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Lanthanide-Induced Shifts in Proton Nuclear Magnetic Resonance Spectra. XI. Equilibrium Constants and Bound Shifts for Cyclohexanones and Cyclohexanols[1]

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Abstract: The results of detailed, exhaustive analyses of the concentration dependence of the lanthanide-induced shifts (LIS) induced by $Eu(fod)_3$ in CCl_4 solution at ambient nmr probe temperature (31°) are reported. The substrates employed are a variety of highly substituted cyclohexanones and cyclohexanols of high conformational purity. It was found that all these systems display both 1:1 and 1:2 (LS and LS_2) LSR-substrate complex formation. No self-association of the $Eu(fod)_3$ could be detected; assumption of this extra equilibrium step resulted in poorer fits to the data. It was found that secondary alcohols are much better binders to LSR than are ketones; these, in turn, are far superior to tertiary alcohols. Also, equatorial hydroxyls bind much more readily than do axial hydroxyls. Values for the parameters K_1, K_2, Δ_1, and Δ_2 (association equilibrium constants and bound shifts for LS and LS_2 formation, respectively) are given for all systems studied; a general discussion is given on the methods of obtaining these parameters, especially as pertains to their accuracy.

Among other areas of application of lanthanide shift reagents (LSR) to problems in structural applications of nmr spectroscopy, considerable useful progress has been made recently in delineating the various association equilibria taking place between an LSR and various organic substrates in solution.[5-8] At least for the case of $Eu(fod)_3$,[9] there is now abundant evidence for the significant involvement of *at least* two complexes: LS and LS_2, where L and S denote the shift reagent and substrate molecules, respectively. It is possible that other shift reagents may show only 1:1 complex formation.[7a,b,e] Also evidence exists that LSR's may self-associate under some circumstances to form L_2, or even L_3, aggregates.[8]

It is well-known that all complexation equilibria involved in LSR-substrate interactions are very rapid on the nmr time scale, at least at typical ambient probe temperatures.[10] Hence, the parameters needed to characterize a given complex are obtainable only through a rigorous statistical analysis of the LSR and/or substrate concentration dependence of the lanthanide-induced shifts (LIS). Such analysis gives much more detailed and specific information than can be obtained from the observation of LIS from just a single sample. In particular, one is able to obtain equilibrium constants (*e.g.*, K_1, K_2, and K_L for LS, LS_2, and L_2 formation, respectively) and "bound shifts" (Δ_1 and Δ_2 for LS and LS_2, respectively) for each species present. These quantities possess the advantage of being intensive properties of the respective complexes. Also, the bound shifts are the parameters of choice for use in any quantitative assessment of the molecular geometry of a substrate.[11] Conversely, the most rigorous test of any kind of structural assessment procedure would lie in the direct utilization of Δ_1 and Δ_2 since with these the number of extraneous degrees of freedom and hence the number of additional needed fitting parameters would be reduced to an absolute minimum.

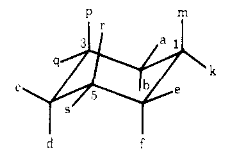
Current practice for the fitting of molecular geometry with LIS data usually makes use of the slopes of the initial portions of a set of LSR doping curves. Even in those cases where such slopes are well-determined experimentally (by no means a universal occurrence), the slope values are a nonanalyzable function of the shifts of at least two species, LS and LS_2. The (equivocally defined) slopes are then fit to some simple form of the pseudo-contact shift equation, and the discrepancies between observed and calculated geometries are blamed on additional shifts arising from a contact mechanism. Our theses are that (a) the methods described in this paper and its precursors, as well as the work of Reuben,[6] make accessible high precision data on one or both of the two complex species generated concurrently and (b) that this provides a more exact basis for geometry fitting and/or assessments of the validity of any form of the pseudo-contact shift equation (or other dependence of these LIS). In other words, geometry fits to a *single* species whose symmetry characteristics can be taken into account allows a better opportunity for the formulation of a physical model for LIS.

The primary purpose of this paper is to present the results of high precision statistical analyses of proton LIS for 28 cyclohexanone and cyclohexanol substrates interacting with Eu(fod)$_3$ in CCl$_4$ solution at a typical ambient probe temperature. All these substrates are either rigid or at least conformationally very biased. It is therefore legitimate to discuss the LIS results in terms of single cyclohexane conformers, *viz.*, those shown in Scheme I (*vide infra*). Thus, one has a basis here upon which to examine the effects of varying the degree and pattern of substitution on otherwise similar substrates, as well as more subtle stereochemical differences. The large body of well-determined K's and Δ's emerging from these data is of inherent interest and will, in our opinion, serve to indicate the considerable, and as yet still untapped, additional power and versatility possessed by the application of LSR methods. Also, we shall present analytical methods more general and extensive than in our previous treatment.[5] For instance, these procedures are extendible by suitable modification to handling any system of equilibria occurring among molecules with single binding sites;[12] *e.g.*, the present treatment provides for any possible involvement of LSR self-association. Finally, we shall discuss the reliabilities of parameters obtained, both in terms of the statistics and in terms of the design of optimal experiments.

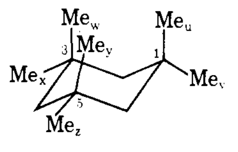
Substrates

Two types of substrates are discussed in this paper: cyclohexanones and cyclohexanols. These are either highly substituted in the C-3 and C-5 ring positions or possess a single, bulky, *tert*-butyl group at C-4. In addition, these molecules afford an opportunity to study effects of various degrees of steric hindrance at the LSR-substrate binding site. Specifically, we shall examine the relative binding abilities of ketones, secondary cyclohexanols, and tertiary cyclohexanols. Also, with alcohol substrates, we are given the additional opportunity of comparing effects of axial and equatorial hydroxyl disposition. The high conformational purity of these substrates serves to make the above comparisons unambiguous.

To facilitate discussion, all protons are denoted by the designations shown below. The structures given here are just a guide to a formal lettering scheme and not actual compounds studied.



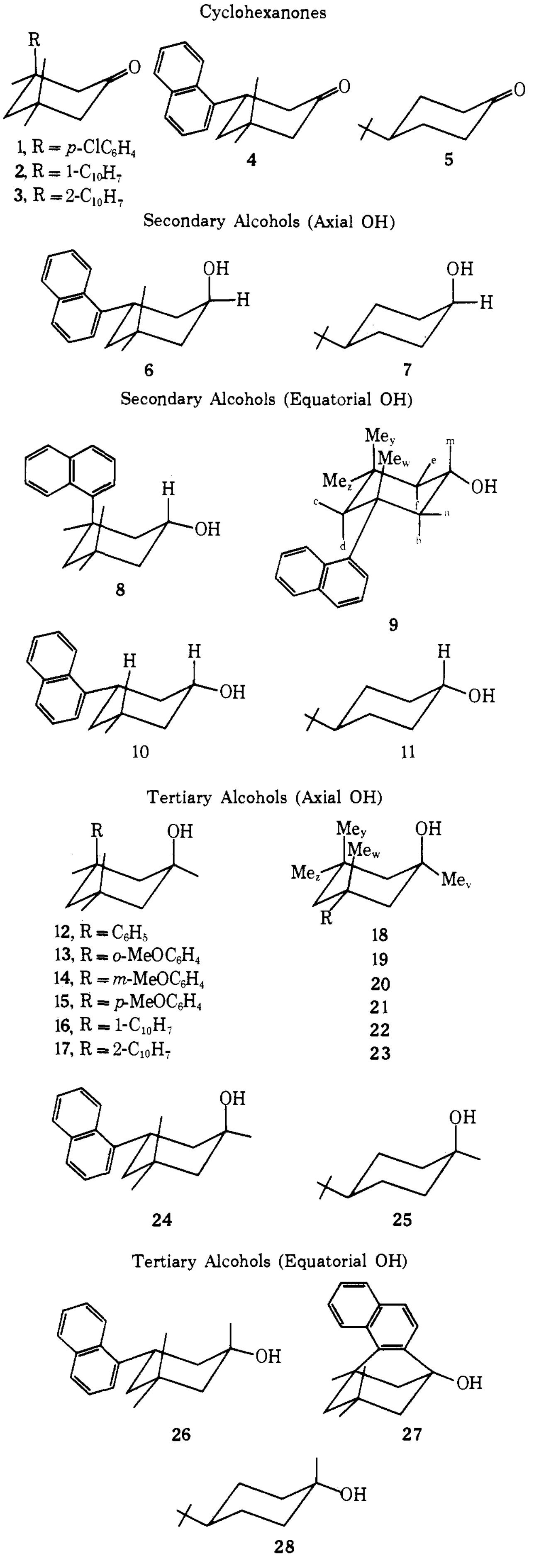
cyclohexane ring proton designations



cyclohexane ring methyl designations

Here we have shown the designations for the protons and methyl groups of cyclohexanols; cyclohexanones obey the same mapping except, of course, at C-1.

Scheme I



The structures, formulas, and numerical designations of the 28 substrates are shown in Scheme I. It should be noted that some structures are drawn with their methyl and proton designations altered to preserve a particular optical series.

Experimental Section

The preparation and characterization of the following compounds have appeared elsewhere: **1** (ref 5), **2** (ref 14), **4**, **24**, **26** (ref 15), **12–15**, **18–21** (ref 16), and **16** and **22** (ref 17). Compound **5** is commercially available and was used after recrystallization from hexane. Compounds **7** and **11** are commercially available as a mixture and were separated by column chromatography on silica. Compounds **6–10** were prepared by reduction of the corresponding ketones with sodium borohydride followed by separation of the isomeric alcohols.[18] Ketone **3** was prepared by the CuCl-catalyzed conjugate addition of 2-naphthylmagnesium bromide to isophorone in the standard fashion.[14,18] The tertiary alcohols **17**, **23**, **25**, and **28** were obtained by the addition of methylmagnesium bromide to the corresponding ketone and column chromatography on silica. Alcohol **27** was prepared by the hydrolysis of the corresponding chloro derivative which was in turn prepared by the action of $AlCl_3$ on ketone **2**.[18]

The conformational and chemical shift assignments given later in this paper are based on analogy with previous results[5,14-17,23] and general chemical shift–structure correlations, as well as consistency arguments involving the very detailed LIS studies which follow.

Sample Preparation and Spectra. The LSR used in these studies was $Eu(fod)_3$ sublimed *in vacuo* at ~160° and then stored *in vacuo* at least 24 hr prior to use over P_4O_{10}. The proton nmr spectrum of the LSR exhibited only a single, clean, symmetrical peak for the *tert*-butyl group; no additional LSR *tert*-butyl resonances appeared at this or any subsequent time during the run. We have found this to be a reliable criterion of adequate LSR purity for the obtention of equilibrium constants and "bound shifts."[19] Substrates were sublimed *in vacuo* or recrystallized from an inert solvent such as hexane. When neither of these procedures was applicable, short-path vacuum distillation was used. The solvent employed was carbon tetrachloride dried over molecular sieves. Finally, TMS (tetramethylsilane, purified as reported previously[5]) was employed as both the internal reference and to give a locking signal.

For a given substrate, the different concentrations of the LSR were prepared by the "constant-S_0 incremental dilution method"[5] with the most highly doped solution prepared first and subsequent solutions made up by dilution with a stock solution of the substrate. In each run, the relative molarity of LSR to substrate (ρ) was varied from $\rho \geq 2.0$ down to 0.05. (ρ values in excess of *ca.* 2 were rarely necessary, but occasionally resonances were tracked down from ρ values as large as 3.5.) From the highest values of ρ down to $\rho = 0.5$, each decrement was 0.1; from $\rho = 0.5$ to $\rho = 0.05$, the decrement was 0.05. This particular way of performing measurements of LIS of a given substrate allows one to obtain the maximum amount of information. In particular, sufficient data are obtained in the most highly curved part of an LIS curve ($\rho = 0.5$ to 1.5) to ensure the best possible determination of K-values. Second, enough highly precise data are obtained by this procedure for $\rho \lesssim 0.5$ (the linear region of an LIS plot) to get superior slopes and intercepts. Also, in the linear region of an LIS plot, the changes in the shifts are the largest; decreasing the size of the decrement makes the tracking of resonances and the analysis of more complex spectra far easier.

All nmr spectra were run on a Varian HA-100 nuclear magnetic resonance spectrometer in the frequency sweep mode and at an ambient probe temperature of 31 ± 1°. Five minutes were allowed for each sample to come to thermal equilibrium after insertion into the probe and before starting the scan. *Failure to do this can result in shift errors of 10–20 Hz (at 100 MHz).* Shifts were measured at a sweep width of 20 Hz/cm and at a scan rate of 2 Hz/sec on carefully calibrated chart paper. The shifts so obtained are estimated to be accurate to ±0.01 ppm or better.

LIS Analysis Methodology

We shall examine interaction mechanisms containing some, or all, of the following steps

$$L + S \rightleftharpoons LS \quad (K_1, \Delta_1) \tag{1}$$

$$LS + S \rightleftharpoons LS_2 \quad (K_2, \Delta_2) \tag{2}$$

$$2L \rightleftharpoons L_2 \quad (K_L) \tag{3}$$

where the quantities in parentheses serve to define a particular step of the mechanism. The parameters derived are those which best fit the observed LIS *vs.* ρ curve. For each proton, this curve is formally defined as

$$\Delta\delta = \delta - \delta_0 = f(\rho, S_0) \tag{4}$$

where $\Delta\delta$ is the LIS, δ is the observed chemical shift (usual δ scale) of the substrate proton, δ_0 is that shift in the absence of the LSR, S_0 is the total substrate concentration and, finally

$$\rho = L_0/S_0 \tag{5}$$

where, in turn, L_0 is the total LSR concentration in moles/liter (M). The reduced concentration variable, ρ, is used to express the LSR concentration instead of the actual concentration L_0, to facilitate comparison of LIS *vs.* ρ curves.

Since the LIS obey the fast-exchange limit, we may represent them as

$$\Delta\delta_i = (S_0)_i^{-1}\sum_{l=1}^{P} n_l C_{l,i}\Delta_l \tag{6}$$

where the i denotes a particular ρ value on a LIS *vs.* ρ curve, l is the summation index for the complexes which are P in number, n_l is the number of substrate molecules in a given complex species, C_l is the concentration in moles/liter of the species, and Δ_l is the species' "bound shift" (*i.e.*, the LIS which would be found for 100% formation of a particular complex). In this paper, we shall consider only two substrate-containing species, LS and LS_2. If we then make the following definitions

$$x_i \equiv [LS]_i, \quad y_i \equiv [LS_2]_i \tag{7}$$

and

$$\alpha_i = x_i/(S_0)_i, \quad \beta_i = 2y_i/(S_0)_i \tag{8}$$

where i has the same meaning as in eq 6, then we can rewrite that equation as

$$\Delta\delta_i = \alpha_i\Delta_1 + \beta_i\Delta_2 \tag{9}$$

The α_i and β_i are just the bound fractions (reduced concentration variables) for LS and LS_2, respectively. Equation 9 is that form from which all subsequent equations are to be derived. Occasionally, we shall also discuss systems where LS_2 formation is absent; in such cases, one can simply set all $\beta_i = 0$ (or, equivalently and alternatively, eliminate the parameters entering into the calculation of the β_i) and solve the resulting special-case equations.

The best-fit *calculated LIS*, $\Delta\delta_i$, are obtained by minimizing the sum of the squares of the deviations between them and the *experimentally measured LIS*, which we shall denote as ϵ_i. The minimized quantity shall be denoted Q and expressed as

$$Q = \sum_{i=1}^{N}(\epsilon_i - \Delta\delta_i)^2 = \sum_{i=1}^{N}(\epsilon_i - \alpha_i\Delta_1 - \beta_i\Delta_2)^2 \tag{10}$$

where N is the number of data points for a given proton. The parameters of eq 10 are, of course, just the equilibrium constants (K's) and the bound shifts (Δ's).

Fits are performed[20] by choosing a set of K's, evaluating the α_i and β_i, and then getting Δ_1 and/or Δ_2. The best K's are found iteratively (nonlinear regression analysis) whereas the Δ's for a given set of K's may be found exactly and analytically (*via* linear regression). The iteration in the equilibrium constants is repeated until the best agreement, in the least-squares sense, is obtained between the calculated and observed LIS. In the next sections, we shall discuss the obtention and relative accuracies of the parameters.

Equilibrium Constants. There are three of these obtaining in eq 1-3: K_1, K_2, and K_L for LS, LS_2, and L_2 formation, respectively. Each must be evaluated *via* nonlinear regression since no analytical solution exists for the system of equations resulting from

$$\frac{\partial Q}{\partial K_1} = \frac{\partial Q}{\partial K_2} = \frac{\partial Q}{\partial K_L} = 0 \tag{11}$$

Fortunately, the methods used in this regression procedure converge rather quickly to the best-fit condition. The only computational difficulties reside in the evaluation of the α_i and β_i. When $K_L = 0$ (no L_2 formation) these may be evaluated analytically.[5] Unfortunately, this is not the case for $K_L > 0$; there, it is necessary to resort to an iterative numerical method of solution. The method chosen is the Newton-Raphson method[6] since it gives solutions accurate to one part in 10^{10} in six iterations or less (per point). The equations employed are presented only for the case of LS, LS_2, and L_2 all being present; when LS_2 formation is absent, the appropriate expressions follow trivially upon setting $K_2 = 0$ and all $\beta_i = 0$.

To get the x_i and y_i it is convenient first to write the K's for eq 1-3. Thus

$$K_1 = \frac{x}{(\rho S_0 - x - y - 2z)(S_0 - x - 2y)} \tag{12}$$

$$K_2 = \frac{y}{x(S_0 - x - 2y)} \tag{13}$$

$$K_L = \frac{z}{(\rho S_0 - x - y - 2z)^2} \tag{14}$$

where

$$z \equiv [L_2] \tag{15}$$

In the above expressions, and in a few equations to follow, we drop the concentration subscripts (the i's) for convenience. Numerical reduction of y and z to expressions dependent only on x is done by solving eq 13 and 14 to give

$$y = \frac{K_2 x(S_0 - x)}{1 + 2K_2 x} \tag{16}$$

$$z = \frac{1 + 4K_L(\rho S_0 - x - y) - \sqrt{1 + 8K_L(\rho S_0 - x - y)}}{8K_L} \tag{17}$$

These latter two expressions are used to provide the values for y and z in the following equation, a rearrangement of eq 12.

$$\mathfrak{F}(x) = K_1(\rho S_0 - x - y - 2z)(S_0 - x - 2y) - x \tag{18}$$

A solution for x, y, and z results when that x giving $\mathfrak{F}(x) = 0$ is found. Equation 18 is the form found to be the most amenable to the Newton-Raphson method. Details of the procedures used are given in Appendix I.

For data sets of the size typically used in our experiments (20-25 points), these procedures require less than 45 sec (on an IBM 360/65) to get a complete set of K's (K_1, K_2, and K_L) for a given substrate nucleus. Considerably less time is required when only two equilibrium constants are sought.

Equilibrium constant determinations are in general less accurate than the other types of parameters obtainable from fast-exchange data. Of the three K's studied in this work, the situation with respect to K_L is the most clear-cut and unambiguous, although the results presented below are perhaps unanticipated. K_1 and K_2 present some problems; although before discussing them in detail, it should be pointed out again that none of the difficulties in obtaining reliable K values affects the reliabilities of the bound shifts in any way. K_2 is well determined only in the ranges $5 \lesssim K_2 \lesssim 500$ for the substrate concentration ranges of our experiments. When K_2 is very small, insufficient LS_2 exists in solution to give an LIS sufficient for the determination of *either* K_2 *or* Δ_2. Fortunately, K_1 is still substantial in these cases and the LIS then obey a "quasi-one-step" equilibrium. Although Δ_2 is essentially lost in this case, we have found that Δ_1 is still very well determined.

When K_2 becomes large ($\gtrsim 500$), good fits are obtained for K_2 ranging over as much as two orders of magnitude. In these cases, K_1 is also ill-determined. However, the *ratio* of the two equilibrium constants is very well determined and this allows the obtention of accurate values of Δ_1 and Δ_2. This difficulty in measuring very high equilibrium constants is an experimental artifact arising from that fact that the titration curves exhibit very high curvature in only a very small region. This problem could be obviated by markedly decreasing S_0. Unfortunately, this is difficult to do and still obtain a good signal-to-noise ratio in the spectra; signal averaging techniques other than those available in pulsed Fourier transform methods are much too time consuming for runs consisting of 20 of more points.[21]

Chemical Shift Parameters. As shown in an earlier publication,[5] the parameters Δ_1 and Δ_2 may be obtained by solving the system of linear equations resulting from

$$\frac{\partial Q}{\partial \Delta_1} = \frac{\partial Q}{\partial \Delta_2} = 0 \tag{19}$$

Since the methods for doing so have already been given,[5] we restrict ourselves here to a discussion of techniques of assuring the optimum accuracy in these shift parameters.

Δ_1 and Δ_2 are intrinsically as accurate as the observed shifts themselves, with only a few exceptions to be discussed later. However, in any case, these parameters can only be as accurate as δ_0 (*cf.* eq 4); *great care must be exercised in obtaining this latter quantity.* Fortunately, δ_0 is often directly observable in the undoped spectrum ($\rho = 0$). Also, the linearity,[5] of δ *vs.* ρ curves at $0 \lesssim \rho \lesssim 0.4$ can be used to estimate δ_0 in many cases, and excellent extrapolation methods are available.[22,23] However, it occasionally happens that a multiplet is too overlapped or "second order" at low LSR concentrations to afford the obtention of a reliable δ_0. In such cases, a different strategy can be used. There will usually be at least one other nucleus in the molecule for which the chemical shift can be determined with high precision over the entire ρ range, including $\rho = 0$ (*e.g.*, a methyl peak), thereby affording a complete set of α_i and β_i values. One can then rewrite eq 10 as

$$Q = \sum_{i=1}^{N} (E_i - \alpha_i\Delta_1 - \beta_i\Delta_2 - \delta_0)^2 \tag{20}$$

where the E_i's are the experimentally observed *total* shifts ($\epsilon_i + \delta_0$) rather than just the LIS ($\Delta\delta_i$). Then, a solution of the equations resulting from

$$\frac{\partial Q}{\partial \Delta_1} = \frac{\partial Q}{\partial \Delta_2} = \frac{\partial Q}{\partial \delta_0} = 0 \tag{21}$$

gives the shift parameters. For good data sets, this method gives quite reliable results.[24] *It is a particularly important*

Table I. Examination of the $L + S \rightleftarrows LS$, $2L \rightleftarrows L_2$ Mechanism for Selected Substrates in Equilibrium with $Eu(fod)_3$ in CCl_4 at 31°

Compound	K_L	K_1	Δ_1 (ppm)	Q (ppm^2)	σ (ppm)[a]
1[b]	0.	96	15.41	0.74	0.21
	0.1	94	15.45	0.72	0.20$_5$
	0.25	92	15.51	0.68	0.20
	0.5	89	15.61	0.63	0.19
	1	84	15.78	0.53	0.18
	5	77	16.48	0.22	0.11
	10	86	16.63	0.23	0.12
	25	123	16.44	0.51	0.17
	50	174	16.20	0.82	0.22
	100	254	15.96	1.14	0.26
27[c]	0.	190	15.12	4.96	0.53
	0.1	187	15.14	4.91	0.52
	0.25	183	15.18	4.84	0.52
	0.5	176	15.23	4.72	0.51
	1	166	15.33	4.51	0.50
	5	137	15.85	3.34	0.43
	10	132	16.20	2.57	0.38
	25	146	16.60	1.58	0.30
	50	175	16.79	1.03	0.24
	100	224	16.89	0.65	0.19[d]

[a] The standard deviation is defined throughout as $\sigma = \sqrt{Q/(N-1)}$. [b] Fit to 19 data points for H_a with $0 \lesssim \rho \lesssim 2.5$, $S_0 = 0.15$ *M*. [c] Fit to 20 data points for H_b with $0 \lesssim \rho \lesssim 3.5$, $S_0 = 0.16$ *M*. [d] No minimum found for Q for K_L as high as 5×10^5. At that value, $\sigma = 0.11$.

Table II. Examination of the $L + S \rightleftarrows LS$, $LS + S \rightleftarrows LS_2$, $2L \rightleftarrows L_2$ Mechanism for Selected Substrates in Equilibrium with $Eu(fod)_3$ in CCl_4 at 31°

Compound	K_L	K_1	K_2	Δ_1 (ppm)	Δ_2 (ppm)	Q (ppm^2)	σ (ppm)
1[a]	0.	252	60	17.04	6.93	0.0072	0.02
	0.1	237	58	17.17	6.92	0.0073$_5$	0.02
	0.25	219	55	17.36	6.89	0.0074	0.02
	0.5	196	51	17.64	6.85	0.0075	0.02
	1	165	45	18.09	6.77	0.0075	0.02
	5	106	22	19.28	6.24	0.0080	0.02
	10	102	13	19.38	5.73	0.0089	0.02
	25	116	7	19.21	4.51	0.0107	0.02$_5$
	50	140	4	19.03	2.86	0.0122	0.03
	100	178	2	18.88	0.99	0.0135	0.03
27[b]	0.	582	72	15.70	8.47	0.0032	0.01
	0.1	549	69	15.76	8.47	0.0033	0.01
	0.25	510	65	15.84	8.47	0.0034	0.01
	0.5	458	60	15.95	8.48	0.0037	0.01
	1	386	51	16.13	8.49	0.0047	0.02
	5	232	25	16.68	8.58	0.0128	0.03
	10	206	16	16.85	8.66	0.0170	0.03
	25	208	9	16.91	8.81	0.0196	0.03
	50	235	6	16.90	8.95	0.0197	0.03
	100	286	4	16.88	9.10	0.0192	0.03

[a] Fit to 19 data points for H_a with $0 \lesssim \rho \lesssim 2.5$, $S_0 = 0.15$ *M*. [b] Fit to 20 data points for H_b with $0 \lesssim \rho \lesssim 3.5$, $S_0 = 0.16$ *M*.

result of this analytical method that the high accuracy of the bound shifts obtained does not depend on the sometimes limited precision with which the K's are determinable (*vide supra*). Further details regarding the application and solution of eq 21 are given in Appendix II.

Results and Discussion

Concerning the Possible Involvement of LSR Self-Association Equilibria. We have shown previously[5] that a two-step mechanism (LS and LS_2 formation) is capable of reproducing the observed shifts to within experimental error. Inclusion of an additional parameter such as K_L would thus seem *a priori* unnecessary. Essential tests of the types delineated by Deranleau[25] are useful here, in the sense that, if the quality of the fits cannot be improved, we can still learn something if they become worse on the inclusion of K_L or *any* additional parameter. Because of the dimeric nature of some rare earth species in the solid state[26] and also because of some recent vapor phase osmometry results,[8] we have been motivated to reexamine the possible involvement of more than one LSR species (eq 14).

In Tables I and II are given the results of the inclusion of L_2 formation and its effects upon the Q values for the fits to the one-step and two-step mechanisms. Looking first at Table I, we see the results of the addition of this extra interaction for the simple one-step (LS formation) mechanism with two different substrates taken as examples; similar results were found for all other substrates studied in this work. Values of K_L ranging from 0 to 100 were tested, and in all cases Q was a relatively large number (*cf.* Table II) and gave standard deviations far larger than experimental error. Thus, a one-step substrate complexation plus a significant LSR self-association equilibrium does not seem a viable mechanism.

Table II gives a representative selection of our results for the effects of LSR self-association on fits to the *two-step* mechanism. It is immediately seen that inclusion of a nonzero K_L increases the Q values markedly, even for quite small K_L values. When $K_L \gtrsim 50$, the range reported from osmometry results, the size of the standard deviation is consistently greater than experimental error. This effect is particularly apparent with substrate **27**, for which Q increases sixfold in going from $K_L = 0$ to $K_L = 50$. In all cases studied, the four-parameter fits were consistently superior to the five-parameter ones; thus, at least for $Eu(fod)_3$ (and possibly also for other LSR's yet to be examined in this fashion), it seems difficult to sustain a mechanism containing LSR self-association.[27]

It should be noted that the analysis presented here cannot distinguish between a completely unassociated LSR monomer and a totally associated LSR dimer. In the latter case, the associated species would then be L_2S and L_2S_2 and the reported values of K_1 and K_2 would be too large by a factor of 2 although, of course, their ratios would still be correct and the values of the bound shift parameters would be unaffected. In any event, we feel that the rigorous criterion afforded by the Q test vitiates the involvement of more than one state of aggregation of the $Eu(fod)_3$ in the substrate-binding processes. A zero self-association constant was hence employed for the LSR in all the reported fits which follow.

Equilibrium Constants (K_1 and K_2). As explained above, these parameters are more difficult to obtain and are less accurate than the bound shifts. However, one can readily obtain one or both of the K's to an accuracy of ±20%; in fact, by exercising suitable care, it is possible to have a standard deviation in K_1 and K_2 less than ±2%, in favorable cases. In any event, the equilibrium constants obtained show consistent trends with structural type and stereochemistry and provide a method of at least crudely quantifying the latter.

An indication of how well, or poorly, a given determination of K_1 or K_2 may have gone is given in Table III. Here, we compare the results of K_1 and K_2 from each of the resonances of four different substrates. It can be seen that, with only a few exceptions, the determined K_1 and K_2 values are consistent. In general the worst deviations from the average are encountered for the resonances having the smallest shifts and, hence, the largest proportional errors. In other cases, most notably the aromatic protons of **27**, the spectrum is very complex, with many resonances overlapping. In these cases, it is very difficult to get numbers sufficiently accurate for K_1 and K_2 although, interestingly

Table III. Determination of K_1 and K_2 for All Protons of Various Substrates in Equilibrium with Eu(fod)$_3$ in CCl$_4$ at 31°

Compound	2		12[a]	25		27	
H	K_1	K_2	K_1	K_1	K_2	K_1	K_2
Me$_v$			171	206	1.6		
Me$_y$	795	36	182			576	73
Me$_x$	533	19	182			435	48
Me$_z$	402	11	173			376	46
t-Bu				255	3.9		
a	478	20	166	200	1.6	438	51
e	613	24	161	= a	= a	453	51
b	498	18	171	209	1.9	582	72
f	531	20	166	= b	= b	560	70
c	516	20	172			423	52
d	492	18	168	208	2.1	469	54
p				203	2.1		
q				225	3.6		
2	510	39	189			643	70
3	[b]	[b]	145			643	70
4	[b]	[b]	138			715	82
5	[b]	[b]	145			1032	126
6	[b]	[b]	189			764	80
7	[b]	[b]				775	94
8	552	22				573	69
Averages[c]							
K_u	538 ± 100	22 ± 8	168 ± 14	215 ± 19	2.4 ± 0.9	587 ± 177	69 ± 21
K_w	536 ± 80	23 ± 8	168 ± 10	209 ± 11	2.3 ± 0.8	536 ± 106	64 ± 14
K_f	577		171	206	1.6	560	70

[a] K_2 is too small to determine for this substrate. [b] Resonances are too overlapped for determination of *K*'s. [c] *E.g.*, $K_{1,u} = \Sigma K_1/N$; $K_{1,w} = \Sigma K_1\Delta_1/\Sigma\Delta_1$; $K_{1,f}$ is the *K* from the proton with the largest Δ_1. Identical definitions follow for the K_2 averages. All summations are done over all *N* protons (or over all protons for which *K* was measurable (see text).

enough, they do not seem to affect adversely the precision of values obtained for the bound shifts.

Three different values, K_u, K_w, and K_f, are presented as representative of the equilibrium constants, at the bottom of Table III. The first of these, K_u, is just the simple average of *K* from all the separate determinations done on the molecule (u = "unweighted"). The second quantity, K_w (w = "weighted"), is an average in which the *K*'s are weighted according to the values of the bound shifts for each resonance. Finally, K_f (f = "fastest moving") is simply the *K* value found for the proton with the largest bound shift. In general, it is best to use K_w when reporting averaged shifts since its standard deviation is less, as might be expected. This is especially important since, from our experience, *K* values generally become much less reliable whenever $\Delta_1 \lesssim 6$ ppm (for ±0.01 ppm standard deviation in the shifts). It is sufficient for most purposes, however, to use the more economically obtained single K_f value since, in general, all three *K* averages fall within less than one standard deviation of K_w of each other.

In Table IV are presented the *K* values for all 28 substrates studied. The more useful general trends are in the K_1 values and are immediately apparent. First, there is an obvious, and perhaps not unexpected, trend related to the degree of substitution on the carbon bound to the oxygen: K_1 (tertiary alcohols) < K_1 (ketones) < K_1 (secondary alcohols). In addition, for alcohols, the stereochemical disposition of the hydroxyl group (axial or equatorial) has a marked effect, *viz.*, K_1 (axial alcohols) < K_1 (equatorial alcohols). The order of presentation of the substrates in Scheme I, as well as in Tables IV-VII, is based on these trends.

The ordering of the *K* values according to compound types is unexceptional and, in the case of the tertiary alcohols, particularly gratifying. These very weak binders, in fact, present a special case in which K_2 cannot be determined. The apparent difficulty (from steric hindrance) in forming the LS$_2$ complex was discussed earlier and leads to fits which follow a "quasi-one-step" equilibrium.

Bound Shifts (Δ_1 and Δ_2). It is these parameters which, we feel, should be used in the direct *quantitative* correlations of LIS with molecular structure. Fortunately, Δ_1 is the

Table IV. K_1 and K_2 (M^{-1}) for Various Substrates Interacting with Eu(fod)$_3$ in CCl$_4$ at 31°[a]

Compound	K_1	K_2	Compound	K_1	K_2
1	260 ± 11	60 ± 4	15	149	<0.5
2	536 ± 80	23 ± 8	16	63	<0.1
3	254 ± 12	10 ± 2	17	196	<0.1
4	546 ± 120	35 ± 8	18	77	<0.5
5	3,103 ± 433	75 ± 10	19	123	4
6[b]	2,500	500	20	86	10
7	10,061 ± 3365	1,201 ± 401	21	83	8
8[c]	117,000	9,000	22	56	6
9[c]	140,000	15,400	23	65	<0.2
10[d]	16,311	1,279	24	38	<0.1
11[e]	5,345	1,024	25	209 ± 11	2.3 ± 0.8
12	168 ± 10	<0.1	26	207 ± 40	19 ± 5
13	233	<0.5	27	536 ± 106	64 ± 14
14	172	<4.5	28	614	31

[a] Values of K_1 and K_2 were determined from the proton with the largest Δ_1 unless otherwise indicated by a footnote or the presence of error estimates. In these cases, the *K*'s reported are K_w values. [b] From Me$_z$. [c] K_2 was very ill-determined here; see text. [d] From Me$_y$. [e] From H$_m$.

Table V. Methyl Group LIS Parameters for Cyclohexanones and Cyclohexanols in Eu(fod)$_3$–CCl$_4$ at 31°[a]

Compound	Parameter	Me$_v$	Me$_w$	Me$_y$	Me$_x$	Me$_z$	*t*-Bu
1	δ_0			0.36	1.31	1.01	
	λ			5.78	3.74	3.47	
	Δ_1			6.32	4.30	4.01	
	Δ_2			2.87	1.83	1.69	
2	δ_0			0.14	1.72	0.99	
	λ			6.07	4.18	3.73	
	Δ_1			5.95	4.26	3.80	
	Δ_2			3.28	2.18	1.94	
3	δ_0			0.32	1.38	1.00	
	λ			6.12	4.02	3.66	
	Δ_1			6.35	4.49	4.15	
	Δ_2			3.14	1.81	1.56	
4	δ_0			1.16		1.11	
	λ			6.02		3.38	
	Δ_1			6.26		3.48	
	Δ_2			3.07		1.73	
5	δ_0						0.91
	λ						2.45
	Δ_1						2.08
	Δ_2						1.30
6	δ_0			1.36		0.94	
	λ			8.29		3.46	
	Δ_1			7.76		3.49	
	Δ_2			4.16		1.71	
7	δ_0						0.86
	λ						3.78
	Δ_1						2.39
	Δ_2						1.89
8	δ_0			0.04	1.64	0.87	
	λ			4.49	3.84	3.56	
	Δ_1			4.02	3.15	2.82	
	Δ_2			2.17	1.91	1.76	
9	δ_0		1.72	0.94		1.23	
	λ		3.43	3.61		3.18	
	Δ_1		3.56	3.66		2.75	
	Δ_2		1.72	1.82		1.61	
10	δ_0			1.14		0.97	
	λ			3.54		3.80	
	Δ_1			3.28		2.88	
	Δ_2			1.79		1.95	
11	δ_0						0.84
	λ						2.19
	Δ_1						1.86
	Δ_2						1.10
12	δ_0	1.18		0.66	1.08	0.90	
	λ	16.68		6.56	3.61	3.99	
	Δ_1	18.84		7.05	3.99	4.55	
	Δ_2						
13	δ_0	1.16		0.67	1.16	0.87	
	λ	10.10		5.74	4.67	3.42	
	Δ_1	10.68		6.03	5.11	3.69	
	Δ_2						
14	δ_0	1.18		0.70	1.08	0.90	
	λ	15.40		5.70	3.65	3.55	
	Δ_1	19.15		7.04	4.38	4.50	
	Δ_2	1.88		0.95	0.84	0.26	
15	δ_0	1.16		0.67	1.04	0.88	
	λ	14.91		5.79	3.20	3.53	
	Δ_1	19.73		7.14	4.03	4.64	
	Δ_2						
16	δ_0	1.24		0.49	1.60	0.90	
	λ	16.29		5.79	3.47	3.84	
	Δ_1	20.57		6.92	4.09	4.75	
	Δ_2						
17	δ_0	1.22		0.65	1.14	0.92	
	λ	16.66		6.55	3.96	3.94	
	Δ_1	18.78		7.02	4.30	4.45	
	Δ_2						
18	δ_0	1.25	1.51	1.29		0.90	
	λ	11.81	4.03	4.13		3.73	
	Δ_1	15.36	5.64	5.73		5.11	
	Δ_2						
19	δ_0	1.17	1.54	1.24		0.88	
	λ	15.18	5.95	6.14		4.73	
	Δ_1	15.42	6.38	6.65		4.90	
	Δ_2	5.55	1.75	1.70		1.53	

Table V (*Continued*)

20	δ_0	1.22	1.48	1.28		0.89	
	λ	12.45	4.38	4.43		4.02	
	Δ_1	16.29	5.93	5.94		5.37	
	Δ_2	4.55	1.45	1.51		1.38	
21	δ_0	1.19	1.44	1.25		0.88	
	λ	13.19	4.40	4.48		4.22	
	Δ_1	15.98	5.61	5.67		5.34	
	Δ_2	5.19	1.57	1.63		1.41	
22	δ_0	1.25	1.93	1.41		0.93	
	λ	13.29	6.60	6.61		4.12	
	Δ_1	15.55	7.71	7.92		4.89	
	Δ_2	6.99	3.39	3.30		2.08	
23	δ_0	1.25	1.59	1.32		0.98	
	λ	12.75	4.55	4.57		4.11	
	Δ_1	15.14	5.52	5.58		5.00	
	Δ_2						
24	δ_0	1.18		1.31		0.92	
	λ	12.63		6.92		3.49	
	Δ_1	16.09		8.67		4.40	
	Δ_2						
25	δ_0	1.09					0.86
	λ	17.62					2.08
	Δ_1	18.43					1.87
	Δ_2	9.57					2.01
		Me_u					
26	δ_0	1.48		1.00		1.21	
	λ	14.15		2.92		4.80	
	Δ_1	15.62		2.97		5.25	
	Δ_2	7.00		1.54		2.38	
27	δ_0			−0.41	1.68	0.88	
	λ			5.00	3.30	2.59	
	Δ_1			4.92	3.43	2.69	
	Δ_2			2.59	1.64	1.25	
28	δ_0	1.09					0.85
	λ	15.44					2.40
	Δ_1	15.23					2.36
	Δ_2	7.99					1.24

[a] All parameters are given in ppm; symbols are as defined in the text.

more easily determined with high accuracy; since it is a function of the fewest molecular degrees of freedom of any LIS parameter, it is this parameter upon which we expect to predicate future structural calculations. In general, the values reported in this section for Δ_1 are good to ±0.02 ppm at worst and in most cases they are better than this. Since nearly all bound shifts are greater than 1-2 ppm, the percentage standard deviations of the bound shifts are usually better than ±0.5% and often less than ±0.1%. The errors in Δ_2 are somewhat larger, although less than ±1%, when Δ_2 is accessible. However, when this latter parameter becomes small ($\lesssim 1$ ppm), the percentage standard deviation can become large; fortunately, this is only a serious problem for small K_2 values ($\lesssim 5$).

The results for the undoped shift values and the bound shift parameters obtained in this work for all 28 substrates investigated are given in Tables V-VII. These three tables list the shift parameters for the methyl protons, the cyclohexyl ring protons, and the aromatic substituent protons, respectively. For each resonance, the values δ_0, Δ_1, and Δ_2 are given along with an additional parameter, λ. This latter quantity is simply the value of the slope for a δ *vs.* ρ plot (at constant $S_0 \simeq 0.15\ M$) taken in the range $0 \lesssim \rho \lesssim 0.4$. That is

$$\lambda_i = \frac{\partial \delta_i}{\partial \rho} = \frac{\partial(\Delta\delta)_i}{\partial \rho} \simeq 2\Delta_2 \qquad (22)$$

The approximate equality at the right of the above expression was derived earlier[5] and holds only when K_2 is large.

In discussing the tables, we turn our attention first to the δ_0 values. In all cases these were obtained by direct observation or by simple extrapolation; it was unnecessary to resort to the more sophisticated techniques outlined by eq 20 and 21 and in Appendix II. (Checks of that technique, however, showed agreement between the calculated and observed shifts within 0.01 ppm.) When deemed necessary, assignments were confirmed by spin decoupling.

Next, we briefly examine the bound shifts and slopes. In general the Δ_1 and Δ_2 values (when the latter are measurable) behave in much the same way as did the initial slopes reported in our earlier work[5,16] (or as the λ values in this paper). For instance, the bound shift values of Me_x and Me_z are nearly equal in all substrates where this pairing possibility exists. Also, the H_a-H_e and H_b-H_f pairs exhibit parallel behavior although substituent effects, especially from aromatic moieties in the C-3 position, are more apparent with these. The magnitudes of the bound shifts show the same general correlation with distance as do the initial slopes albeit there are detailed differences. All *reported* values of Δ_1 and Δ_2 are accurate to ±0.01 ppm, as mentioned earlier; if a bound shift could not be determined either because of small size or because of severe overlapping of resonances, it is omitted. The slopes, obtained by linear regression also showed a similar uncertainty. In all reported cases, however, they exhibited a correlation coefficient $\gtrsim 0.995$.

No attempt was made in this work to carry out a rigorous structural calculation from the bound shifts; applications of these parameters to the testing of various forms of the pseudo-contact equation and to the assessment of the relative amounts of contact and pseudo-contact shift contributions in a given LIS will be left to the future. Rather, the emphasis of the ensuing discussion will rest on the implications of the simultaneous presence of two different complexes, LS and LS_2, in solution. For substantial K_2 values

Table VI. Cyclohexyl Ring Proton LIS Parameters for Cyclohexanones and Cyclohexanols in Eu(fod)$_3$-CCl$_4$ at 31°[a]

Compound	Parameter	a	e	b	f	c	d	p	q	k
1	δ_0	2.91	2.02	2.27	2.11	2.18	1.86			
	λ	14.37	14.35	12.05	12.42	4.74	5.14			
	Δ_1	16.96	16.39	14.14	14.41	5.39	6.01			
	Δ_2	6.93	7.02	5.84	6.06	2.33	2.52			
2	δ_0	3.10	2.04	2.35	2.09	3.04	2.00			
	λ	16.26	16.54	13.62	14.45	5.13	5.86			
	Δ_1	16.77	16.35	14.10	14.69	5.20	6.02			
	Δ_2	8.37	8.78	7.06	7.57	2.69	3.03			
3	δ_0	3.11	1.99	2.29	2.05	2.32	1.88			
	λ	15.19	14.36	12.74	12.79	5.04	5.38			
	Δ_1	17.66	16.10	14.70	14.65	5.56	6.18			
	Δ_2	6.19	6.50	5.48	5.58	2.35	2.34			
4	δ_0	2.65	2.16	2.46	2.21	1.97	1.79	3.93		
	λ	18.21	16.17	14.16	13.28	4.62	5.85	8.67		
	Δ_1	15.76	16.99	13.73	13.93	4.76	6.00	8.71		
	Δ_2	10.06	8.22	7.46	6.72	2.35	3.02	4.58		
5	δ_0	2.31	2.31	2.18	2.18		1.51	1.35	2.02	
	λ	19.89	19.89	17.14	17.14		6.65	8.78	5.82	
	Δ_1	15.96	15.96	14.42	14.42		5.81	7.60	4.92	
	Δ_2	10.78	10.78	9.12	9.12		3.50	4.61	3.10	
6	δ_0	2.07	1.79	1.62	1.34	1.68	1.38	4.04		4.27
	λ	14.58	12.47	6.93	5.42	5.50	5.50	13.23		20.26
	Δ_1	13.64	13.09	7.05	6.42	5.27	5.50	12.20		22.32
	Δ_2	7.30	6.00	3.35	2.65	2.85	2.74	6.66		9.83
7	δ_0	1.75	1.75	1.41	1.41		0.94	1.38	1.44	3.87
	λ	17.98	17.98	8.54	8.54		7.97	16.89	9.00	27.54
	Δ_1	13.35	13.35	6.74	6.74		5.71	11.47	6.12	22.61
	Δ_2	9.01	9.01	4.23	4.23		4.01	8.50	4.42	13.75
										m
8	δ_0	2.85	1.64	1.34	1.12	3.08	1.44			4.24
	λ	17.58	16.71	18.01	17.79	4.46	6.88			26.16
	Δ_1	15.76	13.87	15.97	15.57	3.76	5.78			21.13
	Δ_2	8.71	8.45	9.02	9.12	2.28	3.34			12.79
9	δ_0	2.32	1.83	1.81	1.15	2.38	1.44			4.20
	λ	16.62	15.65	17.64	17.28	4.22	6.28			22.73
	Δ_1	14.38	13.66	15.21	14.80	3.66	5.44			22.10
	Δ_2	8.48	7.92	8.91	8.75	2.05	3.21			11.33
10	δ_0	2.20	1.80	1.20	1.20	1.58	1.16	3.55		3.94
	λ	*b*	*b*	19.06	19.06	4.38	7.08	6.72		24.54
	Δ_1	13.33	*b*	11.87	*b*	3.45	5.36	5.59		21.22
	Δ_2	9.11	*b*	9.02	*b*	2.24	3.66	3.37		12.29
11	δ_0	1.96	1.96	1.65	1.65		1.13	1.74	0.98	3.36
	λ	15.64	15.64	18.42	18.42		5.98	5.03	6.54	24.66
	Δ_1	13.71	13.71	13.93	13.93		5.34	4.29	5.53	22.61
	Δ_2	8.06	8.06	8.64	8.64		2.97	2.56	3.25	12.37
12	δ_0	2.67	1.43	1.20	1.29	2.40	1.22			
	λ	14.43	15.82	9.25	9.10	5.18	6.37			
	Δ_1	16.54	18.41	10.28	10.46	5.78	7.15			
	Δ_2									
13	δ_0	2.90	1.43	1.17	1.19	2.90	1.03			
	λ	15.81	13.07	8.44	7.07	5.91	6.18			
	Δ_1	17.53	14.09	9.17	7.52	6.40	6.71			
	Δ_2									
14	δ_0	2.65	1.40	1.29	1.19	2.40	1.22			
	λ	13.98	14.90	8.52	8.71	4.92	5.92			
	Δ_1	17.19	18.79	10.56	10.81	6.03	7.38			
	Δ_2	2.00	1.60	1.16	1.20	0.76	0.79			
15	δ_0	2.62	1.42	1.28	1.19	2.34	1.20			
	λ	12.86	14.23	7.99	8.07	4.66	5.57			
	Δ_1	16.82	18.94	10.46	10.53	5.85	7.26			
	Δ_2									
16	δ_0	2.94	1.44	1.49	1.35	3.08	1.43			
	λ	13.45	15.85	9.17	9.26	5.14	5.94			
	Δ_1	16.32	19.84	11.00	11.25	6.17	7.25			
	Δ_2									
17	δ_0	2.82	1.44	1.37	1.24	2.52	1.30			
	λ	15.36	16.29	9.32	9.58	5.30	6.54			
	Δ_1	17.22	18.66	10.44	10.71	5.90	7.25			
	Δ_2									
18	δ_0	1.95	1.54	1.72	1.21	1.78	1.57			
	λ	14.79	14.96	12.01	11.30	4.85	4.81			
	Δ_1	20.37	20.11	16.00	14.87	6.63	6.39			
	Δ_2									
19	δ_0	2.05	1.50	1.80	1.20	1.89	1.67			
	λ	18.27	19.93	14.46	14.10	6.39	6.73			

Table VI (*Continued*)

	Δ_1	19.29	20.89	14.64	14.57	6.57	7.05		
	Δ_2	5.38	6.06	5.41	4.59	2.08	2.02		
20	δ_0	1.88	1.51	1.68	1.20	1.78	1.52		
	λ	15.62	15.90	12.68	11.97	5.10	5.15		
	Δ_1	21.39	21.38	16.78	15.78	6.97	6.76		
	Δ_2	5.30	5.60	4.58	4.39	1.71	1.89		
21	δ_0	1.89	1.55	1.66	1.21	1.74	1.52		
	λ	16.71	16.77	13.67	12.92	5.40	5.36		
	Δ_1	20.98	20.66	16.81	15.52	6.83	6.53		
	Δ_2	5.60	5.98	5.03	4.94	1.81	2.08		
22	δ_0	2.24	1.58	1.91	1.34	2.17	1.80		
	λ	16.74	17.26	11.62	11.08	6.27	6.28		
	Δ_1	19.82	20.36	13.57	13.09	7.45	7.34		
	Δ_2	8.36	8.69	5.91	5.64	3.08	3.21		
23	δ_0	2.03	1.50	1.85	1.22	1.91	1.64		
	λ	16.49	16.37	13.17	12.25	5.27	5.31		
	Δ_1	20.11	19.63	15.87	14.57	6.44	6.29		
	Δ_2								
24	δ_0	1.97	1.54	1.54	1.27	1.56	1.37		4.00
	λ	15.93	14.73	8.90	8.38	6.09	6.29		13.49
	Δ_1	19.69	18.21	10.88	10.30	6.61	7.85		16.73
	Δ_2								
25	δ_0	1.62	1.62	1.27	1.27		0.86	1.22	1.49
	λ	16.15	16.15	9.07	9.07		6.96	12.92	6.52
	Δ_1	17.50	17.50	10.06	10.06		7.14	12.48	6.69
	Δ_2	6.95	6.95	3.24	3.24		4.26	10.55	4.01
26	δ_0	2.02	1.92	1.60	1.35	1.75	1.35	3.57	3.57
	λ	16.21	15.03	18.65	19.31	4.08	5.99	7.67	7.67
	Δ_1	17.10	17.43	19.68	21.34	4.41	6.27	8.45	8.45
	Δ_2	8.24	7.47	9.16	9.69	2.01	3.01	3.91	3.91
27	δ_0	1.60	1.49	2.16	1.46	1.57	1.51		
	λ	12.16	17.74	16.53	17.90	4.59	4.88		
	Δ_1	13.44	18.75	15.68	19.20	4.54	5.24		
	Δ_2	5.71	8.69	8.50	8.66	2.32	2.37		
28	δ_0	1.61	1.61	1.30	1.30		1.02	1.68	1.02
	λ	17.69	17.69	19.97	19.97		6.07	5.44	8.13
	Δ_1	17.36	17.36	19.77	19.77		6.22	5.53	7.98
	Δ_2	9.15	9.15	10.20	10.20		3.12	2.76	4.29

[a] All parameters are given in ppm; symbols are as defined in the text. [b] Obscured by overlapping resonances; parameter is not determinable.

($\gtrsim 5$), nearly all the LSR is present as LS_2 at low ρ values ($\lesssim 0.5$). At intermediate concentrations ($0.5 \lesssim \rho \lesssim 1.5$), both LS and LS_2 are present in significant and comparable amounts. Finally, when high LSR concentrations are obtained, nearly all the substrate is present as LS. Thus, if one wishes to do a structural determination from, say, just a single spectrum (assuming, of course, that ones δ_0 values were well-determined separately), it would be best to do this for a large ρ value ($\rho > 2$). Obviously, these are not the conditions usually employed in gathering data for structural fits when approximate methods (as opposed to performing complete nonlinear regressions) are used. Rather, the slopes obtained in the "low ρ region" or single-spectrum values at *low* LSR concentrations are employed. Hence, in many structural assessments, attempts are, in fact, made to fit the simple C_{3v} symmetry pseudo-contact equation to a species, LS_2, which cannot possibly conform to this symmetry assumption.

The data of Table VIII allow additional insights into some of the above points. In this table, we list Δ_1, $2\Delta_2$, and λ for some resonances of selected substrates. (Δ_2 is doubled to facilitate comparison with Δ_1). Also given are the values of three ratios: Δ_1/λ, $2\Delta_2/\lambda$, and Δ_1/Δ_2. The first two ratios provide comparisons between the slope and bound shifts whereas the third ratio demonstrates the correlation, or lack of it, between the bound shifts themselves. Proceeding from the assumption that Δ_1 should serve as the simplest quantity with which to quantitatively assess substrate structure, we examine the implications of the ratios. With substrates **1** and **27**, K_2 is sizable and LS_2 formation is very important in the low ρ region. This is borne out by the quantities given in the table since the approximation of eq 22 ($\lambda \simeq 2\Delta_2$) is very nearly exact; the per cent standard deviations of the ratios for all substrates examined are smaller for $2\Delta_2/\lambda$ than for the other ratios. In the case of substrate **24**, K_2 is very small (and possibly also Δ_2) and LS_2 is not present to any great extent compared to LS. This conclusion is in agreement with the small per cent standard deviation noted for the Δ_1/λ ratio. However, it should be noted that there is *some* LS_2 present; otherwise, the ratio values would be close to one.[22] In all cases, the Δ_1/Δ_2 per cent standard deviations are considerably larger than for either of the other ratios. (This underscores our previous statements regarding the potentially serious inherent limitations involved in the use of initial LIS slopes for quantitative molecular structure evaluations.) This should be expected since the intensive parameters for two different species should show the greatest disparity.

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Appendix I

We give here the expressions used in solving eq 15 for the interaction mechanism encompassed by eq 1-3. In the well-known Newton–Raphson method, the root of a polynomial, $\mathcal{F}(x)$, is found iteratively by

$$x_{k+1} = x_k - \mathcal{F}(x_k)/\mathcal{F}'(x_k) \qquad \text{(I-1)}$$

where x_k and x_{k+1} are the results of the k and $(k + 1)$ iterations, respectively, and the prime denotes single differen-

Table VII. Aromatic Proton LIS Parameters for Cyclohexanones and Cyclohexanols in Eu(fod)$_3$–CCl$_4$ at 31°^{a}

Compound	Parameter	1	2	3	4	5	6	7	8
1	δ_0		7.26	7.21		7.21	7.26		
	λ		6.84	1.24		1.24	6.84		
	Δ_1		7.52	1.08		1.08	7.52		
	Δ_2		3.41	0.66		0.66	3.41		
2	δ_0		7.46	*c*	*c*	*c*	*c*	*c*	8.35
	λ		13.68	*c*	*c*	*c*	*c*	*c*	3.13
	Δ_1		13.64	*c*	*c*	*c*	*c*	*c*	3.14
	Δ_2		7.15	*c*	*c*	*c*	*c*	*c*	1.66
3	δ_0	7.70		7.42	7.68	7.66	7.28	7.39	7.91
	λ	10.16		4.99	1.57	0.75	0.45	−0.60	−0.86
	Δ_1	10.81		5.29	1.48	0.55	0.02	−0.88	−1.63
	Δ_2	4.99		2.48	0.91	0.55	0.44	−0.09	+0.30
4	δ_0		7.31	*c*	*c*	*c*	*c*	*c*	7.96
	λ		3.29	*c*	*c*	*c*	*c*	*c*	3.17
	Δ_1		3.30	*c*	*c*	*c*	*c*	*c*	3.05
	Δ_2		1.73	*c*	*c*	*c*	*c*	*c*	1.66
6	δ_0		7.28	*c*	*c*	*c*	*c*	*c*	8.10
	λ		2.76	*c*	*c*	*c*	*c*	*c*	4.94
	Δ_1		3.08	*c*	*c*	*c*	*c*	*c*	*d*
	Δ_2		1.53	*c*	*c*	*c*	*c*	*c*	*d*
8	δ_0		7.51	*c*	*c*	*c*	*c*	*c*	8.42
	λ		7.78	*c*	*c*	*c*	*c*	*c*	2.74
	Δ_1		6.78	*c*	*c*	*c*	*c*	*c*	2.36
	Δ_2		3.90	*c*	*c*	*c*	*c*	*c*	1.36
9	δ_0		7.40	*c*	*c*	*c*	*c*	*c*	8.37
	λ		4.54	*c*	*c*	*c*	*c*	*c*	3.05
	Δ_1		3.42	*c*	*c*	*c*	*c*	*c*	2.63
	Δ_2		2.31	*c*	*c*	*c*	*c*	*c*	1.50
10	δ_0		*c*	*c*	*c*	*c*	*c*	*c*	7.93
	λ		*c*	*c*	*c*	*c*	*c*	*c*	2.21
	Δ_1		*c*	*c*	*c*	*c*	*c*	*c*	1.99
	Δ_2		*c*	*c*	*c*	*c*	*c*	*c*	1.11
12	δ_0		7.50	7.22	7.09	7.22	7.50		
	λ		3.99	−3.65	−2.57	−3.65	3.99		
	Δ_1		4.08	−4.72	−3.09	−4.72	4.08		
	Δ_2								
13	δ_0		7.59	6.80	7.07	6.78	3.84^b		
	λ		5.75	−3.47	−1.15	0.76	1.40^b		
	Δ_1		5.95	−4.13	−1.48	0.57	1.50^b		
	Δ_2								
14	δ_0		7.09	7.19	6.63	3.79^b	7.16		
	λ		4.14	−3.95	−1.26	-1.54^b	5.31		
	Δ_1		4.74	−5.65	−2.29	-2.24^b	5.77		
	Δ_2		1.11	+0.51	+0.64	$+0.12^b$	1.97		
15	δ_0		7.35	6.70	3.71^b	6.70	7.35		
	λ		3.50	−3.10	-1.71^b	−3.10	3.50		
	Δ_1		3.87	−4.68	-2.38^b	−4.68	3.87		
	Δ_2								
16	δ_0		7.88	7.27	7.56	7.72	*c*	*c*	8.44
	λ		6.69	−7.67	−1.98	−0.45	*c*	*c*	2.74
	Δ_1		7.82	−10.82	−3.02	−0.86	*c*	*c*	3.12
	Δ_2								
17	δ_0	7.93		7.58	7.67	7.66	7.34	7.33	7.77
	λ	6.27		3.88	−2.24	−1.65	−1.61	−2.54	−6.48
	Δ_1	6.73		4.02	−2.80	−2.10	−1.96	−3.13	−7.86
	Δ_2								
18	δ_0		7.32	7.21	7.05	7.21	7.32		
	λ		3.33	1.31	1.11	1.31	3.33		
	Δ_1		4.25	1.74	1.42	1.74	4.25		
	Δ_2								
19	δ_0		7.18	7.05	*c*	*c*	3.82^b		
	λ		4.83	1.69	*c*	*c*	1.72^b		
	Δ_1		4.94	*d*	*c*	*c*	1.68^b		
	Δ_2		1.67	*d*	*c*	*c*	0.73^b		
20	δ_0		6.86	7.11	6.57	3.73^b	6.83		
	λ		3.69	1.43	1.33	0.97^b	3.76		
	Δ_1		4.80	1.97	1.96	1.69^b	5.17		
	Δ_2		1.26	0.46	0.33	0.07^b	1.11		
21	δ_0		7.20	6.72	3.72^b	6.72	7.20		
	λ		3.82	1.72	1.02^b	1.72	3.82		
	Δ_1		4.72	2.67	1.99^b	2.67	4.72		
	Δ_2		1.36	−0.06	-0.48^b	−0.06	1.36		
22	δ_0		7.39	*c*	*c*	*c*	*c*	*c*	8.38
	λ		4.45	*c*	*c*	*c*	*c*	*c*	3.71
	Δ_1		5.16	*c*	*c*	*c*	*c*	*c*	4.29

Table VII (*Continued*)

	Δ_2		2.34	*c*	*c*	*c*	*c*	*c*	1.96
23	δ_0	7.63		7.48	7.67	7.70	7.34	7.34	7.65
	λ	3.93		3.40	1.39	0.77	0.59	0.59	1.30
	Δ_1	4.70		4.08	1.66	0.98	0.70	0.70	1.41
	Δ_2								
24	δ_0		7.27	7.27	7.61	7.79	7.38	7.49	8.11
	λ		3.76	1.58	0.66	0.05	−0.46	−1.94	2.49
	Δ_1		4.55	1.65	0.79	0.06	−0.78	−2.87	2.55
	Δ_2								
26	δ_0		*c*	*c*	*c*	*c*	*c*	*c*	7.95
	λ		*c*	*c*	*c*	*c*	*c*	*c*	3.71
	Δ_1		*c*	*c*	*c*	*c*	*c*	*c*	4.03
	Δ_2		*c*	*c*	*c*	*c*	*c*	*c*	1.83
27	δ_0			7.20	7.58	7.72	7.27	7.35	7.99
	λ			13.26	2.83	1.73	1.46	1.70	3.23
	Δ_1			11.50	2.31	1.43	1.22	1.50	3.06
	Δ_2			7.26	1.58	0.95	0.80	0.91	1.68

[a] All parameters are given in ppm; symbols are as defined in the text. [b] This is an aryl methoxyl group. [c] Undetermined because of resonance overlaps. [d] Insufficient resolved points for statistical analysis.

Table VIII. A Comparison of Initial Slopes and Bound Shifts for Selected Substrates

Compound	Resonance	Δ_1	$2\Delta_2$	λ	Δ_1/λ	$2\Delta_2/\lambda$	Δ_1/Δ_2
1	Me_y	6.32	5.74	5.78	1.09	0.99	2.20
	Me_x	4.30	3.66	3.74	1.15	0.98	2.35
	Me_z	4.01	3.38	3.47	1.16	0.97	2.37
	a	16.96	13.86	14.37	1.18	0.96	2.45
	e	16.39	14.04	14.35	1.14	0.98	2.33
	b	14.14	11.68	12.05	1.17	0.97	2.42
	f	14.41	12.12	12.42	1.16	0.98	2.38
	c	5.39	4.66	4.74	1.14	0.98	2.31
	d	6.01	5.04	5.14	1.17	0.98	2.38
				Av	1.15 ± 0.03 (±2.3%)	0.98 ± 0.01 (±0.8%)	2.35 ± 0.07 (±3.1%)
24	Me_v	16.09		12.63	1.27		
	Me_y	8.67		6.92	1.25		
	Me_z	4.40		3.49	1.26		
	a	19.69		15.93	1.24		
	e	18.21		14.73	1.24		
	b	10.88		8.90	1.22		
	f	10.30		8.38	1.23		
	c	6.61		6.09	1.09[a]		
	d	7.85		6.29	1.25		
	q	16.73		13.49	1.25		
				Av	1.24 ± 0.02 (±1.3%)		
27	Me_y	4.92	5.18	5.00	0.98	1.04	1.90
	Me_x	3.43	3.28	3.30	1.04	0.99	2.09
	Me_z	2.69	2.50	2.59	1.04	0.96	2.15
	a	13.44	11.42	12.16	1.10	0.94	2.35
	e	18.75	17.38	17.74	1.06	0.98	2.16
	b	15.68	17.00	16.53	0.95	1.03	1.84
	f	19.20	17.32	17.90	1.07	0.97	2.22
	c	4.54	4.64	4.59	0.99	1.01	1.96
	d	5.24	4.74	4.88	1.07	0.97	2.21
				Av	1.03 ± 0.05 (±4.8%)	0.99 ± 0.03 (±3.4%)	2.10 ± 0.17 (±8.0%)

[a] Deleted from average.

tiation with respect to x_k. This procedure converges quite rapidly to any desired precision and renders practical the handling of quite complicated equilibria.

The remaining expressions needed for the solution of eq 18 are now given. Differentiation of this equation gives

$$\mathfrak{F}'(x) = -K_1[(\rho S_0 - x - y - 2z)(1 + 2y') + (S_0 - x - 2y)(1 + y' + 2z')] - 1 \qquad \text{(I-2)}$$

Evaluation of this requires two additional derivatives

$$y' = \frac{K_2[S_0 - 2x(1 + K_2x)]}{(1 + 2K_2x)^2} \qquad \text{(I-3)}$$

and

$$z' = -\frac{1}{2}(1 + y')\left[1 - \frac{1}{\sqrt{1 + 8K_L(\rho S_0 - x - y)}}\right] \qquad \text{(I-4)}$$

When $K_2 = 0$, the above equations reduce to the appropriate expressions for equilibria involving LS and L_2 formation only; the simplification is accomplished by setting $y = y' = 0$. Usually, this method proceeds most efficiently by arranging the data so that ρ is monotonically increasing; one proceeds by setting $x = 0$ as the initial guess for the first point and then using the final solution for each successive point as the initial guess for the next. Additional documentation on computational techniques and precautions is available elsewhere.[20]

Appendix II

Solutions for the best bound shifts for a given set of α_i's and β_i's are given in an earlier paper for the case δ_0 = constant.[5] If δ_0 is unknown, it may be taken to be an additional parameter in which case the best δ_0, Δ_1, and Δ_2 can be found by solving the system of equations resulting from eq 20 and 21. In this case, the results are (for LS and LS_2 both present)

$$\delta_0 = [S_E(S_{\alpha\alpha}S_{\beta\beta} - S_{\alpha\beta}^2) + S_\alpha(S_{\alpha\beta}S_{E\beta} - S_{\beta\beta}S_{E\alpha}) + S_\beta(S_{\alpha\beta}S_{E\alpha} - S_{\alpha\alpha}S_{E\beta})]/D \quad \text{(II-1)}$$

$$\Delta_1 = [NS_{E\alpha}S_{\beta\beta} + S_\beta S_E S_{\alpha\beta} + S_\alpha S_\beta S_{E\beta} - S_\alpha S_E S_{\beta\beta} - S_\beta^2 S_{E\alpha} - NS_{\alpha\beta}S_{E\beta}]/D \quad \text{(II-2)}$$

$$\Delta_2 = [N(S_{\alpha\alpha}S_{E\beta} - S_{\alpha\beta}S_{E\alpha}) + S_{E\alpha}S_\alpha S_\beta + S_\alpha S_E S_{\alpha\beta} - S_\alpha^2 S_{E\beta} - S_{\alpha\alpha}S_\beta S_E]/D \quad \text{(II-3)}$$

where

$$D = N(S_{\alpha\alpha}S_{\beta\beta} - S_{\alpha\beta}^2) + 2S_{\alpha\beta}S_\alpha S_\beta - S_\alpha^2 S_{\beta\beta} - S_\beta^2 S_{\alpha\alpha} \quad \text{(II-4)}$$

Here, N is the number of data points, and the S represents various summations, *e.g.*

$$S_{\alpha\alpha} = \sum_{i=1}^{N} \alpha_i^2, \quad S_{\alpha\beta} = \sum_{i=1}^{N} \alpha_i\beta_i, \quad S_\alpha = \sum_{i=1}^{N} \alpha_i, \text{ etc.} \quad \text{(II-5)}$$

When only LS is present, the resulting simpler solutions are

$$\delta_0 = [S_E S_{\alpha\alpha} - S_\alpha S_{\alpha E}]/D \quad \text{(II-6)}$$

$$\Delta_1 = [NS_{\alpha E} - S_\alpha S_E]/D \quad \text{(II-7)}$$

where

$$D = NS_{\alpha\alpha} - S_\alpha^2 \quad \text{(II-8)}$$

References and Notes

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(4) Undergraduate Scholar of The Robert A. Welch Foundation.
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(18) The details of the synthesis and characterization of these compounds will be published elsewhere.
(19) In an earlier publication (ref 5), curves of pronounced nonmonotonicity were reported for the substrates cyclopentanone and tetrahydrofuran interacting with $Eu(fod)_3$ in CCl_4. It has since been discovered that this was caused by the presence of an impurity in the LSR, probably uncomplexed β-diketonate (fod) ligand. Repeat experiments with LSR of much higher purity gave curves which were strictly monotonic and strictly adherent to the two-step mechanism model. The results reported in ref 5 for substrate 1 still stand, however; the LSR used in that case was from a different source and pure. In the present study, the high quality $Eu(fod)_3$ employed was obtained from Merck Sharpe and Dohme, Canada, Ltd.
(20) All fits were done by the program LISA2 (Lanthanide Induced Shift Analysis, version 2) on an IBM 360/65 digital computer. This program is available from the authors.
(21) In principle, it should be possible to extend the lower region of obtainable K_2's by increasing S_0. Unfortunately, solubility problems tend to preclude this. Also, the possibility of unwanted substrate–substrate and, possibly, LSR–LSR interactions is also increased.
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(24) For example, tests of this procedure were done by eliminating points for $\rho < 0.5$ for methyl data sets. The δ_0's obtained were always within 0.01 ppm of the directly measured value. The computation time required to get δ_0, Δ_1, and Δ_2 is of the order of a few milliseconds.
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(27) It should be noted here that vapor phase osmometry (VPO),[8] even in the most carefully carried out experiments, cannot give results of comparable *precision* to nmr measurements. Serious loss of precision can obviously lead to erroneous conclusions concerning just which of many possible postulated LSR–substrate equilibria are actually present. Deranleau[25] has treated in detail the necessity for an extensive and complete data set extending over the entire experimentally accessible range of concentrations. Failure to do so can vitiate the quality of the results to a very substantial degree. The present nmr data do not *allow* the inclusion of any additional equilibria; rather, we emphasize here the fact that the predication of any additional species beyond LS and LS_2 results in fits inferior to those obtained on just the inclusion of these two complexes. Finally, the data sets analyzed in this work contained far more experimental points (20, or more) than the VPO data (no more than six points for Eu). In particular, the number of data points in our data sets was far larger than the number of parameters being fit—a procedure usually deemed necessary to ensure that least-squares fits and the parameters derived therefrom have physical significance.