexes are described by the following schemes under the assumption that the formation of complexes LS_x ($x \geqq 3$) may be neglected.

$$L + S \xrightleftharpoons{K_1} LS \tag{1}$$

$$LS + S \xrightleftharpoons{K_2} LS_2 \tag{2}$$

where K_1 and K_2 are the association constants given as

$$K_1 = [LS]/[L][S] \tag{3}$$

$$K_2 = [LS_2]/[LS][S] \tag{4}$$

If the LIS (of the *i*th nucleus, $i=1$—n) intrinsic to the LS and LS_2 complexes are expressed as $\varDelta_1{}^i$ and $\varDelta_2{}^i$, respectively, the observed shift ($\varDelta\delta^i_{obsd}$) may be given on the fast-exchange condition as

$$\varDelta\delta^i_{obsd} = ([LS]/[S_0])\varDelta_1{}^i + 2([LS_2]/[S_0])\varDelta_2{}^i \tag{5}$$

where $[S_0]$ is the total concentration of the substrate.

The purpose of the present analysis is to obtain the most probable values of K_1, K_2, $\varDelta_1{}^1$—$\varDelta_1{}^n$, and $\varDelta_2{}^1$—$\varDelta_2{}^n$ which reproduce both sets of observed LIS data derived from the successive dilution and the incremental dilution methods. This can be done according to the following steps. (a) The values of K_1 and K_2 are assumed. (b) Equations (3) and (4) are solved for [LS] and $[LS_2]$ using the Newton-Raphson method. (c) The expected LIS value ($\varDelta\delta^i_{calcd}$) is calculated by Eq. (5) with assumed values of $\varDelta_1{}^i$ and $\varDelta_2{}^i$. The best values of $\varDelta_1{}^i$ and $\varDelta_2{}^i$ can then be obtained by minimizing the sum (S) given as

$$S = \sum_{i=1}^{n}\sum_{j=1}^{N_i} w_j\{\delta^i_{obsd}(j) - \delta^i_{calc}(j)\}^2 \tag{6}$$

where N_i is the total number of observed data for the *i*th nucleus and w_j is the weight for the *j*th observed LIS value. All the values of w_j were set equal to unity. (d) The steps (a) to (c) are repeated for various sets of K_1 and K_2 until the parameters which minimize S

are finally found.

The computation outlined above was performed with the program SHIFT using a HITAC 8800/8700 system at the Computer Centre of the University of Tokyo.

Results and Discussion

By the addition of Eu(fod)$_3$ the NMR spectrum of *n*-hexylamine becomes first-order and all the resonances due to the α—ε methylene protons and the ω methyl protons are easily assigned. The results of the successive dilution and the incremental dilution methods are shown with open circles in Figs. 1 and 2, respectively. In the former method the molar ratio ρ([L$_0$]/[S$_0$], the ratio of total concentrations) is kept constant (0.951), whereas in the latter method [S$_0$] is maintained at 0.097 M. In Table 1 are given the best values of K_1, K_2, $\Delta_1{}^i$'s, and $\Delta_2{}^i$'s which were obtained by the analysis described above. The LIS values calculated using these parameters are shown by the curves in Figs. 1 and 2. The agreement between the calculated curves and the observed data is quite satisfactory.

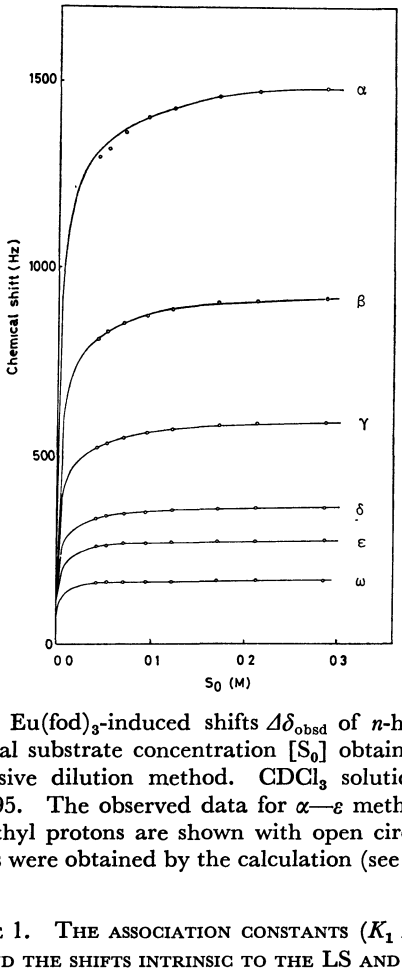

Fig. 1. Eu(fod)$_3$-induced shifts $\Delta\delta_{\text{obsd}}$ of *n*-hexylamine *vs.* total substrate concentration [S$_0$] obtained by the successive dilution method. CDCl$_3$ solution, 37 °C, ρ=0.95. The observed data for α—ε methylene and ω methyl protons are shown with open circles. The curves were obtained by the calculation (see text).

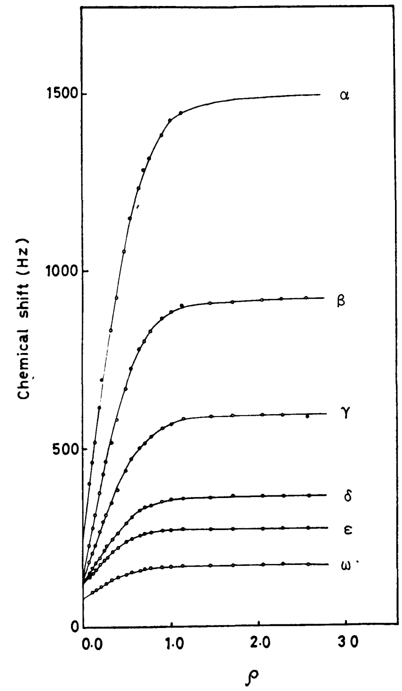

Fig. 2. Eu(fod)$_3$-induced shifts $\Delta\delta_{\text{obsd}}$ of *n*-hexylamine *vs.* ρ ($\equiv$[L$_0$]/[S$_0$]) obtained by the incremental dilution method. CDCl$_3$ solution, 37 °C, [S$_0$]=0.097 M. The observed data for α—ε methylene and ω methyl protons are shown with open circles. The curves were obtained by the calculation (see text).

TABLE 1. THE ASSOCIATION CONSTANTS (K_1 AND K_2) AND THE SHIFTS INTRINSIC TO THE LS AND LS$_2$ COMPLEXES (Δ_1 AND Δ_2) FOR THE Eu(fod)$_3$–*n*-HEXYLAMINE SYSTEM

Proton	Δ_1,[a] Hz	Δ_2,[a] Hz
α	1264.5 (6.8)	1373.6 (14.8)
β	793.2 (1.9)	936.7 (6.2)
γ	473.2 (1.6)	528.0 (5.3)
δ	245.5 (1.9)	304.4 (6.3)
ε	152.3 (1.5)	219.2 (4.9)
ω	89.7 (1.1)	124.4 (3.6)
	K_1=535.5[b]	K_2=13.9[b]

a) The calculated standard deviation is shown in parentheses. b) In the unit of M^{-1}.

In Figs. 3 and 4 the calculated concentration ratios [LS]/[S$_0$], [LS$_2$]/[S$_0$], and [LS$_2$]/[LS] are shown for the successive dilution and the incremental dilution processes, respectively. As is clearly seen in these figures, the ratio [LS$_2$]/[LS] increases rapidly to K_2[S$_0$] as ρ approaches zero in the incremental dilution method,

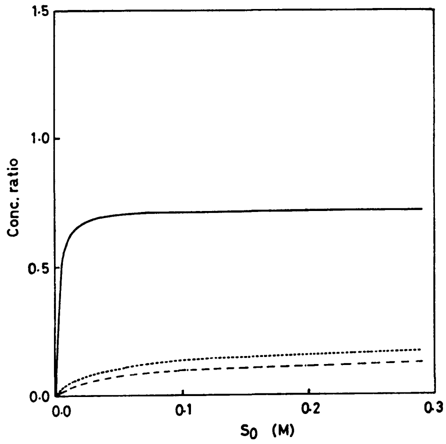

Fig. 3. The calculated concentration ratios [LS]/[S$_0$] (———), [LS$_2$]/[S$_0$] (——), and [LS$_2$]/[LS] (----) *vs.* [S$_0$].

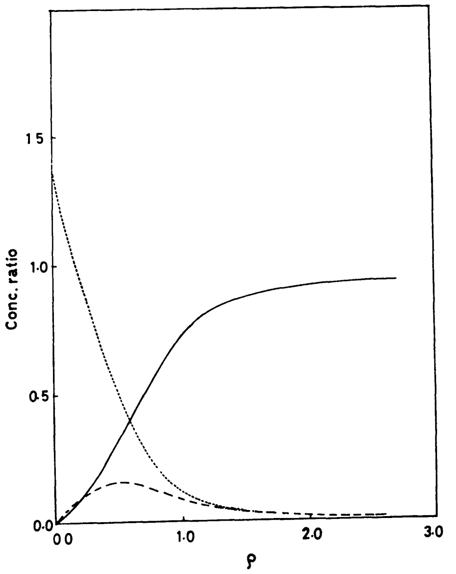

Fig. 4. The calculated concentration ratios [LS]/[S_0] (——), [LS_2]/[S_0] (——), and [LS_2]/[LS] (-----), *vs.* ρ.

whereas the ratio decreases gradually to zero as [S_0] is lowered in the successive dilution method. This point should be borne in mind in deriving the shift ratios for the LS complex. Since the successive dilution and the incremental dilution methods have quite different patterns with respect to the complex formation, a combined analysis of LIS values of the two methods enhances the reliability of the parameters listed in Table 1.

In a previous paper[4] a method of obtaining the shift ratio for the LS complex was proposed. It is interesting to apply this method to the present system. The ratio of the LIS of the *i*th nucleus and that of the *s*th nucleus is derived from Eqs. (3)—(5) as

$$\frac{\Delta\delta^i_{\text{obsd}}}{\Delta\delta^s_{\text{obsd}}} = \frac{\Delta_1{}^i+2K_2[S_0]\Delta_2{}^i+2K_2(\Delta_1{}^i-\Delta_2{}^i)[LS]}{\Delta_1{}^s+2K_2[S_0]\Delta_2{}^s+2K_2(\Delta_1{}^s-\Delta_2{}^s)[LS]} \tag{7}$$

The extrapolations of the shift ratio to [S_0]=0 and to ρ=0 give the following relations.

$$\lim_{[S_0]\to 0}\left(\frac{\Delta\delta^i_{\text{obsd}}}{\Delta\delta^s_{\text{obsd}}}\right) = \frac{\Delta_1{}^i}{\Delta_1{}^s} \tag{8}$$

$$\lim_{\rho\to 0}\left(\frac{\Delta\delta^i_{\text{obsd}}}{\Delta\delta^s_{\text{obsd}}}\right) = \frac{\Delta_1{}^i+2K_2[S_0]\Delta_2{}^i}{\Delta_1{}^s+2K_2[S_0]\Delta_2{}^s} \tag{9}$$

These equations indicate that the ratio of shifts intrinsic to the LS complex can be obtained only by extrapolating the shift ratio derived from the successive dilution method to [S_0]=0. The extrapolation of the shift ratio derived from the incremental dilution method to ρ=0 leads to a value which has also the contribution of LS_2 properties.

In Figs. 5 and 6 are shown the shift ratios obtained by the successive dilution and the incremental dilution methods, respectively. The LIS of the β proton is taken as reference. The curves in these figures indicate the shift ratios calculated using the parameters listed in Table 1. In Table 2 the observed and calculated shift ratios extrapolated to [S_0]=0 and to ρ=0 are

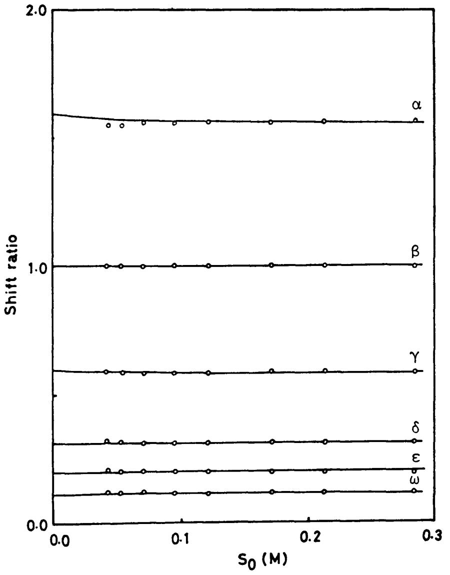

Fig. 5. The ratios of Eu(fod)$_3$-induced shifts of *n*-hexylamine *vs.* [S_0] obtained by the successive dilution method. The shift of β proton is taken as reference. The observed data are shown with open circles. The curves were obtained by the calculation (see text).

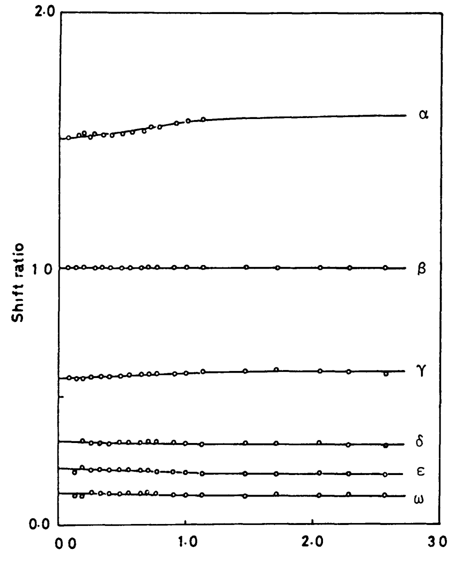

Fig. 6. The ratios of Eu(fod)$_3$-induced shifts of *n*-hexylamine *vs.* ρ obtained by the incremental dilution method. The shift of β proton is taken as reference. The observed data are shown with open circles. The curves were obtained by the calculation (see text).

compared. It is noted that the shift ratios extrapolated to [S_0]=0 differ significantly (*ca.* 10% for the ε proton) from those extrapolated to ρ=0 and these differences are also confirmed by the calculation. These results indicate that all the theoretical analysis and experimental procedures described above are self-consistent and useful.

It may be worthwhile to mention about the so-called "*S* value". This is often used to represent the magnitude of LIS in the conventional method of adding a

Table 2. The shift ratios extrapolated to $[S_0]=0$ and $\rho=0$

Proton	$[S_0]=0$		$\rho=0$	
	Obsd[a]	Calcd	Obsd[b]	Calcd
α	1.56_0	1.59_4	1.50_1	1.49_7
β[c]	1.000	1.000	1.000	1.000
γ	0.58_7	0.59_6	0.57_1	0.57_2
δ	0.31_5	0.31_0	0.32_0	0.32_1
ε	0.20_5	0.19_2	0.22_0	0.22_4
ω	0.12_0	0.11_3	0.12_2	0.12_8

a) Observed by the successive dilution method.
b) Observed by the incremental dilution method.
c) Chosen as reference.

solid shift reagent to a substrate solution or in the incremental dilution method. Like the shift ratio extrapolated to $\rho=0$ given in Eq. (9), the S value contains the contribution of LS_2 properties. Therefore, its use may lead to some erroneous results in the structure determinations.

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