NMR SHIFT REAGENTS: INTRINSIC LIS PARAMETERS IN MIXTURES

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The lanthanide-induced nmr shift (LIS) effect has become a valuable aid for the structural analysis of organic molecules bearing a Lewis-basic functional group.[1-3] However, the dependence of the LIS effect upon the composition of mixtures of substrates can make analysis of such mixtures difficult. Several methods to obtain intrinsic, composition-independent LIS parameters have been proposed,[2-5] but all have limitations.

I wish to report in this communication a novel method for obtaining intrinsic LIS parameters by an analysis of the interdependence of the LIS values of two or more substrates as the solution composition is changed. The model assumes that departures from solution ideality are due solely to equilibria of the following type:

$$L + B_j \rightleftharpoons C_j, \qquad (1)$$

$$K_j = [C_j]/([L][B_j]), \qquad (2)$$

where L is "free" LIS reagent, B_j is "free" substrate j, C_j is complexed substrate j, and brackets denote equilibrium concentration of the enclosed species. These complexes usually exhibit rapid chemical exchange[1-3] so that the nmr spectra of free and complexed substrate coalesce to a single nmr spectrum. The resultant chemical shift may be expressed as a function of the equilibrium concentration of "free" LIS reagent,[6] or _vice versa_:

$$\delta_j = \Delta_j K_j[L]/(1 + K_j[L]), \qquad (3)$$

$$\text{or } [L] = \delta_j/\{K_j(\Delta_j - \delta_j)\}, \qquad (4)$$

where δ_j is the observed shift of substrate j with respect to the shift of substrate j in the absence of LIS reagent, and where Δ_j is the limiting shift of completely complexed substrate j with respect to the shift of substrate j in the absence of the LIS reagent.

Within the framework of the above model, the intrinsic LIS parameters of a given substrate-LIS reagent pair are K and Δ. Values for K and Δ may be obtained from a study of the stoichiometric concentration dependence of the observed shift.[7] Recently, Willcott et al[5] showed by this type of study that the above model is an acceptable description of the LIS effect displayed by the $Eu(DPM)_3$-THF system. However, a similar study of a mixture of substrates would be difficult to perform unambiguously because of the complexity of the interacting equilibria.

Characterization of substrate mixtures can be simplified by the use of the observed shift of some monitor substrate m as an internal standard to assess the "free" LIS reagent concentration. The novelty of this approach is that the intrinsic parameters K and Δ can be found without explicitly using the stoichiometric solution composition. By letting j of eq (4) be called m, substituting eq (4) into eq (3), and inverting the result, one obtains:

$$\delta_j^{-1} = \delta_m^{-1} \, K_m\Delta_m/(K_j\Delta_j) + (K_j - K_m)/K_j\Delta_j \qquad (5)$$

Eq (5) demonstrates that the plot of the reciprocal of the shift of some unknown substrate j vs. that of the monitor substrate m is a straight line whose slope (S_j) and intercept (I_j) characterize the substrate j. A similar plot can be made for each substrate present in the mixtures.

The intrinsic LIS parameters can be determined by using a monitor substrate whose K_m and Δ_m values are known viz:

$$K_j = K_m(\Delta_m I_j/S_j + 1) \qquad (6)$$
$$\Delta_j = \Delta_m/(\Delta_m I_j + S_j)$$

However, if K_m and Δ_m were not known, then S_j and I_j would serve to characterize the substrate j.

The above model applies rigorously only to monofunctional (one binding site) substrates which behave ideally in solution. Eq (5) would seem to apply generally to complexation reactions, but in practice the substrates are likely to form complexes between themselves. Hence this method will probably be most useful when the complex described by eq (1) is far stronger than any intersubstrate complex. (The substrate-LIS reagent complex is known to be very strong.)[5]

The LIS effect of polyfunctional substrates is not rigorously described

by eq (5). However, if a substrate behaves ideally in solution, then its LIS
effect can always be expressed solely as a function of free LIS reagent concen-
tration. (Proof of this assertion is cumbersome but straight forward.)
Therefore, the LIS effect can rigorously be characterized by adjusting solution
composition so that the nmr absorption shift of some monitor substrate remains
constant from sample to sample. In this case, the observed chemical shifts
would serve as the intrinsic LIS parameters of the polyfunctional substrate.

Results of an example of the monitor shift method are presented in the
Table. Six mixtures of methanol, ethanol, ethyl acetate, acetone, and $Eu(DPM)_3$
were prepared in CCl_4. The measured chemical shifts obtained with an A-60 nmr
spectrometer were plotted according to eq (5), as illustrated in the Figure
(absorption assignments are given in the Table). Note that all absorptions of
ethyl acetate had nearly identical slope/intercept ratios and that the intercept
of absorption B was near zero, in agreement with theory.

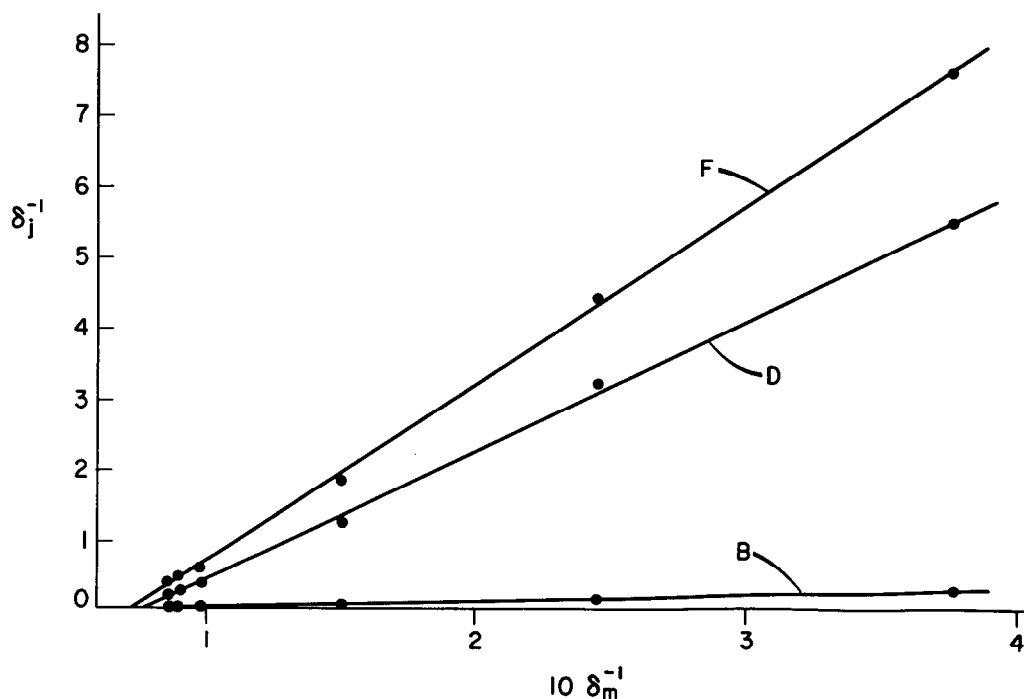FIGURE: δ_j^{-1} vs. δ_m^{-1} in ppm^{-1}

TABLE: Intrinsic LIS Parameters of a Mixture of Substrates

Absorption*	Slope**	Intercept** (ppm^{-1})
A	11.9 ± .7	-0.94 ± .14
B	0.583 ± .008	-0.0036 ± .0017
C	0.53 ± .03	+0.007 ± .010
D	18.5 ± 1.1	-1.45 ± .21
E	12.4 ± .9	-0.95 ± .18
F	25.6 ± 1.0	-1.90 ± .20

*CH_3OH CH_3CH_2OH $CH_3CH_2O_2CCH_3$ CH_3COCH_3 TMS internal reference
   C   G   B   F   A   E   D
**Absorption G was shift monitor.   95% confidence limits.   Temp. = 38°C.

In summary a novel monitor shift method for obtaining intrinsic LIS values has been devised which has the following advantages not fully possessed by other such methods.[2-5]

1. It is applicable to mixtures of substrates, and in a modified form is applicable to polyfunctional substrates.

2. It is applicable to a broad range of solution compositions and hence the composition may be selected to maximize the quality of the nmr spectrum rather than to satisfy other criteria, such as attaining complete complexation of substrate by LIS reagent.

3. It provides a pair of intrinsic parameters and hence is more characteristic of a substrate than a single parameter method.

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