Lanthanide-Induced Shifts in Proton Nuclear Magnetic Resonance Spectra. III. Lanthanide Shift Reagent–Substrate Equilibria[1]

B. L. Shapiro* and M. D. Johnston, Jr.[2]

Contribution from the Department of Chemistry,
Texas A&M University, College Station, Texas 77843.

Received June 2, 1972

Abstract: Lanthanide shift reagents (LSR) can interact with substrates *via* a two-step mechanism: L + S ⇄ LS, LS + S ⇄ LS_2. This was shown by a detailed four-parameter analysis of the concentration dependence of the lanthanide-induced shifts (LIS) of the system 3-(*p*-chlorophenyl)-3,5,5-trimethylcyclohexanone–$Eu(FOD)_3$ in CCl_4 solution at 30°. Agreement between the equilibrium constants (222 ± 15 and 63.4 ± 4.3, for the first and second steps, respectively) was excellent with a percentage standard deviation of the determination among the various protons of 6%. The theoretical curves for the LIS fit the data to better than 0.25% standard deviation. The best fits to a single-step mechanism, L + S ⇄ LS, were much poorer with deviations as large as 55 Hz between the experimental points and theoretical curves, compared with only 4 Hz (out of more than 1500) for the two-step mechanism. Also, the calculated equilibrium contant, $K = 99 \pm 12$, had a substantially larger per cent standard deviation. It was shown theoretically that plots of $1/\Delta\delta$ *vs.* S_0 at constant L_0 under the conditions $S_0 \gg L_0$ as well as plots of $\Delta\delta$ *vs.* L_0/S_0 at constant S_0 (under the same relative concentration conditions) may be used to obtain reliable values of the limiting LIS value for the LS_2 species. Thus these methods, previously used by others, are still reliable. This was a useful finding since these methods are much easier to use than the four-parameter fit required to completely fit the two-step mechanism to the experimental data. It is shown theoretically that plots using these simpler methods have slopes of either $1/2\Delta_2L_0$ ($1/\Delta\delta$ plot) or $2\Delta_2$ ($\Delta\delta$ *vs.* L_0/S_0 plots). Values of the limiting LIS for tetrahydrofuran, both in the presence of $Eu(FOD)_3$ and $Eu(DPM)_3$, were derived and found to be in good agreement with values obtained by other workers using different methods.

An important problem facing workers employing lanthanide shift reagents (LSR) in studies of molecular structure is the determination of the equilibria taking place between the LSR and substrate molecules. If we denote, for purposes of brevity, the substrate molecule as S and the LSR molecule as L, the problem then is as follows: to determine which of the complexes L_jS_k are present (where j and k are integers denoting the stoichiometry). Since these interactions are well known to obey the fast-exchange limit, the lanthanide-induced shifts (LIS) should conform to the following equation

$$\Delta\delta = \frac{1}{S_0}\sum_{i=1}^{N} n_i C_i \Delta_i \qquad (1)$$

where S_0 is the total concentration (moles/liter) of substrate in solution, both free and complexed, n_i is the number of substrate molecules in a given complex, C_i is the concentration (moles/liter) of that complex, Δ_i is the incremental shift which would be observed for total complex formation, and, finally, N is the number of different types of complexes present.

In using this equation, it is necessary to derive *at least* $2N$ parameters: N limiting incremental shifts and at least N equilibrium constants (K_i). If a complex can be formed in more than one way, the number of equilibrium constants increases. Previous attempts[3,4] to fit LIS data in the fast-exchange approximation have assumed that only a single 1:1 complex, LS, is formed. These attempts yielded results in apparent agreement with this simple mechanism. It is the purpose of this paper to show that this simple mechanism is not correct at least in some important cases (and possibly generally) and to give results for an alternate mechanism which fits the experimental data far better.

Experimental Section

All nmr spectra were run on a Varian HA-100 nuclear magnetic resonance spectrometer in the frequency sweep mode at an ambient probe temperature of 30°. Shifts were measured on carefully precalibrated chart paper and are estimated to be accurate to ±0.01 ppm or better.

All reagents used, except for 3,5,5-trimethyl-3-(*p*-chlorophenyl)-cyclohexanone (I), were obtained from standard commercial sources. I was prepared by the cuprous-catalyzed conjugate addition of *p*-chlorophenylmagnesium bromide to isophorone, analogous to several previously reported syntheses,[5] and was fully characterized by elemental analysis, properties, derivatives, and X-ray structure determination.[6]

The LSR used in these studies was Eu(III) tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione, hereafter denoted as $Eu(FOD)_3$. For each run, the LSR was sublimed and stored over P_4O_{10} *in vacuo*. The solvent employed for all samples was molecular sieve dried CCl_4. The liquid substrates were distilled and stored over molecular sieves. The solid substrate was sublimed and stored *in vacuo*.

Tetramethylsilane (TMS) was used as an internal reference for all measurements. It was first washed with concentrated sulfuric acid (to remove nontrivial amounts of tetrahydrofuran which often occur in commercially available TMS) and then with potassium bicarbonate. After distillation, it was also stored over molecular sieves.

The runs were performed in the following manner. The concentration of the substrate (S_0) was kept constant and only the LSR concentration (L_0) varied. The initial sample was prepared in a clean, oven-dried nmr tube by first putting in ~300 mg of $Eu(FOD)_3$

---

[1] For part II, see B. L. Shapiro, M. D. Johnston, Jr., and R. L. R. Towns, *J. Amer. Chem. Soc.*, **94**, 4381 (1972).

[2] Postdoctoral Fellow of the Robert A. Welch Foundation.

[3] I. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Chem. Commun.*, 1281 (1971).

[4] D. R. Kelsey, *J. Amer. Chem. Soc.*, **94**, 1764 (1972).

[5] B. L. Shapiro, M. J. Gattuso, and G. R. Sullivan, *Tetrahedron Lett.*, 223 (1971).

[6] R. L. R. Towns and B. L. Shapiro, *Cryst. Struct. Commun.*, **1**, 151 (1972).

and the appropriate amount of substrate, so that after the addition of CCl_4 and TMS, S_0 was at the desired value. Since the correctness of the substrate concentration is crucial, a solution approximately 0.5 M in substrate was added to the tube (its exact amount determined gravimetrically) rather than the pure substrate. The greater weight of the former thus insured accuracy in the concentration of the initial sample. Successive samples were then prepared by adding aliquots of a substrate stock solution (usually 0.15 M in CCl_4 with 3% TMS) of the same S_0 as in the initial sample. The concentrations were all determined gravimetrically to an estimated accuracy of better than 0.1%. As a check against the possibility of a large ΔV of mixing between the sample in the nmr tube and the substrate stock solution, the volume of the sample in the tube was carefully monitored during the entire run by measuring the sample height and comparing to the volume calculated from a precalibration of the tube. Effects from this possible complication were in all cases, discussed in this work, less than 1%.

This "incremental dilution" technique has advantages over the more conventional technique of adding solid LSR directly to a sample. First, the weight of the stock solution added in a given dilution is substantial (usually 0.1 g or more). Thus on a percentage basis, the weighings are much more accurate compared to addition of the solid LSR; amounts in this latter type of run are only a few milligrams at a time. Second, the possibilities of the LSR being contaminated by water from the atmosphere are greatly minimized. Finally, the accuracy of the results at low ρ ($= L_0/S_0$) is much greater. This is important since, as shall be shown later, points obtained in this concentration region are the most applicable to structural determinations.

Finally, all data were fit to the appropriate form of the fast-exchange equation (*vide infra*) by the method of least squares. In all cases the fits were done by a direct comparison of the LIS to ρ. The computations were performed on an IBM 360-65 digital computer; numbers were expressed exclusively in the double-precision mode. The authors will be glad to provide listings of the programs used to anybody who may desire them.

Data Analysis

Two different mechanisms will be considered for LSR–substrate equilibria. The first mechanism, along with its appropriate form of the fast-exchange equation, is given below

$$\mathrm{L} + \mathrm{S} \rightleftarrows \mathrm{LS} \tag{2a}$$

$$\Delta\delta = x\Delta_1/S_0 \tag{2b}$$

where Δ_1 is the limiting LIS for the LS complex, x is defined as the molar concentration of that complex ([LS]), and the other symbols are as defined previously. The fit requires two parameters, Δ_1 and the equilibrium constant K_1. The equilibrium constant is given as

$$K_1 = \frac{x}{(L_0 - x)(S_0 - x)} \tag{3}$$

On rearrangement, x can be extracted from the solution of a quadratic equation and the result substituted into eq 2b to give

$$\Delta\delta = \frac{\{S_0^{-1} + (1+\rho)K_1 - \sqrt{[S_0^{-1} + (1+\rho)K_1]^2 - 4K_1^2\rho}\}\Delta_1}{2K_1} \tag{4}$$

where ρ, the molar equivalent ratio, is defined as L_0/S_0. The equation, in other forms, is well known and has been used in numerous studies of fast-exchange equilibria in nmr.[7]

Iterative fits can be done on this equation to get values of K_1 and Δ_1 giving the best agreement between the observed LIS and the assumed mechanism.[7b] If we denote a given observed LIS as ϵ_i and its theoretically calculated value as δ_i, the i subscript here used to denote individual points (concentrations), the "best" values for the parameters can be obtained by minimizing the quantity

$$Q = \sum_{i=1}^{P}(\epsilon_i - \delta_i)^2 \tag{5}$$

where P is the number of data points. We shall briefly outline an efficient procedure for deriving the best-fit parameters. First, one selects a trial guess of K_1 and calculates a value α_i for each data point, where

$$\alpha_i = x_i/(S_0)_i \tag{6}$$

This value can be obtained by solving for x_i in eq 3. The best Δ_1 corresponding to the trial equilibrium constant can then be obtained *analytically* by minimizing Q with respect to Δ_1, *viz.*

$$\frac{\partial Q}{\partial \Delta_1} = 0 = \frac{\partial}{\partial \Delta_1}\left[\sum_{i=1}^{P}(\epsilon_i - \alpha_i\Delta_i)^2\right] \tag{7}$$

Taking the derivative and solving for Δ_1 then gives

$$\Delta_1 = S_{\epsilon\alpha}/S_{\alpha\alpha} \tag{8}$$

where we use a shorthand notation for summations

$$S_{\epsilon\alpha} = \sum_{i=1}^{P}\epsilon_i\alpha_i \tag{9}$$

$$S_{\alpha\alpha} = \sum_{i=1}^{P}\alpha_i^2$$

This "summation shorthand" will be employed throughout since some of the expressions to be derived later are very complicated. Since the limiting shift can be obtained analytically for a given trial guess of an equilibrium constant, convergence of the least-squares fit is quite rapid despite the fact that a quadratic function is being evaluated.[7b]

The other mechanism to be studied in this paper is a "two-step" mechanism. The mechanism, along with its appropriate form of the fast-exchange equation, is

$$\begin{gathered}\mathrm{L} + \mathrm{S} \rightleftarrows \mathrm{LS} \\ \mathrm{LS} + \mathrm{S} \rightleftarrows \mathrm{LS_2}\end{gathered} \tag{10a}$$

$$\Delta\delta = \frac{1}{S_0}[x\Delta_1 + 2y\Delta_2] \tag{10b}$$

Here, Δ_2 is the limiting shift of the LS_2 complex and y is defined as the molar concentration of the LS_2 complex, for notational convenience. The equilibrium constants for the first and second interaction steps, respectively, are then given by

$$K_1 = \frac{x}{(S_0 - x - 2y)(L_0 - x - y)} \tag{11a}$$

and

$$K_2 = \frac{y}{x(S_0 - x - 2y)} \tag{11b}$$

Analytical solutions are obtainable for x and y by solving a cubic equation, using standard mathematical methods.[8] The solution procedure proceeds most

---

[7] (a) I. D. Kuntz, Jr., and M. D. Johnston, Jr., *J. Amer. Chem. Soc.* 89, 6008 (1967); (b) M. D. Johnston, Jr., F. P. Gasparro, and I. D. Kuntz, Jr., *ibid.*, 91, 5715 (1969).

[8] M. Abramowitz and I. A. Stegun, Ed., "Handbook of Mathematical Functions, National Bureau of Standards Applied Mathematics Series, 55," U. S. Government Printing Office, Washington, D. C., 1964, p 17.

easily by first solving for y in terms of x by the rearrangement of eq 11b to give

$$y = \frac{K_1 x(S_0 - x)}{k + 2xK_1} \qquad (12)$$

where $k = K_1/K_2$. The cubic equation is then obtained by rearranging eq 11a and has the following form

$$x^3 + Px^2 + Qx + R = 0 \qquad (13)$$

In this equation

$$P = k\left(K_1^{-1} - \frac{2\rho S_0}{k - 4}\right) \qquad (14a)$$

$$Q = \frac{S_0{}^2 k(2\rho - 1) - k^2[S_0(\rho + 1) + K_1^{-1}]K_1^{-1}}{k - 4} \qquad (14b)$$

and

$$R = \frac{k^2 \rho S_0{}^2}{K_1(k - 4)} \qquad (14c)$$

Equation 13 has three roots; only one at a time, of course, can be physically relevant. Before giving the solutions, we shall make the following variable changes

$$q = \frac{1}{9}(3Q - P^2) \qquad (15a)$$

$$r = \frac{1}{6}(PQ - 3R) - \frac{1}{27}P^3 \qquad (15b)$$

$$b = (q^3 + r^2)^{1/2} \qquad (15c)$$

$$s_1 = (r + b)^{1/3} \qquad (15d)$$

and, finally

$$s_2 = (r - b)^{1/3} \qquad (15e)$$

There are then two physically relevant solutions, depending on the relative magnitudes of K_1 and K_2. First, for $k < 4$

$$x = s_1 + s_2 - \frac{1}{3}P \qquad (16a)$$

and for $k > 4$

$$x = -\frac{1}{2}(s_1 + s_2) - \frac{1}{3}P - \frac{i\sqrt{3}}{2}(s_1 - s_2) \qquad (16b)$$

At $k = 4$, there occurs a special case since P, Q, and R all encounter singularities. However, an averaging of the solutions for $k = 3.999$ and $k = 4.001$ gives a value of x which is sufficiently accurate for most purposes.

The least-squares procedure can now be performed. The most economical way to perform the fits is to select trial values of K_1 and k and solve (again *analytically*) for Δ_1 and Δ_2 and keep iterating the equilibrium constants until the variance is minimized. The best pair of limiting shifts, corresponding to a given pair of equilibrium constants, is evaluated as follows. First, evaluate for each data point

$$\begin{aligned} \alpha_i &= x_i/(S_0)_i \\ \beta_i &= 2y_i/(S_0)_i \end{aligned} \qquad (17)$$

Then, minimize Q (here, the sum of the squares of the deviations between the experimental and theoretical calculated LIS) with respect to Δ_1 and Δ_2

$$\frac{\partial Q}{\partial \Delta_1} = 0 = \frac{\partial}{\partial \Delta_1}\sum_{i=1}^{P}(\epsilon_i - \alpha_i\Delta_1 - \beta_i\Delta_2)^2 \qquad (18a)$$

and

$$\frac{\partial Q}{\partial \Delta_2} = 0 = \frac{\partial}{\partial \Delta_2}\sum_{i=1}^{P}(\epsilon_i - \alpha_i\Delta_1 - \beta_i\Delta_2)^2 \qquad (18b)$$

Evaluating these derivatives and solving the resulting simultaneous equations then give

$$\Delta_1 = \frac{S_{\alpha\epsilon}S_{\beta\beta} - S_{\beta\epsilon}S_{\alpha\beta}}{S_{\alpha\alpha}S_{\beta\beta} - S_{\alpha\beta}{}^2} \qquad (19a)$$

and

$$\Delta_2 = \frac{S_{\beta\epsilon}S_{\alpha\alpha} - S_{\alpha\epsilon}S_{\alpha\beta}}{S_{\alpha\alpha}S_{\beta\beta} - S_{\alpha\beta}{}^2} \qquad (19b)$$

where the summation shorthand is as done previously. Iterative convergence using this procedure is fairly rapid, especially since eq 19 allows the analytical determination of two of the parameters, the limiting shifts.

Results and Discussion

Much progress has been made in applying LSR's to the study of molecular geometry in solution and excellent techniques for this are now available.[9] However, structural determinations have nearly all been derived from *observed* LIS, rather than from the *intrinsic* parameters, the limiting incremental shifts. These latter must be derived and applied to structural analysis before any really rigorous test of the validity of the pseudocontact equation or the structural rigidity of a particular complex can be substantiated. Thus, the desirability of acquiring reliable values of the limiting incremental shifts is obvious. Also, the equilibrium constants are of some importance since they give information on the stability of a complex. However, for most purposes, it is the Δ_i which are, by far, of the most immediate interest and utility.

In the work of Armitage, *et al.*,[3] and of Kelsey[4] it was found that the LIS obey an equation of the following form, under the conditions $S_0 \gg L_0$

$$\frac{1}{\Delta\delta} = \frac{S_0}{L_0\Delta_1} + \frac{1}{L_0\Delta_1 K_1} \qquad (20)$$

Thus plots of $1/\Delta\delta$ *vs.* S_0 (at constant L_0) should give a straight line of slope $1/(L_0\Delta_1)$. This equation was derived under the assumption of a 1:1 complex formation and is very similar to the Scott[10] modification of the Benesi–Hildebrand[11] equation.

The fits[3,4,12] so far obtained to eq 20 have yielded excellent straight lines and this has been used as evidence for the simple one-step mechanism. However, as demonstrated by Deranleau,[13] the Scott equation is seldom a rigorous test for 1:1 complex formation. In order to ascertain what a particular interaction mechanism may be, it is necessary to vary the concentrations

---

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

(10) R. L. Scott, *ibid.*, 75, 787 (1956).

(11) H. A. Benesi and J. H. Hildebrand, *ibid.*, 71, 2703 (1949).

(12) I. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Can. J. Chem.*, 50, 2119 (1972).

(13) D. A. Deranleau, *J. Amer. Chem. Soc.*, 91, 4044, 4050 (1969).

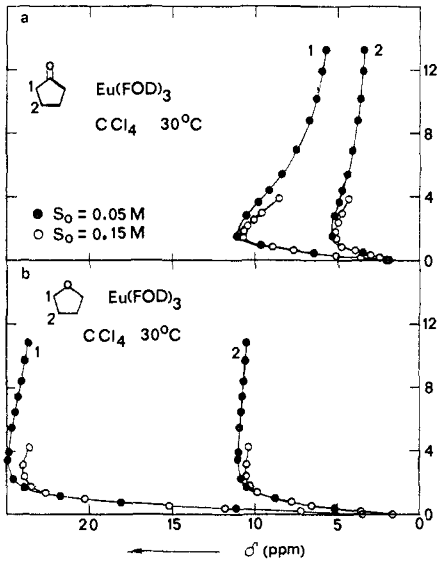

Figure 1. Observed chemical shifts of the substrates cyclopentanone (a) and tetrahydrofuran (b) *vs.* the molar equivalent ratio ($\rho = L_0/S_0$) of LSR to substrate at two fixed substrate concentrations: 0.05 and 0.15 *M*.

of *all* interacting reagents over as wide a range as possible.[13] The restriction $S_0 \gg L_0$ truncates the concentration domain of the LSR so that only one step in a multistep interaction mechanism would be expected to predominate. Indeed, for the conditions in which the Scott equation is applicable, almost any interaction mechanism can give a straight line plot.[13,14] This is demonstrated both by Deranleau's work and by results shown later in this paper. In determining an interaction mechanism, the best way to proceed is by a direct analysis of the data in terms of the unmodified form of the fast-exchange equation (eq 1). Modified forms including approximations, such as eq 20, have the disadvantage that they give unduly heavy weighting to the least accurate points.[15] Equation 1, on the other hand, weights all the data points equally.

Before proceeding further, it is best to look at the results shown in Figure 1. Here are plotted the observed LIS of tetrahydrofuran (THF) and cyclopentanone *vs.* the molar equivalent ratio, ρ, for Eu(FOD)$_3$. It is easily shown from the functional behavior of eq 4, the *exact* solution for 1:1 complex formation, that if only 1:1 complex formation were occurring, then plots such as those shown in Figure 1 would be strictly monotonic. The striking nonmonotonicity exhibited in Figure 1 is thus evidence that the simple one-step mechanism does *not* hold, even for relatively weak bases such as ketones. Similar nonmonotonic behavior has been observed by Roth, *et al.*,[16] for *tert*-butylamine and quinone. These authors proposed that multiple complex formation caused the observed behavior although their conclusions were only tentative and no explicit assumption of an interaction mechanism or analysis of data conforming to such a mechanism was explicitly given. In light of the discussion given below, some of their conclusions about the relative importance of various complexed species were probably inadequate.

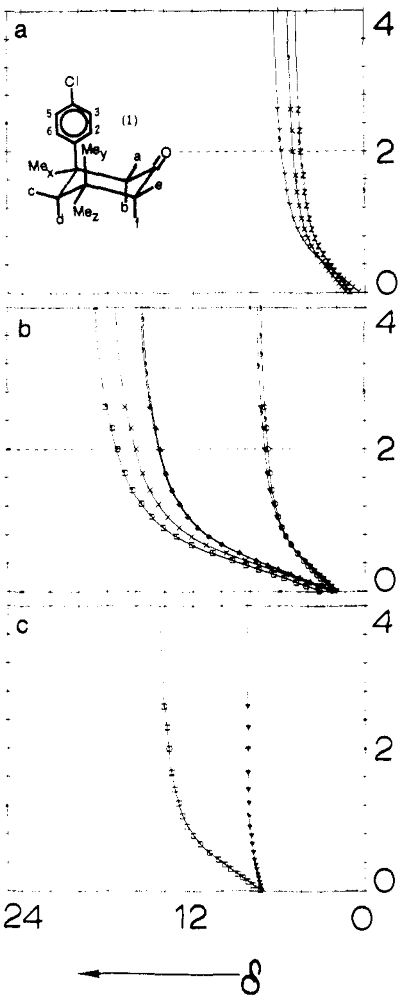

Figure 2. Results of theoretical fits of the two-step mechanism, $L + S \rightleftarrows LS$, $LS + S \rightleftarrows LS_2$, to the observed LIS data for 3-(*p*-chlorophenyl)-3,5,5-trimethylcyclohexanone at constant S_0 = 0.15 *M*. The curves were computer drawn from the four-parameter fit described in the text. The largest deviation on these curves is 4 Hz for the H$_a$ resonance, for an observed total incremental shift of more than 1500 Hz. The protons are, reading from left to right at the top of each drawing, (a) Me$_y$, Me$_x$, Me$_z$; H$_a$, H$_e$, H$_f$, H$_b$, H$_d$, H$_c$; (c) H$_2$ (= H$_6$) and H$_3$ (= H$_5$). The size of the data points does not reflect the accuracy of the data.

Only the formation of two or more complexes can explain this nonmonotonicity.[17] The most attractive alternative to 1:1 complex formation is the formation of the complexes LS and LS$_2$ by the two-step mechanism for which the mathematical analysis was given in the previous section of this paper. In order to test the validity of this mechanism, a detailed comparison of the one- and two-step mechanisms was performed on the substrate 3-(*p*-chlorophenyl)-3,5,5-trimethylcyclohexanone (hereafter, I). This compound has 11 distinct proton resonances in its nmr spectrum and a well-documented X-ray structure.[6] In Figure 2 and

---

[14] With one very important exception, LS$_2$ formation *via* $L + 2S \rightleftarrows LS_2$. This has been illustrated by other workers (ref 12). In the concentration ranges they employed, they got considerable curvature when attempting to fit observed LIS data to this mechanism.

[15] M. D. Johnston, Jr., Ph.D. Dissertation, Princeton University, 1970.

[16] K. Roth, M. Grosse, and D. Rewicki, *Tetrahedron Lett.*, 435 (1972).

[17] It should also be noted that nonmonotonicity can only be observed when the limiting incremental shifts of the different complexes are unequal. There is also the possibility that, at very high concentrations of LSR, complexes such as L$_2$S and L$_2$S$_2$ may be present and cause the observed nonmonotonicity. These possibilities are being investigated at the present but it is felt that they are not major hindrances to applications of LSR's under the usual conditions employed.

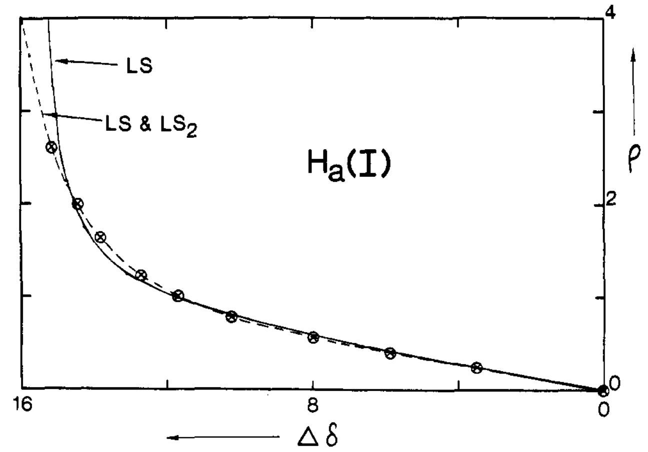

Figure 3. A comparison of fits to the experimental data for the H_a resonance (LIS) of I for the one- and two-step mechanisms (solid and dashed curves, respectively). In this comparison, the averaged K_1 (= 222) and K_2 (= 63.4), derived from the LIS of all the protons, are used to draw the two-step curve whereas the best possible fit for the one-step mechanism, derived for the H_a proton only, is used to draw the one-step curve. Despite this, the two-step mechanism fits the data far better. The size of the data points does not reflect the accuracy of the data.

Table I. A Comparison of the Results of Fits of the Observed LIS of 3-(*p*-Chlorophenyl)-3,5,5-trimethylcyclohexanone (I) to the One-Step and Two-Step Mechanisms

	One-step fit			Two-step fit			
Proton[a]	K_1[b]	Δ_1[c]	σ^*[d]	K_1[e]	Δ_1[c]	Δ_2[c]	σ^*[d]
Me_x	103	3.92	17	246	4.40	1.84	3
Me_y	118	5.80	24	225	6.49	2.90	2
Me_z	92	3.68	17	209	4.12	1.70	2
H_a	84	15.63	15	199	17.52	7.00	3
H_b	89	12.98	16	228	14.56	5.87	3
H_c	105	4.93	19	241	5.53	2.35	3
H_d	91	5.53	17	217	6.20	2.53	2
H_e	97	15.08	19	204	16.90	7.09	3
H_f	93	13.24	17	220	14.85	6.08	3
H_3, H_5[f]	326[g]	1.01	65	290[g]	1.09	0.66	9
H_2, H_6[f]	120	6.92	24	232	7.73	3.46	3

[a] Structural designations are defined in Figure 2. [b] Results of averaging: $K_1 = 99 \pm 12$ (see footnote *g*, below). [c] In ppm. [d] In Hz, normalized to a limiting shift for the LS complex of 10 ppm. Presented in this form for convenience in comparison of the relative standard deviations of the limiting shifts. [e] Result of averaging: $K_1 = 222 \pm 15$ with $K_2 = 63.4$. Since the ratio of K_1 to K_2 was kept constant at 3.5 for all these fits, K_2 is not shown. The fits actually improved somewhat when K_2 was allowed to float freely and not be fixed to K_1. (This was done with the H_a proton and σ^* decreased by 0.5 Hz and K_1 and K_2 became, respectively, 220 and 62.0 with a ratio of 3.55.) Unfortunately, the amount of computer time required for the calculations became prohibitive. The limiting chemical shifts are, however, much less sensitive to experimental error than are the equilibrium constants and were probably accurate to $<\pm 1\%$ when the equilibrium constant ratio was fixed at 3.5. [f] Chemically equivalent protons because of the rotating phenyl ring. [g] These values were deleted in taking the mean and standard deviation since the observed LIS were very small.

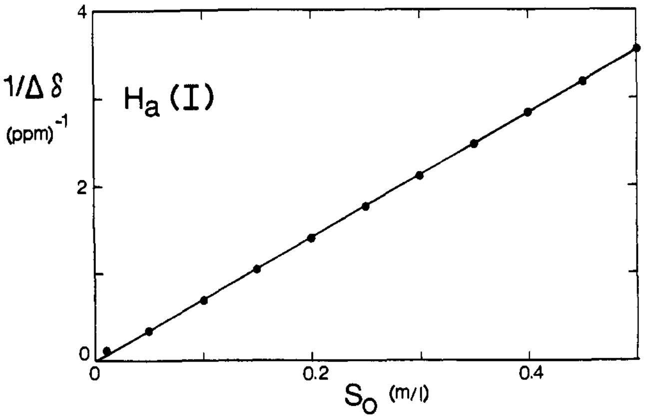

Figure 4. Results of a *Gedankenexperiment* for a fit of $1/\Delta\delta$ *vs.* S_0, according to the method of ref 3 and 4. Here, the LIS were predicted from the four-parameter fit and used to generate the points shown in the plot. The point falling off the line is at $S_0 = 0.01$ *M* (with constant $L_0 = 0.01$ *M*). That this point should deviate is consistent with the fact that the condition $S_0 \gg L_0$ no longer obtains. A linear regression analysis on this line gave a correlation coefficient of 0.99990 for shifts accurate to ±0.1 Hz.

Table I are shown the results of a least-squares fit of the concentration dependence of the LIS of all the protons of I to the two-step mechanism. In Figure 3 and Table I are given detailed comparisons of the best fits *via* both the one- and two-step mechanisms. Only the H_a proton LIS are given in Figure 3, since all other protons showed similar behavior. All these fits were performed directly on the unmodified fast-exchange equation (eq 1) and *no* approximations of any sort were employed. *This is the most rigorous way possible to compare two mechanisms when spectroscopic techniques are employed.*[13] The agreement between the experimental points and the best-fit curves is far better for the two-step mechanism.[18] This can be seen by looking at Figure 3 or by comparing the "normalized standard deviations" of the two sets of results. (σ^* as

$$\sigma^* = 1000(\sigma/\Delta_1) \tag{21}$$

defined is useful in comparing the shifts, for it is simply the "real" standard deviation, in hertz, normalized to take into account the different sizes of the shifts for different protons. The factor of 1000 is included to make all the data correspond to a Δ_1 of 10 ppm.) For the single-step mechanism, the average value of σ^* is ±22.7 Hz and for the two-step mechanism, ±3.2 Hz. This represents more than a sevenfold difference in the variance. A more rigorous comparison of the mechanisms is to see how well the equilibrium constants (K_1) agree among the protons. Neglecting the value derived for the H_3 proton, since its shifts are very small, the equilibrium constant derived from the one-step mechanism was 99 ± 12 and that from the other mechanism was 222 ± 15, or per cent standard deviations of ±12 and ±6%, respectively.

These results very strongly favor the two-step mechanism. This is not too surprising if one recalls that the first LSR ever used was an LS_2 type (dipyridine) adduct.[19] However, the apparent superiority of this mechanism raises very important questions. Why did the previous attempts[3,4] yield such good plots and are the parameters derived from these plots reliable? These are questions of urgent importance to answer since the earlier methods are much easier to employ and the associated calculations are tremendously simpler. In Figure 4 are shown the results of

---

(18) The good agreement for the two-step mechanism is quite important. It has been pointed out (ref 12) that earlier methods (ref 3 and 4) cannot give good values for *large* equilibrium constants. This (now resolved) difficulty is most likely owing to complications arising from the assumption of an inadequate mechanism, as well as the fact that these methods (ref 3 and 4) depend upon a *y* intercept, usually very small, to derive the equilibrium constant.

(19) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969).

a *Gedankenexperiment* in which the parameters derived from the two-step mechanism are used to calculate the behavior of $1/\Delta\delta$ *vs.* S_0 for constant L_0 for the resonance of the H_a proton of I. The conditions ($L_0 = 0.01\ M$ and $0.01 \leq S_0 \leq 0.5\ M$) are similar to those in Kelsey's[4] work. In this test, values of $\Delta\delta$ were derived from the four parameters (K_1, K_2, Δ_1, Δ_2) of the two-step mechanism fit and rounded to conform to typical experimental error (± 0.1 Hz) and then used to generate "data" corresponding to the above concentration conditions. The general appearance of the straight line is excellent; the only point falling off the line is at $S_0 = 0.01\ M$ where, of course, the condition $S_0 \gg L_0$ does not hold. A linear regression analysis performed on this line gave an excellent fit with the correlation coefficient being 0.99990. Thus, the two-step mechanism is capable of reproducing results obtained by plots of $1/\Delta\delta$ and *is in no way inconsistent with previous findings*.

Having seen that the two-step mechanism can account for the linearity of plots of $1/\Delta\delta$ *vs.* S_0, it remains to check the validity of the parameters derived from such plots. First, the equilibrium constants derived are most likely unreliable since they are derived from the assumption of an inadequate mechanism and are thus off by some factor, namely an activity coefficient.[20,21] However, the derived values of the limiting shift are "correct" although the value obtained is not Δ_1 but rather $2\Delta_2$, the factor of 2 entering in to correct for stoichiometry. A proof of this rather interesting result follows.

The primary conditions obtaining in the plots of $1/\Delta\delta$ *vs.* S_0 are that $S_0 \gg L_0$ and that L_0 be held constant. Thus, S_0 is much greater than the concentrations of LS and LS_2 (x and y, respectively, below) and the equilibrium constants take the following form (*cf.* eq 11)

$$K_1 \approx \frac{x}{S_0(L_0 - x - y)} \tag{22a}$$

and

$$K_2 \approx \frac{y}{xS_0} \tag{22b}$$

Furthermore, under the above conditions, $x \ll 2y$ usually holds, giving the following reduced form of the fast-exchange equation

$$\Delta\delta \approx 2y\Delta_2/S_0 \tag{23}$$

Solving for x and y in eq 22, substituting y into eq 23, and inverting

$$\frac{1}{\Delta\delta} = \frac{(1 + K_1S_0 + K_1K_2S_0^2)}{2K_1K_2S_0L_0\Delta_2} \tag{24}$$

Under the usual experimental conditions, the first two terms in the numerator are negligible compared with the third. Thus, eq 24 simplifies to

$$\frac{1}{\Delta\delta} \approx \frac{S_0}{2L_0\Delta_2} \tag{25}$$

to an excellent degree of approximation. Thus, the linearity of $1/\Delta\delta$ *vs.* S_0 holds and the slope is $1/(2L_0\Delta_2)$. Results comparing the values obtained for Δ_2 by the two-step mechanism and by eq 25 are given in Table II (as methods A and B) and the agreement is excellent.

Table II. Comparison of Three Methods for Deriving the Limiting Incremental Shift for the Species LS_2 (for Compound I)

Proton[a]	Method A[b]	Method B[c]	Method C[d]
Me_x	1.84	1.85	1.87
Me_y	2.90	2.90	2.90
Me_z	1.70	1.70	1.74
H_a	7.00	7.02	7.20
H_b	5.87	5.88	6.03
H_c	2.35	2.34	2.38
H_d	2.53	2.54	2.59
H_e	7.09	7.11	7.20
H_f	6.08	6.10	6.22
H_3, H_5[e]	0.66	0.66	0.62
H_2, H_6[e]	3.46	3.48	3.44

[a] Structural designations are given in Figure 2. [b] Derived from the four-parameter fit. [c] Derived from a plot of $1/\Delta\delta$ *vs.* S_0 at constant L_0 (ref 3 and 4). For further discussion of the way these parameters were derived, see text. [d] Derived from a plot of $\Delta\delta$ *vs.* ρ at constant S_0. Experimental details are discussed in the text. [e] Chemically equivalent protons owing to rotation of the phenyl ring.

One additional question remains to be answered. Are structural determinations employing merely the observed LIS and not the limiting shifts reliable? Here, the answer is in the affirmative, provided a few precautions are taken. Careful observation of the plots in Figures 1 and 2 shows that, up to $\rho \sim 0.7$, the shifts are linear in concentration.[22] Indeed, for all data (on several compound types) obtained recently in this laboratory, regression analyses performed in the range $0 \leq \rho \leq 0.4$ are invariably excellent with better than 99% correlation. (In these experiments, S_0 was kept constant and L_0 was varied.) Since structural determinations performed at such concentrations give excellent agreement factors,[9] LIS at small ρ should be simply proportional to Δ_1 or to Δ_2. Proof of this fact follows. First, the condition $S_0 \gg L_0$ should hold.[23] Then, we do the experiment by varying ρ ($= L_0/S_0$) and keeping S_0 constant. Taking eq 22 as a starting point and proceeding as before, we arrive at the following results

$$\frac{\partial(\Delta\delta)}{\partial\rho} \approx \frac{\Delta_1}{S_0K_2} + 2\Delta_2 \approx 2\Delta_2 \tag{26}$$

Thus, the slope at small ρ of a plot of the LIS *vs.* ρ is simply $2\Delta_2$. In Table II (method C) are given results for Δ_2 of I, derived *via* eq 26 from the experimental data, and the values derived by this method agree very well with those of the two-step mechanism and those derived from plots of $1/\Delta\delta$ *vs.* S_0 at constant S_0.

---

(20) I. Prigogine and R. DeFay, "Chemical Thermodynamics," Longmans, Green, & Co., Ltd., Norwich, United Kingdom, 1954.

(21) M. W. Hanna and D. G. Rose, *J. Amer. Chem. Soc.*, 94, 2601 (1972).

(22) Good linearity at low LSR concentrations is very important. When using the slope of LIS plots at low LSR concentration in structural determinations or to measure Δ_2, *extreme* caution must be exercised to be sure that no competitive substrates ("scavengers") are present in solution. The most commonly occurring scavengers in our work have been water from the atmosphere and THF from the TMS. Fortunately, the linearity of the plots at small LSR concentration is extremely sensitive to the presence of scavengers and, when such are present, severe curvature in the plots is observed. This has been found by us to be of great use in assessing the purities of our samples and in assessing the quality of a given run.

(23) When K_1 is large, as well as S_0, linearity often holds up to higher values of ρ usually employed in our experiments. Why this is so is apparent in eq 26.

Under the appropriate conditions, this slope should be independent of S_0. The less approximate form of eq 26 provides a test of whether or not given experimental conditions are "appropriate." If two runs at different S_0 are performed and agree, then the correct limiting shift has been obtained; otherwise, additional measurements at higher S_0 are necessary.[24] In Table III are given results of measurements of Δ_2 for the α and β protons of THF and cyclopentanone at $S_0 = 0.05$ and 0.15 M. Agreement between the values is good. Thus, use of this "slope method" can give reliable values of the limiting shift and provided the value is extracted from the linear portion of the curve (low ρ), *isolated values of the LIS, even at a single concentration, can in principle be used for structural determinations.* The latter fact of course depends on the applicability of the particular form of the pseudocontact equation used. Tests of its rigor necessarily depend on acquiring reliable limiting shifts and it is preferable to use the data derived at several concentrations (and derive the slope) rather than to base all results on one, isolated concentration. Further work on this subject will be reported in the future.

Table III. Estimated Values of the Limiting Shift of LS_2 (Incremental) for THF and Cyclopentanone in the Presence of $Eu(FOD)_3$

Compound	Proton	Δ_2 ($S_0 = 0.05\ M$)[a]	Δ_2 ($S_0 = 0.15\ M$)[a]
Tetrahydrofuran[b,c]	H_α	9.77	10.16
	H_β	4.11	4.22
Cyclopentanone	H_α	4.78	4.94
	H_β	1.78	1.78

[a] Evaluated from the slope of the LIS curve at low ρ (this work). All values are in ppm. [b] For THF, Kelsey (ref 4) obtained values of 9.74 and 3.96 for the α and β protons, respectively, from plots of $1/\Delta\delta$ *vs.* S_0 at a constant L_0 of $\sim$0.01 M. Agreement here is excellent. His values have been halved (*cf.* eq 25). [c] We have also derived values of Δ_2 for THF in the presence of $Eu(DPM)_3$. These were, for the α and β protons, respectively, 15.44 and 6.95 ppm. Professor M. R. Willcott at the University of Houston, using methods similar to those in ref 3 and 4, derived values of 15.4 ± 0.2 and 7.0 ± 0.1 ppm. Considering the fact that these data were gathered from different laboratories (see also footnote *b*), that the reagents came from different sources, and that the methods employed were quite different, the agreement between these data is a very encouraging sign.

Summary and Conclusions

It has been shown, by a detailed analysis using a four-parameter fit, that LSR–substrate systems can obey a two-step equilibrium, $L + S \rightleftarrows LS$, $LS + S \rightleftarrows LS_2$, within experimental error. Fits to a simple one-step mechanism exhibited significant deviations. These results are *not* inconsistent with previous findings[3,4] and, indeed, substantiate the reliability of earlier used methods. That is, values of the limiting shifts from previous methods are reliable, whereas equilibrium constants thus obtained are not. However, the process actually observed in earlier methods is the second step of the two-step mechanism. Thus, we have shown that a plot of $1/\Delta\delta$ *vs.* S_0 may be used (at constant L_0), or a plot of $\Delta\delta$ *vs.* ρ (at constant S_0) may be used, to give reliable limiting incremental shifts. This is a useful finding since these latter methods are much easier to employ than is the more complicated multiparameter fit. In addition, the LIS at a single concentration of LSR, provided it be in the linear region of the LIS curve, can in principle be used for structural determinations, although this procedure is obviously perilous and is not recommended. Thus, the methods of Willcott and Davis[9] are still applicable and, in fact, theoretical justification for their use is now at hand.

Acknowledgments. The authors wish to thank the Robert A. Welch Foundation of Houston, Tex., for their generous support of this research. Also, we wish to thank Professors M. R. Willcott (University of Houston) and A. G. Marshall (University of British Columbia) for several interesting discussions and for providing us with some preprints of their experimental findings prior to publication.

---

(24) There is some danger in letting S_0 become too large. At very high substrate concentrations, substrate–substrate interactions might complicate matters considerably, especially if the substrate contains aromatic substituents (which could induce sizable ASIS). Keeping S_0 small ($<$0.5 M) should eliminate such problems. (When S_0 is substantial, such self-association effects can induce substantial shifts, even when K is small, of the order of 0.05; *cf.* ref 7a.)