planet, and exits through the northern magnetosphere, traveling through "north ecliptic interplanetary space" to pass over the north pole of the sun. The other is directed to use Jupiter for a pull that swings it into a similar path, but south of the ecliptic and then over the south pole of the sun. The progress of the mission in solar latitude is shown in Fig. 8. Each spacecraft is spin stabilized and carries about 30 kg of experiments. To take advantage of the almost unique opportunity to compare results from two spacecraft simultaneously operating in two different places, both spacecraft carry a standard "core" of experiments weighing about 17 kg. The remaining 13 kg in spacecraft A need not necessarily be the same as in spacecraft B.

The advantages of this method are that the use of two spacecraft permits the resolution of space and time ambiguities, it is possible to reach solar polar latitudes, the Jovian magnetosphere can be looked at on the way, and the spinning spacecraft render the measurement of particle anisotropies less complex technically.

Summary

Our narrow view of the sun and its surrounding atmosphere is quite inadequate if we are to understand the sun as a star and describe the behavior of its corona. Nor can measurements in the ecliptic plane enable us to determine the interstellar cosmic-ray intensity.

There is ample evidence that an exploratory journey out of the ecliptic to high solar latitudes would be highly rewarding. Rather simple experiments could lead to major advances in our understanding of solar wind physics, of cosmic-ray modulation, of the structure of the interplanetary magnetic field, of solar particle propagation, of interplanetary dust, and of the basic nature of the sun itself.

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Determination of Molecular Conformation in Solution

Applications of nuclear magnetic resonance to the topology of molecules in solution are reviewed.

M. Robert Willcott, III, and Raymond E. Davis

Immediately after the discovery of three signals in the proton nuclear magnetic resonance (NMR) spectrum of ethanol by three physicists (*1*), chemists appropriated the method as a tool for the deduction of detailed chemical structure. The complexity of the instrument, then and now, is offset by the facile interpretation of the experimental results in many instances. At present more than 2700 papers per year refer to NMR (*2*). Most of these accounts appear in chemical journals. Increasingly sophisticated NMR experiments are being developed through improvements in instrumentation. Each new method attracts specialists who generate new descriptions of the molecules under investigation. Typically, these new methods are not quickly assimilated into the chemical community due, in great part, to the time lag between understanding the experiment and obtaining funds for the purchase of new equipment (*3*).

Hinckley's recent description (*4*) of a convenient sample modification with paramagnetic ions has run counter to this trend. The additional cost of the experiment need not exceed $1, the required chemicals are readily available, and the experiment can be performed in two to four times the period normally used to obtain a single NMR spectrum. The most important feature of the Hinckley report is that the interpretation of the modified proton NMR signal frequencies in terms of the structure of the compound under investiga-

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tion seems to be as quick and easy as the acquisition of the spectra. Indeed, the qualitative understanding of the spectra is so easy that more than 800 papers have cited this technique as an adjunct device for structure determination by the fifth anniversary (December 1974) of the original report (*5, 6*).

The majority of the authors of these accounts deal explicitly with pragmatic "proof of structure," while a small, but competent, minority express concern about the validity of the various pragmatic schemes. These critical observers note that a theory for chemical shifts induced by paramagnetic ions had been in existence for more than 15 years and that the ubiquitous claims of structure determination were sweeping most of this theory aside. Nineteen different groups of investigators have independently attempted to answer this objection by incorporating some of the mathematical expressions of the theory in computer programs which link structure and theory.

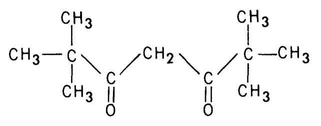
In this article, we first point out the theory and dissect the portion or portions required for a meaningful interpretation. Then we describe a typical experiment, show representative spectra, and discuss the computer methods used to assess structure. Finally, we mention the errors that can creep into these interpretations. Enough details and examples are provided to indicate whether the technique offers advantages for a particular kind of research.

A definition of molecular conformation is mandatory. In present usage, we intend that a proper three-dimensional description of the molecule under investigation be considered the molecular conformation. In some cases the determination of conformation for a molecule will involve only the assignment of *cis* and *trans* geometries about olefin linkages or across rings. In more elaborate examples, the determination of conformation will involve assessment of the geometry about carbon-carbon single bonds as well as the determination of the configurations at chiral centers.

The Experiment

Experiments of the sort introduced by Hinckley are performed in a two- or multistep sequence of operations. In the first step, a conventional NMR spectrum of a substance containing at least one Lewis base site is obtained. We refer to this material as the substrate. The spectrum of the substrate consists of many lines displayed as a function of frequency and is analyzed in terms of line positions (chemical shifts) and repeated spacings (coupling constants) (*7*). In the second step, a particular paramagnetic ion, a rare earth chelate, is added to the same solution and a new spectrum is obtained. Inspection of this new spectrum reveals different chemical shifts but the same coupling constants. The altered chemical shifts usually, but not always, cover an increased frequency range. If a second portion of rare earth chelate is added, the perturbation of chemical shifts is even greater. This property has led to the invention of the descriptors lanthanide shift reagent (LSR) and lanthanide ion induced chemical shift (LIS).

Even though all of the lanthanide ions produce paramagnetic effects (*8*), europium, praseodymium, and ytterbium give the most easily interpretable spectra. The ions are prepared for use in aprotic solvents by chelation of lanthanoid(III) cations with anions of bulky β-diketones. Various considerations go into selecting the best diketone-lanthanide pair for a particular experiment (*9*). The useful diketone ligands have the property of shielding the lanthanide ion from the solvent and substrate. This shielding may be viewed whimsically as wrapping the paramagnetic ion in a ball of wax. Foremost among the diketones are dipivaloylmethane (DPMH) (**1**) (*4, 10*) and 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dione (FODH) (**2**)



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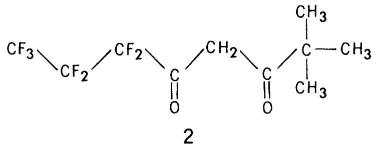

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(*11*). These chelates are crystalline, well-characterized materials that can be handled in the same way as any other research laboratory chemical (*12*).

No consistent description of the state of aggregation (for example, monomer or dimer) of the LSR in solution is available. The extent of this problem was revealed at a symposium on LSR's, held at the American Chemical Society Meeting in Dallas, April 1973 (*13*). Whatever their intimate description, these chelate complexes have the ability to disperse NMR signals more than 100 parts per million without severe loss in sensitivity or resolution.

Separation of the NMR signals in a complicated molecule can be dramatic. An example of the effect produced by the se-

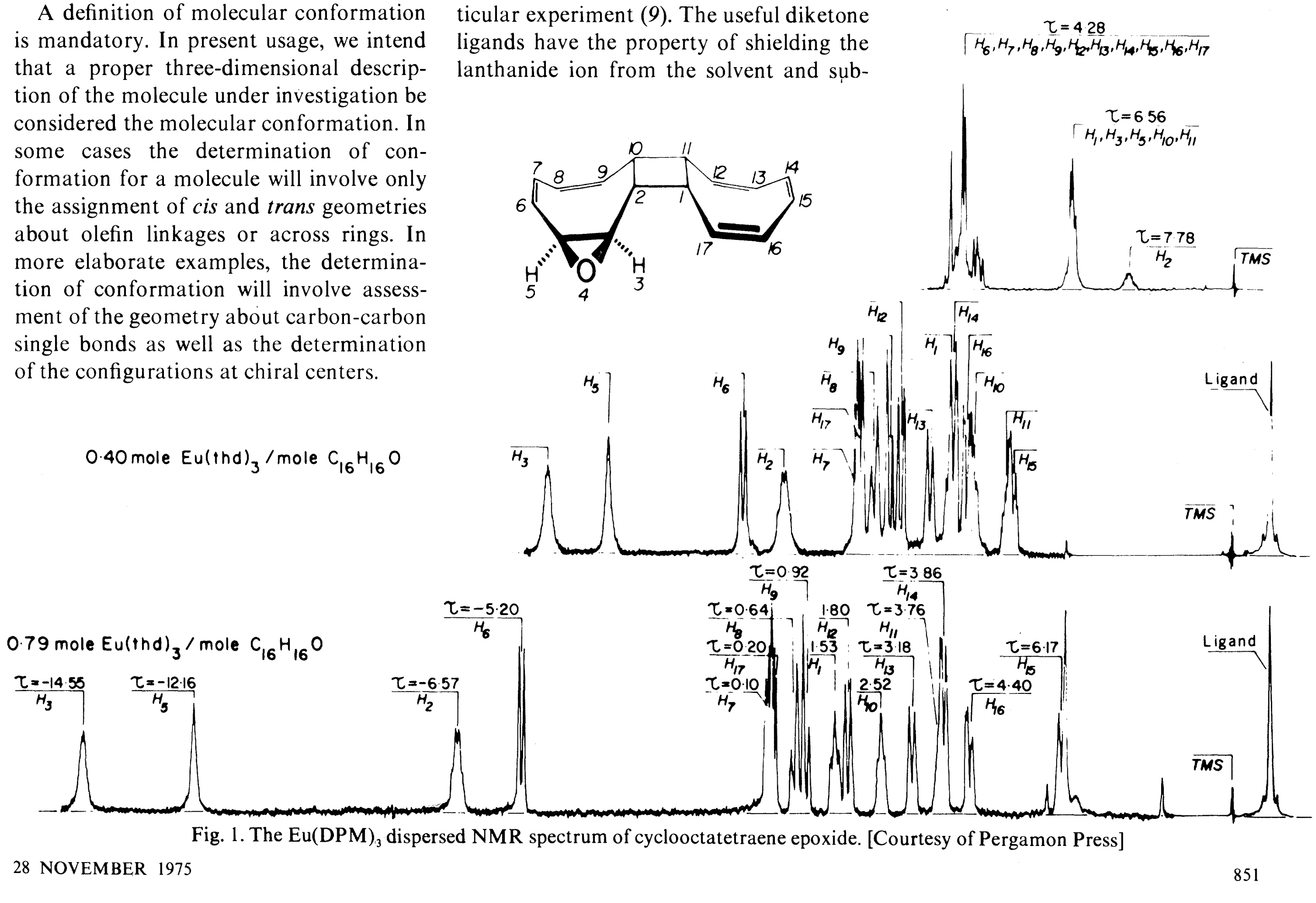
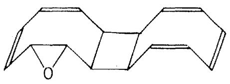


Fig. 1. The Eu(DPM)$_3$ dispersed NMR spectrum of cyclooctatetraene epoxide. [Courtesy of Pergamon Press]

Table 1. Best-fit lanthanide substrate arrays for six different LIS data sets.

Data set	Reference	R (%)	Distance (Å)	Rho	Phi
Yb(DPM)$_3$	(*48*)	1.3	3.33	57.	141.
Eu(fod)$_3$	(*29*)	3.6	3.50	62.	140.
Eu(fod)$_3$	(*49*)	4.5	3.50	54.	130.
Yb(fod)$_3$	(*49*)	4.9	3.50	52.	128.
Eu(DPM)$_3$	(*50*)	1.1	3.47	58.	137.
Eu(DPM)$_3$	(*51*)	4.2	3.46	52.	150.

quential addition of an LSR, such as Eu(DPM)$_3$, to an NMR solution of the tetracyclic epoxide **3** is shown in Fig. 1 (*14*).



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We discuss the configuration and conformation of this epoxide later. For now, notice that each addition of LSR produces a single spectrum and that the total shift is a function of added LSR. This happens only if a rapid exchange between the lanthanide and substrate is taking place. The NMR time scale is such that these exchange rates are 100 per second or greater. Notice also that each resonance can be tracked through a series of dispersed spectra and assigned an index (expressed as induced shift per mole of substrate per mole of LSR). These indices can be obtained by various data reduction methods, some of which may be more accurate than others. The problem of finding an optimum method has been reviewed by several investigators who reported at the Dallas symposium (*13*).

Lest this one illustration, the contents of this article, and our enthusiasm lead you to conclude that LSR experiments are a panacea, we must offer some caveats. The proper combination of substrate and shift reagent must be selected; a convincing interpretation can best be made of the spectra of monofunctional (that is, one Lewis base site) molecules; the solvent is usually carbon tetrachloride, benzene, or chloroform. These limitations are relaxed by the finding that many compounds have a preferred site of LSR complexation and are thereby effectively monofunctional (*15*) and that lanthanide ions in water can be used for the study of biological systems (*16*). In the latter case, the lanthanide ion is not used as a chelate complex, but the interpretation of the induced shifts follows the same rules.

A Physical Model

In order to deduce a structure from an NMR spectrum, the chemist considers signal intensities, chemical shifts, and coupling constants, probably in that order. The relative intensities are informative because each hydrogen atom in the molecule gives rise to a unit signal. Chemical shifts, determined by the environment of the nucleus, indicate such features as olefinic, aldehydic, and aliphatic groups quickly and reliably (*17*). In principle, the combination of intensity measurements and chemical shift determination permits a sorting and counting of the various hydrogen atoms in a molecule. In fact, this task can be experimentally demanding and becomes virtually impossible for medium-sized organic molecules (for example, those containing 10 to 30 carbon atoms consisting of primarily saturated C-C bonds) since many resonances occur at approximately the same frequency. In the event a Lewis base site is present, addition of the LSR will increase the difference in frequency of the various absorptions and will facilitate the sorting and counting. Thus, the outcome of a shift reagent experiment, consisting of intensities and induced chemical shifts, renders trivial the distinction between substrates containing different numbers of hydrogen.

Isomers contain the same number of atoms and might present a special problem in interpretation, especially if the various isomers show similar LIS indices. Fortunately this problem does not often emerge. Paasivirta has examined many bicyclic alcohol isomers and found that every compound gave a distinct set of LIS indices (*18*). Williamson *et al.* have examined the LSR characteristics of all of the hexanols and reached the same conclusion (*19*). We have studied several sets of stereoisomers and have not yet observed two compounds with the same set of LIS indices (*20*).

Since these results suggest that the LIS indices are characteristic of a molecule, it would seem possible to use pattern recognition techniques to deduce the structure of the substrate (*21*). In the limit an appropriate algorithm could function with no a priori structural information. In current practice, pattern recognition is facilitated by incorporation of information about possible substrate structures early in the mathematical process.

An intellectually economical model for understanding the chemical shifts induced by paramagnetic ions was provided by McConnell and Robertson (*22*) 13 years before Hinckley's account of the LSR experiment. They derived a two-parameter equation to describe the magnetic field perturbation ($\Delta H/H_0$) due to a point dipole.

$$(\Delta H/H_0)_i = K\,\frac{(3\cos^2\theta_i - 1)}{r_i^{\,3}} \qquad (1)$$

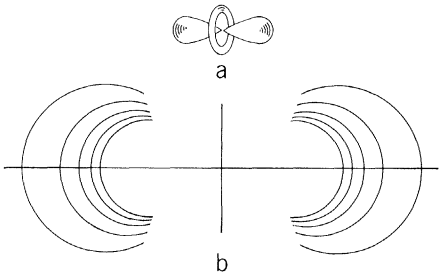


Fig. 2. (a) Three-dimensional plot of the function $(3\cos^2\theta - 1)/r^3$; (b) partial cross section along the principal axis showing the contours of equal shift perturbation.

where r_i is the distance from a point dipole to the ith nucleus, θ_i is the angle between the principal axis of the dipole and the line from the dipole to the ith nucleus, and K is a constant. This equation is simplified, but it is sufficient for precise interpretation of virtually all of the reported LIS data sets (*23*). Since the algebraic form of this dipolar axially symmetric field is the same as that of a d_{z^2} atomic orbital, the three-dimensional plot of the function (Fig. 2) looks like the atomic orbital (*24*). Figure 2 also shows a cross section along the principal axis and indicates several contours of equal field strength. Those closest to the center represent the greatest field strength.

The computer approaches to interpretation of the LIS results (*19, 25–43*) are built on the assumption that an oriented complex is formed between the lanthanide (L) and the substrate (S). The basic interaction, ignoring stoichiometry, is that shown in Eq. 2.

$$\mathrm{L} + \mathrm{S} \rightleftarrows \mathrm{L\text{-}S} \qquad (2)$$

Since the steric relation between the lanthanide and the substrate is not known initially, different investigators typically test various lanthanide-substrate arrays and ask whether they represent reasonable complexes. Although the mechanics of the determination of the "best" description can vary markedly in detail, the resulting lanthanide-substrate structures are similar.

In the next section we discuss one particular algorithm (*31*), PDIGM (*44*), and some examples of its use. We then compare the various methods which accomplish similar analyses, and comment on some of the limitations of the LSR method for structure determination.

Computer Simulation of the LSR Result

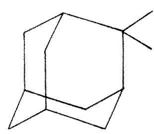
All reported calculations link the calculated and observed LIS indices by this hypothesis: *The observed shifts are caused by the dipolar interaction and contain random errors.* No other physical causes for the shift are admitted. We discuss the limitations imposed by this regularizing hypothesis in the section "Probable Errors in the Model." Our approach is to test possible L-S arrays as follows. We assume that the lanthanide has an axially symmetric field, that the principal magnetic axis coincides with the lanthanide-heteroatom line of centers, and that a single set of internal coordinates represents adequately the L-S complex. A test structure for the substrate is described via Cartesian coordinates with the coordination site at the origin. A lanthanide is provided at fixed distances *d* from the origin, and its location is systematically varied through the polar angles ρ and ϕ. At each incremental lanthanide location, a set of r_i and θ_i for Eq. 1 is generated and an unscaled set of LIS indices $(\Delta H/H)_{ci}$ is calculated. These are scaled to the observed values $(\Delta H/H)_{0i}$ by a linear least squares procedure. We assess the fit with the agreement factor *R* (Eq. 3) (*45, 46*). If the observed induced shifts are known to different degrees of reliability, relative weights can be introduced into the definition of *R* (*45*).

$$R = \left[\frac{\Sigma(\text{obs.} - \text{calc.})^2}{\Sigma(\text{obs.})^2} \right]^{1/2} \qquad (3)$$

The locus of the lanthanide positions for a constant *d* is a sphere centered on the origin of the coordinate system. The *R* values for each incremental location of the lanthanide ion can be used to plot contours of equal fit on the sphere (*47*). Since the contours are monotonic and regular, the plot is an easily used visual aid. Typically there are regions in which the agreement is as good or better than the error in the experimental indices, and regions in which the agreement is clearly worse.

The agreement factor *R* is a quantity useful in hypothesis testing (*46*). The minimum *R* factors (MINR's) for two different molecular models can be utilized to form a statement about the probability that one model is to be preferred over the other, *with the assumption that the chemical shift perturbations are caused by an axially symmetric dipolar field and random errors only.*

The precision of the interpretation of LIS data can be calibrated with the rigid substrate 2-adamantanol (**4**).



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The Yb (DPM)$_3$ shift data for 2-adamantanol (*48*) and the calculated indices for the best fit array are shown in Fig. 3. The MINR of 1.3 percent was found for the ratio of the observed to the calculated values shown on the formula in Fig. 3C.

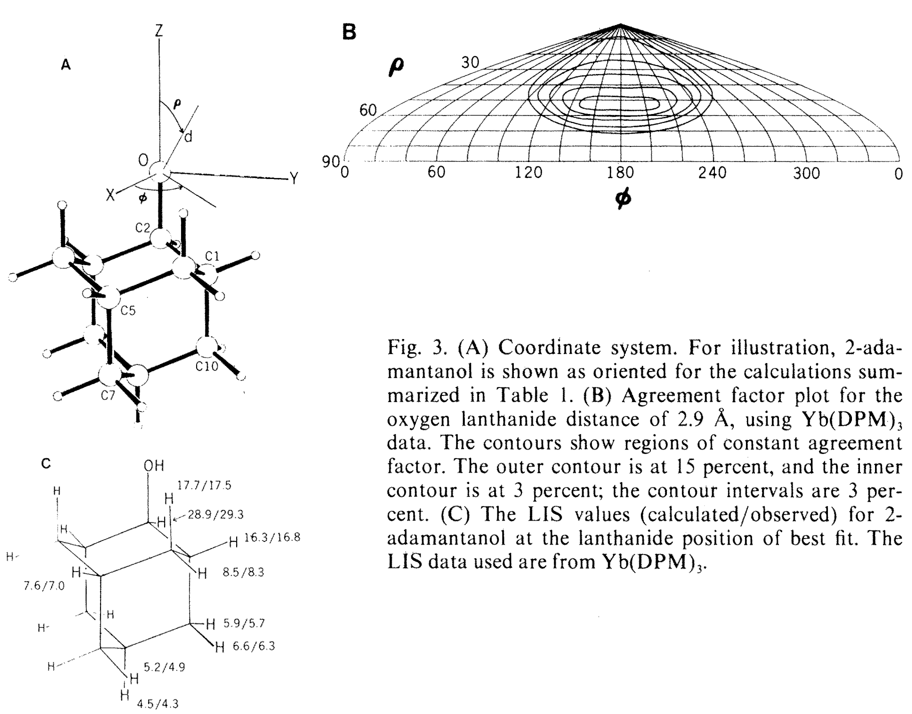


Fig. 3. (A) Coordinate system. For illustration, 2-adamantanol is shown as oriented for the calculations summarized in Table 1. (B) Agreement factor plot for the oxygen lanthanide distance of 2.9 Å, using Yb(DPM)$_3$ data. The contours show regions of constant agreement factor. The outer contour is at 15 percent, and the inner contour is at 3 percent; the contour intervals are 3 percent. (C) The LIS values (calculated/observed) for 2-adamantanol at the lanthanide position of best fit. The LIS data used are from Yb(DPM)$_3$.

Since the precision of the experimental data is about 2 percent (*49*), this agreement factor is intuitively reasonable.

The LIS behavior of 2-adamantanol is the subject of several independent investigations. The use of different shift reagents and even different data reduction schemes causes the absolute values of the induced shifts to cover a large range. We find that the precision dictated by any of these data sets ranges from 1.1 to 4.9 percent (Table 1). Thus, we conclude that the precision of the L-S structure does not depend sensitively on the experimental parameters selected. Even though the precision of any particular L-S array may be high, the accuracy of the description need not be as high.

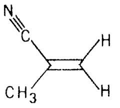
Structural differences exist in the interpretations of this L-S pair which are given by Cockerill and Rackham [correlation of shift with distances only (*50*)], Demarco (*29*), Farid (*32*), Uebel (*28*), and ourselves (*31*). Variation in details of the reporting of the L-S structures makes it difficult to compare exactly the results of Demarco, Farid, Uebel, and ourselves, but the reported oxygen-lanthanide distances are 3.0 ± 0.2 Å and the C-O-L bond angles are 125° ± 6°. There is no question that some, if not all, of the L-S structures are inaccurate, especially since any two interpretations of these data give slightly different results. Unfortunately, no external standard for accuracy is agreed upon, and we must use precision to fix our results.

We have found that the contour plots for most substrates are essentially independent of details of the method used to convert observed chemical shifts into relative shift indices. The contours (but not the MINR values) are insensitive to deviations of 0.1 Å in the specification of the internal coordinates and to deviations of 0.2 Å in location of the lanthanide. Adjustment of the internal coordinates causes apparent, but statistically insignificant deviations, in the minimum agreement factor when the L-S array is in the region of a "best" solution (*52*).

Three factors alter the contour plots (and the agreement factors) strongly. These are (i) the structure of the substrate, (ii) the assignments of the resonance signals, and (iii) the conformation of the molecule. These three cases result from a formal alteration of the internal coordinates of some of the nuclei in the substrate by an angstrom or more. Changes of this magnitude inform the investigator of important three-dimensional features of the L-S array, especially the topology of the substrate. Thus, Eq. 1 provides the basis for a method of probing the structure of molecules in solution. Before discussing nine examples of structure determination using shift reagents, we want to put this procedure for the study of the topology of molecules in perspective. The LSR method does not provide ab initio determination of structure at this time. Instead, we propose a structure and test its suitability via its LSR behavior as correlated by Eq. 1 or some variant. Concurrently we must always consider all of the ancillary information at our disposal; among other things, this could be empirical formula, spectroscopic data, chemical reactivity, or steric constraints. Even in the cases where this information seems redundant, prudence dictates that all of the evidence be examined for self-consistency.

Examples

This LIS potential for structure verification is exemplified by the three methylated acrylonitriles **5**, **6**, and **7**. Each isomer was purified and its NMR spectrum was dispersed with Yb(DPM)$_3$. The three resonances in each molecule were followed as a function of added shift reagent, and the data were reduced to the values in Fig. 4 (*53*). These LIS data sets for the three substrates were each tested against the three structures. The MINR values for the nine combinations of structure as a function of the data are displayed in a three by three array (Table 2). Four of the nine combinations are readily rejected, but five possible descriptions remain.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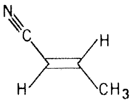
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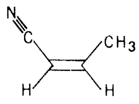
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This ambiguity arises because the number of independent variables in the computation is four (the empirically determined scale factor and the three positional parameters for the lanthanide), and we have only three observations (*54*). Hypothesis testing via the agreement factor ratio is precluded by the number of degrees of freedom (–1). In two of these cases MINR's corresponded to unreasonable Yb positions. When the physically justifiable constraint of C-N-Yb linearity was applied, the results are unambiguous (Table 3) (*55*).

Spectral interpretation for the cyclooctatetraene dimer epoxide **3** looks like a more demanding problem, but the structure determination is actually made easier by the observation of 16 signals. The compound was made by the epoxidation of the all-*cis* cyclooctatetraene dimer, a substance of impeccable characterization (*56*). We accepted the hydrocarbon framework, and then formulated a heirarchy of structural questions (see Fig. 5): (i) Is the epoxide between C-5 and C-6 or between C-3 and C-4? (ii) Is the epoxide ring parallel or perpendicular to the cyclobutane ring? (iii) Is the cyclobutane ring planar or folded? (iv) Are the assignments of the resonances correct?

The answer to the first question is trivial. The symmetry of the C-5 to C-6 epoxide is such that it would exhibit only eight groups of resonances. We observe 16 resonances, so we must select the C-3 to C-4 epoxide (Fig. 5, c and d) as the starting point for our LIS discussion. The parallel : perpendicular distinction was made by evaluating the MINR's for the two molecules and by hypothesis testing on the MINR ratio. The ratio, 30/6 or 5, allows us to reject the perpendicular isomer at the 99.9 percent confidence level. The decisions about ring fold and assignments are coupled; reorganization of the cyclobutyl ring might alter the r and θ relationships (Eq. 1) in the cyclobutyl and distal rings, perhaps enough to reorder the assignment of signals. We found through a systematic exploration that reversing two assignments of Fig. 1 and folding the ring by 20° generates a MINR of 5 percent. The substrate topology is best represented by structure d of Fig. 5.

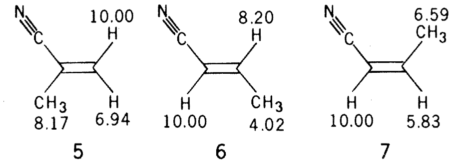


Fig. 4. Observed LIS values for methylacrylonitriles **5**, **6**, and **7**. Values for each compound are scaled so that the most shifted proton resonance has relative value 10.00.

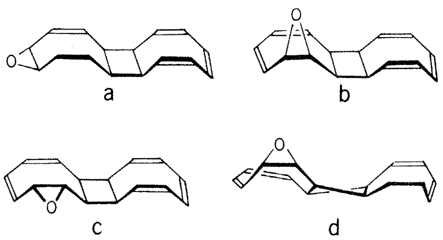


Fig. 5. The conformations considered for compound **3**. (a) The C-5–C-6 isomer. (b) The C-3–C-4 epoxide perpendicular to ring isomer. (c) The C-3–C-4 epoxide parallel to ring isomer. (d) With the cyclobutane ring twisted 20°.

Table 2. Minimum R values (%) for binary combinations of methylacrylonitrile models **5** to **7** with sets of relative slopes; no restraint of lanthanide positions (*53*).

Model	LIS data set		
	5	**6**	**7**
1-CH$_3$	2.8	14.4	0.3
cis-2-CH$_3$	6.0	22.6	2.5
trans-2-CH$_3$	29.2	0.7	23.9

Table 3. Minimum R values (%) for binary combinations of methylacrylonitrile models **5** to **7** with sets of relative slopes; collinearity restraint imposed on lanthanide positions (*53*).

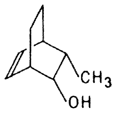
Model	LIS data set		
	5	**6**	**7**
1-CH$_3$	2.9	31.7	9.7
cis-2-CH$_3$	6.0	26.6	2.8
trans-2-CH$_3$	29.3	1.5	27.1

Table 4. The LIS data and results for methylbicyclooctenols **8** to **11**. LIS data for the four compounds **8** to **11**, tentatively described as compounds A to D, not necessarily respectively.

Resonance	LIS data set			
	A	B	C	D
	Assigned resonances			
H-1	3.22	2.52	2.38	2.73
H-2	3.62	2.61	1.54	1.48
H-3	4.71	3.78	1.61	1.82
H-4	6.18	5.88	5.76	5.97
H-5	10.00	10.00	10.00	10.00
H-6	4.54	7.66	6.30	4.66
CH$_3$	7.60	2.52	2.95	6.83
	Unassigned resonances			
H-7, 8a	2.3	2.5	7.4	8.0
H-7, 8b	2.0	2.0	2.2	3.9
H-7, 8c	2.0	2.0	2.2	3.9
H-7, 8d	1.7		2.2	3.5

The correction of the resonance assignments for this epoxide was found by scanning the computer output. This suggested that permutations of assignments could be detected during computation and that automatic assignment of all resonances could be made by the AUTO-ASSIGN feature of our program. This automatic feature of the program makes assignments for each incremental lanthanide position in such a way as to minimize R (Eq. 3). Clearly these possible assignments must be considered in terms of other knowledge (such as chemical shifts, coupling patterns, and the like).

Auto-assignment of partial data sets can be advantageous, as shown by the following example. Willcott, Davis, and Holder (*57*) studied a set of four bicyclo[2.2.2] octanols (**8** to **11**) and determined their structures by a series of carefully related chemical reactions. They concurrently raised the question of whether the LIS data for each molecule could be interpreted in terms of an unambiguous configuration (*57*). Before this question can be answered, several features of the four NMR spectra must be considered. The seven resonances which can be assigned via the usual correlations are those of partial structure **12**.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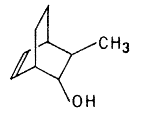
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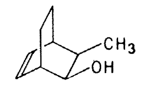
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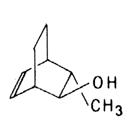
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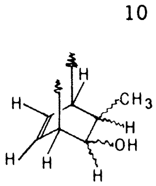

12

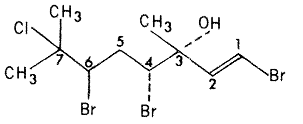
The ethano bridge resonances are similar in the unperturbed spectra and are strongly coupled to several other resonances. At the highest concentrations of LSR, these ethano resonances, although well separated, are so complex as to preclude assignment. Thus, the summary of the Eu(DPM)$_3$ results in Table 4 is divided into seven assigned and four unassigned signals. Inspection of the MINR's found using only the seven assigned resonances allows us to deduce only one structure of the four

(Table 5). The use of auto-assignment makes the further structure determination straightforward. We enter the four poorly determined ethano resonances, make optimum matches, and obtain Table 6. At this point, the ambiguities have been removed and a structure proof results.

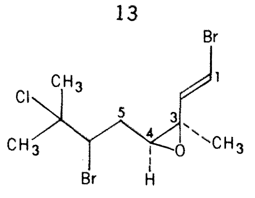
Less than a week was required for the experiments and interpretation. The chemical proof of structure was more lengthy (*57*). Of course they both give the same results and complement each other very well. As the limits of the LIS method are clarified, we expect it can and will supplant some long and difficult chemical proofs of structure.

Thus far we have considered small rigid substrates (the acrylonitriles), a large substrate of unknown configuration and of limited conformational mobility (the cyclooctatetraene dimer), and a set of rigid molecules of unknown configuration (the bicyclooctenols). Descriptions of these proposed molecular shapes were verified from the LIS data via the dipolar equation. The use of supplementary information to guess structures saves both time and effort and can make the LSR method succeed in more difficult problems. For instance, the conformation of a flexible molecule was determined by combining information from the nuclear Overhauser effect (NOE), the coupling constants, and the LIS data in the following example.

The California sea hare *Aplysia californica* concentrates the tetrahaloterpenoid catabolite **13** in its digestive tract (*58*). We used the LIS method to help fix the topology of the epoxide **14** derived from this alcohol.



13



14

In this way we determined which of eight racemic stereoisomers best represented the alcohol. The *cis* disposition of the H and CH_3 on the epoxide ring were demonstrated by an NOE measurement (*58*). After account was taken of the *trans* olefin (from the H-H coupling of 15 hertz) (*17*), only the relative configuration of the groups at C-6 remained to be settled. The results of dispersing the spectrum with $Yb(DPM)_3$ at 220 megahertz are shown in Fig. 6.

The molecular models were constructed sequentially; we added pieces of the model as soon as we understood the already constructed portions of the molecule. The first model for the PDIGM calculation included only the epoxide ring, the substituent H and CH_3 groups, and a set of dummy hydrogens corresponding to rotamers about the C-4 and C-5 bond. The experimental LIS shifts for the ring H and CH_3 groups could be simulated by a variety of lanthanide locations ranging over at least 0.5 Å. In spite of the abundance of lanthanide fits, we found the behavior of the calculated shift perturbation of the CH_2 group at position 5 to be patterned so that only the assignment of H-5 (7.06 ppm) to the 300° and H-5′ (4.32 ppm) to the 60° conformations was reasonable. In addition the magnitudes of the spin-spin couplings $J_{5,4}$ and $J_{5',4}$ accord well with this assignment.

Table 5. Minimum *R* values (%) for binary combinations of models **8** to **11** with data sets for compounds A–D, including only the seven assigned resonances.

Model	LIS data set			
	A	B	C	D
8	4.7	21.5	11.6	5.3
9	38.0	9.0	7.8	31.0
10	33.0	5.0	5.2	30.0
11	15.6	20.8	12.9	4.1

Table 6. Minimum *R* values (%) for the critical combinations of models **8** to **11** with data sets for compounds A–D, including the seven assigned resonances and allowing automatic assignment of the four ethano bridge resonances.

Model	LIS data set			
	A	B	C	D
8	4.8			30.4
9		14.0	9.2	
10	30.4			5.8

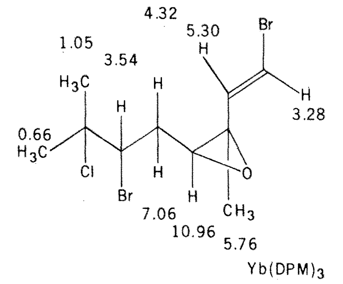


Fig. 6. The $Yb(DPM)_3$ induced shifts for epoxide **14**.

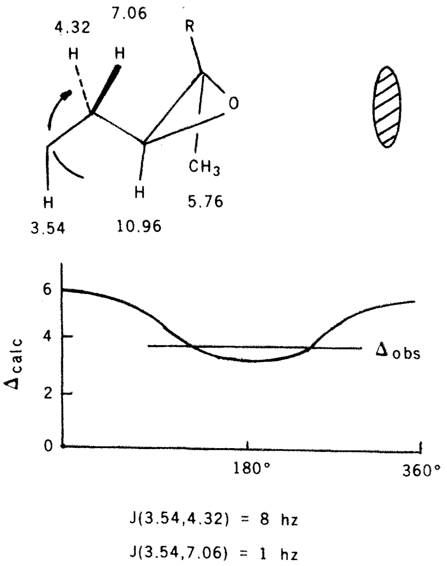
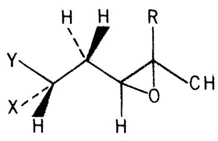


Fig. 7. The angular dependence of the H-6 LIS for compound **14**. 0° is for the conformation shown.

A second cycle of this approach was used to calculate the shift for H-6 (see graph of Fig. 7). In this case the LIS description alone was ambiguous; the 60° and 300° conformations were similar in calculated shift. Even the values of $J_{5,6}$ and $J_{5',6}$ were ambiguous, corresponding to those expected for a skew and gauche conformation, respectively, a condition met by either rotamer. The LIS data, though, tell us that the couplings to H-5 and H-5′ are ordered so that only the conformation **15** fits in all respects.



15

This fixed the conformation of H-6 in our model, an unanticipated bonus. The configuration at this center was revealed when the geminal dimethyl groups at position X gave good fits, while the geminal dimethyl groups at Y did not (*59, 60*).

Probable Errors in the Model

We have intended this article as an indication of the utility of a new tool for structure determination, not as a treatise for the NMR specialist. Nevertheless, we feel compelled to at least mention the errors that exist to some extent in all of the schemes for correlating structure and LIS data. We supply leading references to critical discussions of each of the points.

The performance of the experiment can introduce sizable errors in the LIS values before the calculation. LaMar and Faller (*61*) and Bleaney *et al.* (*62*) have both offered advice about optimizing the experiment by using several lanthanides, and have provided rules for selecting the best ones. Specific methods for the data reduction of a measured set of induced shifts are available from Shapiro (*63*).

All of the stereochemical interpretations of the LIS experiment have utilized only the dipolar (pseudocontact) shift. The other principal component of the induced shift, the contact shift, has been either ignored or played down. The contact shift is caused by unpaired spin density at the resonating nucleus. This spin density is transmitted through chemical bonds. As an example, the Ni(II) induced shifts in some aminotroponates reported by Eaton, Phillips, and Caldwell are dominated by the contact shift (*64*). A comprehensive interpretation of the contact shift requires a calculation of the free spin densities, a nontrivial task. The LIS's of ^{13}C, ^{14}N, and ^{19}F resonances frequently contain a sizable contact shift contribution (*65*). Fortunately, incursion of the contact shift in structural interpretations of the LIS proton experiment is reflected primarily in the accuracy of the L-S description. The precision remains high (*66*), and most structural decisions can still be confidently made.

Crystal properties have been determined for several LSR's and LSR-substrate combinations. The single crystal structures (*67*) and the magnetic susceptibility tensors (*68*) do not possess axial symmetry; that is, there is no principal magnetic axis with the mathematical form of Eq. 1. A general form of the dipolar interaction without the axial symmetry restriction is given by Eq. 4,

$$\Delta H/H_0 = K_1(3\cos^2\chi - 1)/r + K_2 \sin^2\chi \cos 2\psi/r^3 \qquad (4)$$

where r, χ, and ψ are the spherical polar coordinates of the nucleus if the paramagnetic center is at the coordinate origin and the polar axis is taken to be any one of the principal magnetic susceptibility axes.

The deduction of the form of the magnetic interaction in the liquid phase must involve the averaging of all possible orientations of the L-S complex. For instance, upon rotation about α (Fig. 8) this average takes the form of Eq. 1 (*36, 69*).

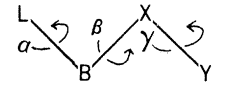
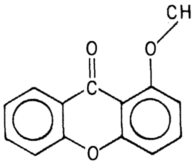
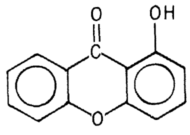


Fig. 8. Schematic representation of possible types of mobility in the L-S complex. L represents the lanthanide, B is the Lewis base site, and X-Y is the remainder of the substrate.

Even if the substrate B-X-Y (Fig. 8) is rigid, another mobile aspect of the L-S complex can be treated in the computation by integrating (averaging) over the angle β. This refinement has been published by Armitage *et al.* (*36*), and a comparable algorithm has been reported by Wing, Uebel, and Andersen (*28*). Internal motions in the substrate, for example, methyl rotations, must be accounted for by averaging over all positions any proton can occupy during the NMR experiment. Most investigators have concluded that an "average" H at the geometric center of the methyl proton array is acceptable (*70*). At this time it appears that substrate conformational problems involving several internal degrees of freedom cannot be solved by LIS data alone unless there is a considerable bias in favor of one form. The *Aplysia californica* epoxide (*60*) seems to be such a case, as is adenosine triphosphate (*33*) and chloroquine (*34*).

The Lewis base coordination site is usually assumed, although not required by the theory, to lie on the principal magnetic axis of the lanthanide. Roberts *et al.* (*35*) and Ammon *et al.* (*26*) have tested this assumption by allowing the axis orientation to vary; they found that it is usually within a few degrees of passing through the Lewis base. We have observed one curious exception in 1-methyoxyxanthone, **16**.


16


17

This substrate gave MINR's of about 15 percent for coordination assumed either to carbonyl or to methyl, but an MINR of 4 percent was obtained when a "coordination site" midway between the two groups was chosen. The similarity to a 1,3-bidentate ligand is obvious. When 1-xanthol, **17**, is used as the substrate, the DPM ligands are displaced and an insoluble chelate is precipitated, corroborating the role of a bidentate ligand (*71*). A rigorous treatment requires the proper orientation of the principal magnetic axis.

Prognosis

Most of the considerations which go into understanding the LSR experiment have just been mentioned. A rigorous interpretation requires perhaps a dozen fundamental parameters, all of which must be adjusted for the individual case. Two factors prevent this elaborate optimization. First, we rarely have enough observable signals. Second, we have the problems of experimental error, so that adjustment of some parameters causes changes in the computed values which are smaller than these errors.

How, then, do we use the LSR experiment to study structure? We can suggest a posture by recalling some of the history of the molecular orbital (MO) methods. Hückel described a limited model for MO calculations and advocated its use in spite of its limitations. The Hückel calculations served to initiate many chemists in MO methodology, and frequently gave "correct" answers. After a reasonable time, the limitations of Hückel theory became an impediment to a sophisticated understanding of MO's, and improvements were added to the computational method. The concurrent increase in computing capabilities has allowed creation of powerful semiempirical methods and ab initio procedures. However, both of these types of calculations rely on Hückel theory to make the initial guess of a trial function. The LSR calculations might be expected to behave in the same way. The basis of all of the computations will be an L-S structure, and the improvements (analogous to semiempirical MO methods) will be added to these.

At this time it seems to us essential to accumulate as much experience with the LSR method as possible in terms of a minimum model. Refinements must be introduced as failures to achieve interpretation occur. In this way the resolution of the L-S structure and the improvement of the dynamic description will come about. In the meantime, the large number of successful applications of the simple model should encourage its continued use (*72*).

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NEWS AND COMMENT

Caucus of Labor Committees: Radicals with Own Edge on Truth

What do B. F. "Ratman" Skinner, Herman "Megadeath" Kahn, "the aging Swedish fascist planner" Gunnar Myrdal, "CIA physicist" Hans Bethe, and "Rockefeller food control specialist" Lester Brown all have in common?

Pretty much the same thing that the Rand Corporation, the Hudson Institute, the Brookings Institution, and the Tavistock Institute of Human Relations in Great Britain all have in common, too. All have been attacked during the last 3 years from a radical group claiming to be on the political left, best known as the National Caucus of Labor Committees (NCLC).

At a time when radical groups of the left and right, active in the middle and late 1960's, are quiescent or busy with internal problems, the NCLC has been actively demonstrating against prominent American scientists and intellectuals at scientific gatherings, in university lecture halls, and at least once—it is alleged—by "trashing" their laboratories. For certain scientists, phone calls—sometimes information-seeking, sometimes harassing—from persons identifying themselves as from NCLC or one of its related organizations have become a common, and for some a daily, fact of life. Moreover, the group's tactics, its choice of targets, and its apparently generous funding have raised suspicions about its true backing and goals among scientists and others who have followed its activities closely (see box).

The NCLC is a large, well-disciplined organization with perhaps 200 members (it claims 1000), with "cells" in some 20 American cities and another dozen or so in Europe and in Latin America. The cells communicate directly to the group's headquarters in a rundown building in the garment district in New York City through an elaborate system of Telex links. The Euro-