

## NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

### LANTHANIDE SHIFT REAGENTS. USEFUL TOOLS FOR STUDY OF CONFORMATIONAL EQUILIBRIA IN SOLUTION?<sup>1</sup>

JOHN D. ROBERTS,\* GEOFFREY E. HAWKES, JANJA HUSAR,  
ALLEN W. ROBERTS and DONALD W. ROBERTS

Gates and Crellin Laboratories of Chemistry,<sup>2</sup> California Institute of Technology, Pasadena, California 91109 and the Department of Chemistry, Stanford University, California 94305

(Received 10 December 1973)

**Abstract**—Difficulties encountered in the use of lanthanide shift reagents for study of conformational equilibria of simple organic molecules in solution are reviewed. It seems clear that, despite these difficulties, significant conformational information is to be gained from the effect of these reagents on NMR chemical shifts.

The elucidation of the stereochemistry of organic molecules has provided one of the most important and fascinating areas of research in organic chemistry over the last hundred years. Extensive investigations of conformational equilibria have occupied only about the last third of that period, but have added new perspectives to studies of organic reactions including the mechanisms of biochemical reactions. Having spent quite a few years concerned with the determination of mechanistic pathways through the use of kinetic and tracer techniques, the senior author became convinced about 1955 that successful understanding of the details of reaction mechanisms depended on knowing much more about conformational equilibria and the rates of conformational equilibration than was known at the time. Fortunately, the utility of NMR spectroscopy for this purpose was just beginning to be demonstrated by W. D. Phillips and H. S. Gutowsky, and there seems to be almost no end to new developments in its application to the study of conformations and, indeed, to stereochemistry in general. This is not to mean that all problems have been solved, and one of the vexing ones which remains is the straightforward determination of conformations of both simple and complex molecules in solution. X-ray diffraction provides superbly detailed information about conformations in crystals but for many substances, especially those of biochemical interest, we can expect that strong solvent-solute interactions may produce large changes in solution.

One of the most important uses of NMR has been

to obtain information about conformational equilibria by use of spin-spin couplings of various nuclei and relations such as the Karplus equation between such couplings and torsional angles. Unfortunately, the differences in the couplings are often small and may be difficult to measure for multi-spin systems with small chemical-shift differences so that the method is not as yet very practical for determining the conformational preference of, say, an n-butyl group in solution. With stereospecific deuterium substitution and careful deuterium decoupling at high fields, much useful information might be obtained, but, in any case, corroboration by other means would be highly desirable, to say nothing of avoiding the difficult synthetic work required.

The development of lanthanide shift reagents by Hinckley<sup>3</sup> only four years ago has brought many new applications to stereochemistry and a promise of new help in determining conformational equilibria. The elegant example of *cis*-4-*t*-butylcyclohexanol<sup>4</sup> (Fig 1) provides a vivid demonstration of the power of an added paramagnetic lanthanide chelate, here tris (dipivalomethanato) europium(III) (Eu(DPM)<sub>3</sub>),<sup>†</sup> to change NMR chemical shifts and simplify the spin-spin coupling patterns of the protons of an organic molecule which has a group, such as OH, with which the lanthanide chelate can coordinate. It is immediately obvious from Fig 1 that the degree of incremental proton shifts is greater, the closer the protons are to the point of coordination and a simple relationship of  $r^{-2.2}$  was proposed.<sup>4</sup>

More detailed analysis<sup>5</sup> suggests that the situation is far more complicated and, assuming that only a single coordination species is formed, two different basic mechanisms of shift changes are

<sup>†</sup>The abbreviations DPM and fod are used here for the unwieldy names dipivalomethanato and 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato, respectively.

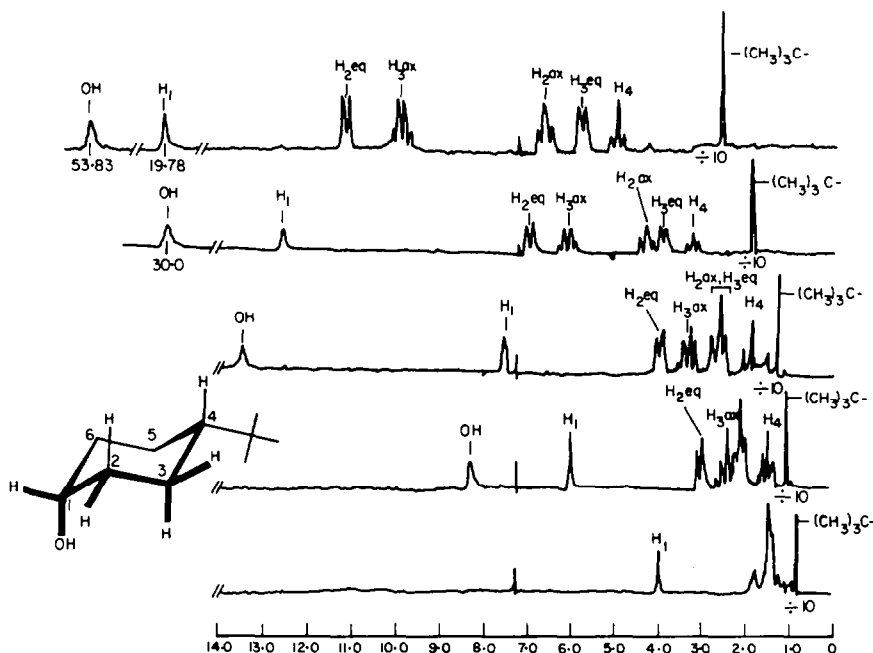


Fig 1. Change in proton spectrum of *cis*-4-*tert*-butylcyclohexanol with successive additions of  $\text{Eu}(\text{DPM})_3$ . The horizontal scale is in ppm. (Simulated by permission of the authors\* and the Journal of the American Chemical Society).

possible, neither of which would be expected to show a  $r^{-2}$  dependence. One of these, the *contact interaction*, is basically a "through-the-bonds", relatively short-range, effect while the other, the *pseudocontact* or *dipolar interaction*, operates through space. Hopefully, with proper choice of lanthanide, contact interactions can be small, except for some carbon shifts.<sup>6</sup> The dipolar effect at a given nucleus,  $i$ , has a formidable mathematical form,<sup>5</sup> except for axially symmetrical complexes where it becomes proportional to  $(3 \cos^2 \chi_i - 1)/r_i^3$ , with  $r_i$  being the distance of  $i$  from the lanthanide and  $\chi_i$  the angle between the vector connecting  $i$  to the metal and the principal magnetic axis of the metal chelate. The degree to which ordinary lanthanide chelate complexes are effectively, if not actually, axially symmetric has been a matter of controversy,<sup>5</sup> but it seems likely now that the  $(3 \cos^2 \chi_i - 1)/r_i^3$  relationship does indeed hold for simple complexes where contact interactions are absent.<sup>7,8</sup>

The simplicity of the  $(3 \cos^2 \chi_i - 1)/r_i^3$  proportionality between lanthanide-induced shifts and the molecular geometry of the substrate-chelate geometry has provided powerful impetus to structural and conformational studies based on this relationship which, of course, has the very desirable property of being applicable to molecules in solutions. The lure of measuring interatomic distances by NMR with naught but an added pinch of lanthanide chelate has been irresistible. As always, how-

ever, there are pitfalls along the way. The approach here to some of these will sacrifice rigor for clarity and will start in a simple way and introduce complications more or less as they arise.

Fig 2 shows a possible (albeit left-handed) coordinate system for application of the dipolar equation to a complex of an alcohol and lanthanide chelate,  $\text{EuL}_3$ . It is convenient to put the oxygen at the zero of the coordinate system, C1 along the Z axis, and C2 in the Y, Z plane. ROM is the oxygen-metal distance,  $\angle \text{COM}$  is the carbon (C1)-oxygen-metal angle, and  $\theta$  is a torsional angle for rotation of the metal around the C1-oxygen bond. Thus, there are

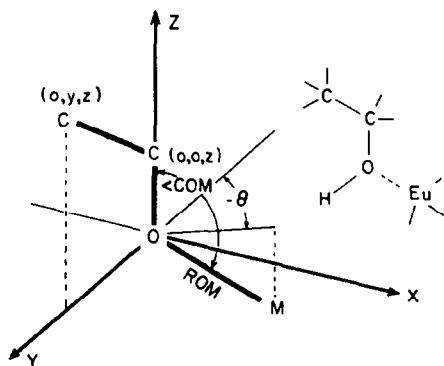


Fig 2. Coordinate system for calculation of dipolar shifts in the coordination of a lanthanide chelate with an alcohol.

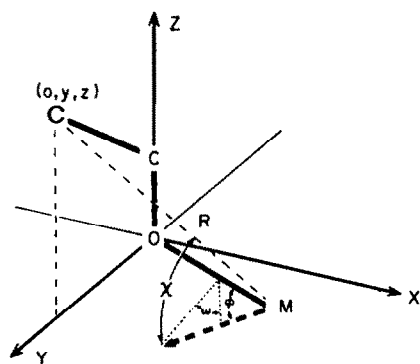


Fig 3. Angles for defining the orientation of the effective magnetic axis of a lanthanide chelate-substrate complex.

three coordinates which determine the geometrical position of the metal with respect to the substrate molecule. The shifts are assumed to be produced by a magnetic dipole centered on the metal (Fig 3) which makes angle  $\chi_i$  with the line of length  $r_i$  between nucleus  $i$  (here C2) and the metal. The problem would be especially simple if the magnetic axis were actually, or effectively, coincident with the O-M bond. We do not know in advance that it is, and so we define an angle  $\phi$  which the effective magnetic axis makes with the O-M bond, and a rotational angle  $\omega$  which is  $0^\circ$  if the magnetic axis lies in the plane determined by C1-O-M and is *trans* to C1.\* We then have five parameters in all—ROM,  $\angle$ COM,  $\theta$ , which define the position of the metal, and  $\phi$  and  $\omega$ , which define the spatial relation of the magnetic axis of the chelate to the substrate.

At the time our work was begun, there were no hard data on what values these parameters might have and it seemed important to see the extent to which they could be fixed using molecules of known geometry. The borneols were chosen for this purpose because they provide eleven different proton and ten different carbon shifts. A computer program CHMSHIFT<sup>7</sup> was developed which seeks to match the experimental shifts and calculated values of  $(3 \cos^2 \chi_i - 1)/r_i^3$  without necessarily restricting any of the five parameters or the slope or intercept to particular values. It will be noted that a

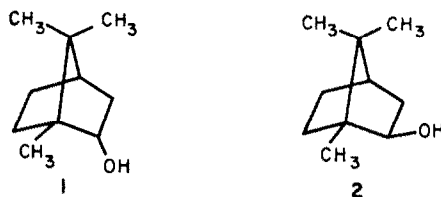
\*The angle  $\omega$  is not well defined when  $\phi$  is close to  $0^\circ$  or  $180^\circ$ .

†This result agrees with the findings of a similar study on cholesterol by C. D. Barry, C. M. Dobson, D. A. Sweigart, L. E. Ford and R. J. P. Williams, *Nuclear Magnetic Resonance Shift Reagents* (Edited by R. E. Sievers), p.173. Academic Press, New York (1973), and supports the approaches of other workers<sup>8</sup> as well as being concordant with theoretical predictions made by J. M. Briggs, G. P. Moss, E. W. Randall and K. D. Sales, *Chem. Commun.* 1180 (1972). See also Ref 7 for additional bibliography on this subject.

condition of the treatment at this point is that it assumes there is a unique value of the torsional angle  $\theta$  or, at least, some value which represents a viable average for two or more conformations with different  $\theta$ 's. This point will be discussed in more detail later.

Now, in making analyses of this kind, there is a serious possibility of error arising from the way the experimental values are obtained. Numerous workers<sup>5,9</sup> have agonized over the stoichiometry of formation, state of aggregation, etc., of the lanthanide chelate-substrate complexes and how the magnitudes of the induced shifts should be reported. There is undoubted merit in the oft-expressed misgivings about the reported shifts, especially when there are effects of moisture and the solutions may have limited degrees of chemical stability. In our work, the reported induced shifts are extrapolated values for 1:1 mole ratios of chelate and substrate obtained from linear least-square fits to shift-chelate plots at constant (usually 1M) substrate and low chelate concentrations. The correlation coefficients for these plots are normally 0.99 or better. If indeed there are significant amounts of more than one species present, with different values of ROM,  $\angle$ COM,  $\phi$  and  $\omega$ , then it should hardly be expected that CHMSHIFT would work very satisfactorily.

The actual results of the application of CHMSHIFT to praseodymium (Pr(fod)<sub>3</sub>)-induced carbon and proton shifts of borneol (1) and isoborneol (2) (Figs 4 and 5) are generally impressive. The



correlation coefficients are high, save for the carbon shifts of C1 and C2, the geometrical parameters of the metal are eminently reasonable with  $\theta$  values such as to put the metal in sterically favorable positions. Of special interest is the fact that the  $\phi$  values are quite small which means that the magnetic dipoles are effectively directed along the coordination bonds.† The metal-oxygen distances of about 2.7 Å (here, in fact, determined with a magnet!) are gratifyingly close to metal-nitrogen distances found by X-ray diffraction.<sup>5</sup>

The matter of C1 and C2 being poorly correlated by the dipolar equation could be a fault of the whole approach, or could be due to contact interactions. It is clear that contributions of contact interactions to carbon shifts are quite important with amine-substrate complexes and the deviations of C1 and C2 of the borneols from the predictions of the dipolar equations fall directly into the observed

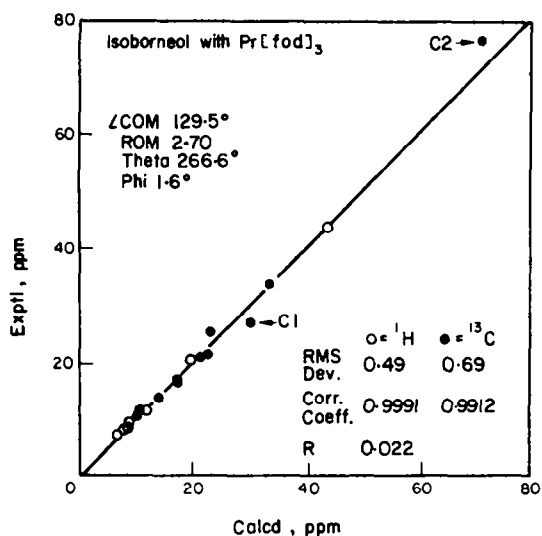


Fig. 4. Correlation of  $\text{Pr}(\text{fod})_3$ -induced experimental and calculated proton and carbon shifts of isborneol. The points for C1 and C2 were not included in the least-squares fit.

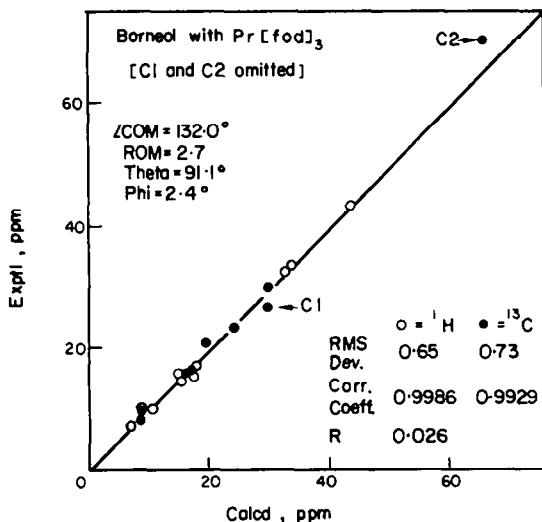
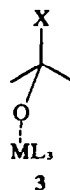


Fig. 5. Correlation of  $\text{Pr}(\text{fod})_3$ -induced experimental and calculated proton and carbon shifts of borneol. The points for C1 and C2 were not included in the least-squares fit.

patterns of such shifts.<sup>10-13</sup> It is not intended to explore here many aspects of the problems of contact *vs* dipolar interactions with lanthanide chelates, but it should be pointed out that contact contributions of so far unknown (and not quantitatively predicta-

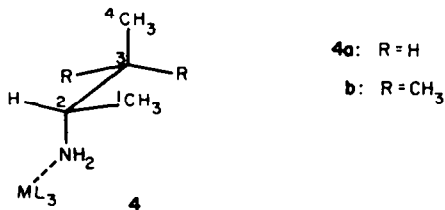
ble) magnitudes render determination of ROM,  $\angle\text{COM}$ , etc. quite difficult where there are relatively few atoms in the system and the close-in carbons would be most helpful to the analysis, if their large shifts were not suspect.

Another serious problem has to do with the importance, if any, of contact interactions to lanthanide-induced proton shifts. No hard evidence is available on this point, although proton shifts generally seem in close accord with predictions of the dipolar equation, as can be seen from Figs 4 and 5. It is possible that the critical test of the immunity of proton shifts to contact shifts is yet to be made. There is substantial theoretical<sup>14,15</sup> and experimental evidence<sup>14</sup> that contact shifts should be largest for the transoid arrangements (3) of metal chelate and the nucleus under consideration (X). If X is hydrogen, and other groups are attached to C1, then



3 will always be an *unfavorable* conformation on steric grounds.

We have previously shown<sup>11,13</sup> that the magnitude of lanthanide-induced contact shifts at  $\beta$  carbons is a function of the degree of alkyl substitution at the  $\beta$  carbons. The greater contact shifts with increased substitution accord with expected greater degree of hyperconjugative stabilization,<sup>11,13</sup> but they also accord with greater importance of conformation 3. Clearly, the more highly substituted X is, the more important 3 will become. The same kind of argument will account for the remarkable difference in contact contributions to europium-induced shifts of C1 and C3 of 2-butylamine<sup>11</sup> and 3,3-dimethyl-2-butylamine.<sup>13,15\*</sup> Here, we expect 4 to be the favored conformation about the C2-C3 bond which, of course, puts C3, but not C1, transoid to the metal chelate. Clearly, with compounds such as 4a and 4b, conformations with H2 transoid to the

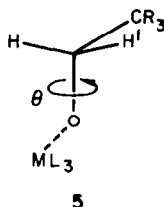


\*The C1 shift of 4b not reported in Ref 13 is -46 ppm while that of C3 is +45 ppm with  $\text{Eu}(\text{fod})_3$ ; unpublished experiments by Dr. R. A. Cooper.

metal are hardly expected to be important. At best, we must conclude that the jury is still out on the occurrence of lanthanide-induced contact shifts involving hydrogen, but at least we can see that, with

all but very special compounds,\* the favored conformations are expected to be those where contributions to proton shifts from contact interactions are not likely to be important. This is indeed fortunate.

If, in fact, it should turn out that  $ROM \sim 2.7 \text{ \AA}$ ,  $\angle COM \sim 125\text{--}130^\circ$  and  $\phi \sim 0^\circ$  for alcohols and amines, then the only important one of the five variables which has to be fixed for a new complex is the torsional angle  $\theta$ . This would appear to be easy to do by looking at the lanthanide-induced shifts of the three nuclei attached to the  $\alpha$  carbon—for example, the two hydrogens and the carbon in 5.



However, the  $\beta$ -carbon shifts are suspect because of contact shifts, as mentioned earlier, while the  $\alpha$ -hydrogen shifts, despite their seeming favorability, simply do not provide a sharp indication of  $\theta$ . The reason is a fortuitous cancellation. It will be clear from Fig 3 that both  $\chi_i$  and  $r_i$  for these hydrogens will change rapidly as one changes  $\theta$ . The fact is, however, that when  $r_i$  is large,  $\chi_i$  is small, and when  $r_i$  is small,  $\chi_i$  is large. Amazingly, these effects with the  $(3 \cos^2 \chi_i - 1)/r_i^3$  dependence almost exactly cancel one another, as can be seen from Fig 6, which shows that the shifts of H and H' of 5 are virtually independent of  $\theta$ . This can have some other effects, as will be explained later.

If  $\theta$  has to be determined by lanthanide-induced shifts of atoms attached to other than C1, then, for conformationally mobile molecules, the added complexity is introduced of possible rotational isomerism about the C1-C2 (or other) bonds in the molecule. Finessing this problem for the moment, we might consider how well  $\theta$  can be determined from observed shifts. Assuming  $ROM = 2.5$ ,  $\angle COM = 129.5$ , and  $\phi = 0^\circ$ , we can plot the calculated shifts against  $\theta$ , and such a plot is shown in Fig 7. It will be seen that there are regions where the calculated shifts change dramatically with respect to one another, which should be very helpful in fixing  $\theta$ . Unfortunately, the value of  $\theta$  which corresponds to that obtained from CHMSHIFT (verti-

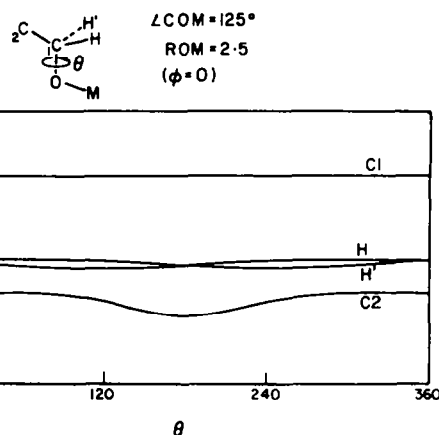


Fig 6. Variation of calculated dipolar shifts of C1, H, H' and C2 with  $\theta$  for a primary alcohol-lanthanide chelate complex.

cal line at  $276.4^\circ$  in Fig 7) comes in a region quite distressingly devoid of rapid changes in the calculated shifts. This is, in fact, not really surprising, no matter how disappointing it is. As mentioned earlier,  $\theta$  will assume values where the metal and bulky ligands will be away from bulky groups on the substrate and, indeed, generally oriented away from the substrate altogether. This will tend to make  $r_i$  large and  $\chi_i$  small, a situation which is hardly conducive to large changes in the calculated shifts with  $\theta$  or, as will be seen, for  $\angle COM$  and  $ROM$ .

These considerations raise serious questions as to how "hard" the fits of the five parameters are to the experimental values. In an attempt to clarify this situation, we have calculated for a specific set of isoborneol-chelate coordinates what the calculated lanthanide shifts should be and then determined the degree to which CHMSHIFT could converge on these parameters. One planned idiosyncrasy of CHMSHIFT, which makes this a more stringent test than it might otherwise be, is the fact that CHMSHIFT (unlike almost all other computer programs) never gives exactly the same answer with identical sets of input data. The reason for this is that CHMSHIFT changes each of the five parameters it uses to locate the metal and effective magnetic axis, back and forth, until it locates a maximum in the correlation coefficient between calculated and observed shifts. Successive cycles through the five parameters are carried on until convergence to 0.00001 in the correlation coefficient is achieved, or else, until a preset number of cycles (normally ten) has been explored. The feature which adds the flavor of experiment to the whole thing is that the order of varying the parameters in each cycle is determined by a sequence of random numbers which is generated by a sub-program controlled by a time-of-day clock in the computer.† Thus, there is virtually no chance of

\*Added in proof—See paper in this issue by S. J. Angyal which gives strong evidence for stereospecific proton contact shifts with polyols and lanthanide ions.

†This principle was previously used with substantial success in a Westheimer-Kirkwood type calculation of barriers to rotation about single bonds, J. D. Roberts, *Abstracts of 20th National Organic Chemistry Symposium of the American Chemical Society* pp. 64-86. Burlington, Vt., June (1967).

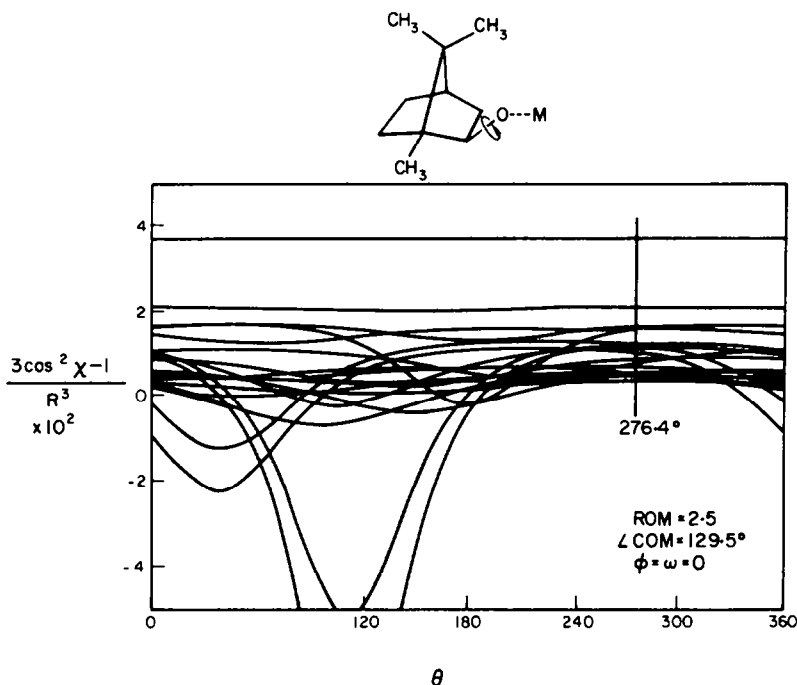


Fig 7. Calculated dipolar shifts for protons and carbons of isoborneol as a function of  $\theta$ .

obtaining the exact same sequence in the steps of the calculation. Clearly, the results of repetitive calculations provide an excellent measure of what might be termed the "softness" of parameters. The

results for the theoretical isoborneol shifts mentioned above are shown in Table 1.

Depending on one's point of view, Table 1 could provide evidence for either an optimistic or a pes-

Table 1. Test of CHMSHIFT on theoretical shifts for isoborneol

	ROM	$\angle$ COM	$\theta$	$\phi$	$\omega$	$A^\circ$	Corr. coeff.
Input <sup>b</sup>	2.50	129.5	276.4	0.0	0.0	1.0	—
Output							
Protons only <sup>c</sup>	3.25	121.6	275.4	2.7	349.3	0.76	0.99955
	2.13	137.2	279.5	0.5	294.0	1.09	0.99977
	2.18	135.7	279.2	0.4	285.0	1.08	0.99980
	3.04	123.4	276.2	1.8	350.2	0.82	0.99975
	2.80	125.9	276.0	0.9	342.0	0.90	0.99991
	2.61	126.4	276.9	(0.0) <sup>d</sup>	(0.0) <sup>d</sup>	1.08	0.99994
Protons and carbons <sup>e</sup>	2.52	128.7	276.4	0.1	345.0	0.99	0.99998
	2.47	132.2	271.7	0.5	79.5	1.00	0.99984 <sup>f</sup>
Average <sup>g</sup>	2.63	129.2	276.3	1.0	292.1	0.95	0.99982
	$\pm 0.29$	$\pm 4.1$	$\pm 1.8$	$\pm 0.6$	$\pm 65.9$	$\pm 0.08$	$\pm 0.00009$

<sup>a</sup>The slope of the least-squares line is  $A$  and the theoretical shifts were read in on the same scale as the calculated shifts produced by the program.

<sup>b</sup>The theoretical shifts correspond to the given parameters with the same geometric parameters of the atoms of isoborneol as used with CHMSHIFT.

<sup>c</sup>The theoretical carbon shifts were not used.

<sup>d</sup>The values of  $\phi$  and  $\omega$  in this run were restrained to remain 0.0 and the resulting parameters are not included in the averages.

<sup>e</sup>All protons and carbon shifts, save those of C1 and C2.

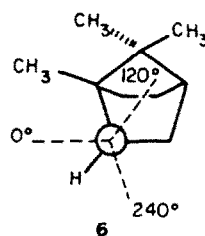
<sup>f</sup>Did not converge in ten cycles.

<sup>g</sup>With standard deviation from the mean.

simistic outlook. There is indeed a certain softness in the derived values, perhaps most surprising even in the slopes of the least-squares fits which correspond to excellent correlations. Some idea of the problems involved may be seen in Fig 8 which shows how with  $\theta = 276.4^\circ$  as in Fig 7, variations of the other parameters cause changes in the calculated shifts. For ROM and  $\angle$ COM, the shift of only one atom is seen to change markedly (the upper line) and this is C2 which can not be used in analysis of real cases because of the possibility of contact effects. The calculated shifts do change rather rapidly with respect to one another as  $\phi$  is varied, and this means that the finding of small  $\phi$  values can be regarded with some confidence.

As far as gaining conformational information is concerned, it is rewarding that the torsional angle  $\theta$  looks as if it can be determined within a few degrees. Clearly, there is a problem as to whether a  $\theta$  of  $276.4^\circ$  is a real or represents some sort of an average of the simple staggered conformations which would have  $\theta$  as  $0^\circ$  (*trans* to C3),  $120^\circ$  (*trans* to H2) and  $240^\circ$  (*trans* to C1). The possible arrangements are shown in 6, which is a projection of the isborneol molecule when viewed down the oxygen-C2 bond. The occurrence of the conformation with the  $120^\circ$  angle is unlikely on steric grounds because the lanthanide would be in very close proximity to the Me group *syn* to C2 (C8).

One thing is certain, the functions governing the calculated shifts are by no means sufficiently linear



or quasilinear to allow  $\theta = 276.4^\circ$  to be approximated by 30% of  $\theta = 0^\circ + 70\%$  of  $\theta = 240^\circ$ . Fig 9 shows that there is a very poor correlation between the calculated values for  $\theta = 276.4^\circ$  and the 30:70 mix of conformations with  $\theta = 0^\circ$  and  $\theta = 240^\circ$ . Another tack on this equilibrium problem is to see what happens when CHMSHIFT is fed calculated shifts corresponding to a mix of conformations and instructed to see if any single value of  $\theta$  will give a good fit. Obviously, this would not necessarily work well for all or even a few conformational mixes and, indeed, several tries with shifts calculated for the 30% of  $\theta = 0^\circ$  and 70% of  $\theta = 240^\circ$  gave uniformly poor results, as will be seen by comparing Table 2 with Table 1.

A third approach is to determine whether the shifts calculated for the best mix of conformations correlate better with the observed proton shifts than does the CHMSHIFT fit assuming a single  $\theta$  value. To do this, the following equations were used for isborneol, where  $f_1, f_2, f_3$  are mol frac-

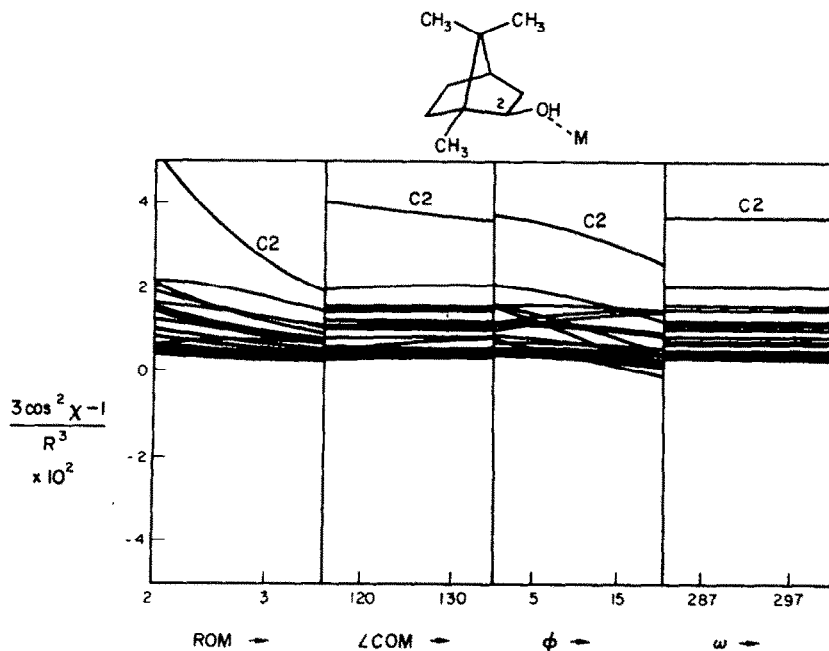


Fig 8. Calculated changes in  $(3 \cos^2 \chi - 1)/R^3$  for isborneol with variations of ROM,  $\angle$ COM,  $\phi$  and  $\omega$  over the indicated ranges with  $\theta = 276.4^\circ$ .

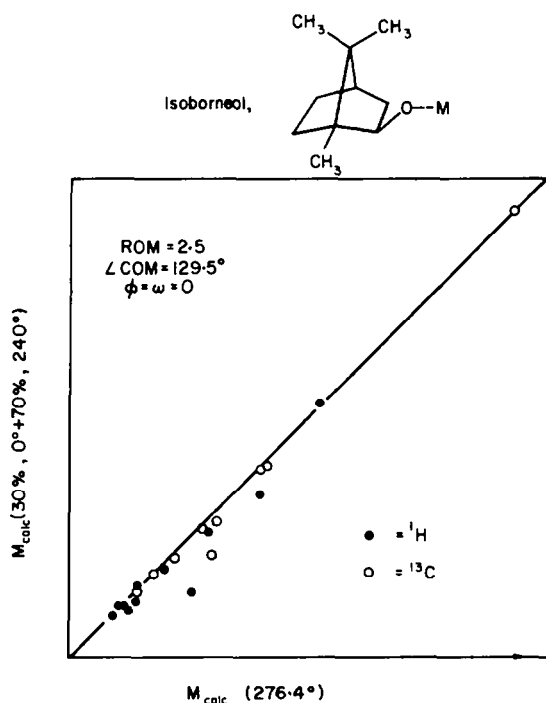


Fig 9. Plot of calculated proton and carbon shifts for isborneol assuming a single value of  $\theta = 276.4^\circ$ , and assuming a 30%–70% mix of conformations with  $\theta = 0^\circ$  and  $\theta = 240^\circ$ , respectively.

tions of conformations with  $\theta = 0^\circ$ ,  $120^\circ$  and  $240^\circ$ , respectively;  $m_1(i)$ ,  $m_2(i)$  and  $m_3(i)$  are the calculated shifts of atom  $i$  for the respective  $\theta$  values;  $m_0(i)$  are the experimental shifts, and  $C$  is a proportionality constant.

$$f_1 + f_2 + f_3 = 1 \quad (1)$$

$$m_0(i) = C[f_1 m_1(i) + f_2 m_2(i) + f_3 m_3(i)]. \quad (2)$$

The  $m_n(i)$  values were calculated for each conformation using ROM = 2.5 Å,  $\angle\text{COM} = 129.5^\circ$ , and  $\phi = \omega = 0.0$  on the assumption that the equilibrium

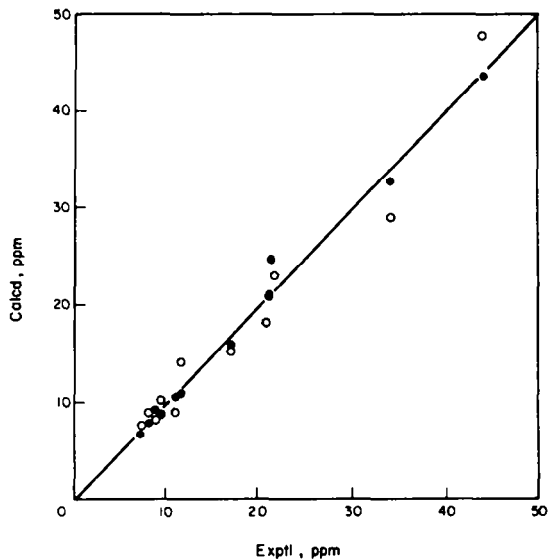


Fig 10. Plot of experimental  $\text{Pr}(\text{fod})_3$ -induced proton and carbon shifts of isborneol against calculated shifts, with a single value of  $\theta = 276.4^\circ$  (filled circles) and the shifts calculated on the basis of a regression analysis giving the best fit to a mix of three conformations with  $\theta = 0^\circ$ ,  $120^\circ$  and  $240^\circ$  (open circles). Carbons 1 and 2 were not included.

Table 2. Test of CHMSHIFT on theoretical shifts for a mixture of lanthanide–isborneol conformations

	ROM	$\angle\text{COM}$	$\theta$	$\phi$	$\omega$	$A^\circ$	Corr. coeff.
Input <sup>a</sup>	2.50	129.5	$0^\circ, 30\%$ $240^\circ, 70\%$	0.0	0.0	1.0	—
Output							
Protons only <sup>c</sup>	3.23	124.4	344.8	1.9	180.0	0.8	0.9851 <sup>f</sup>
	2.01	104.1	273.5	15.5	158.7	2.0	0.9849 <sup>f</sup>
Protons and carbons	3.12	128.3	338.8	0.5	123.0	0.8	0.9800 <sup>f</sup>
	2.50	129.9	330.6	4.1	221.4	1.1	0.9878 <sup>f</sup>

<sup>a</sup> The slope of the least-squares line is  $A$  and the theoretical shifts were read in on the same scale as the calculated shifts produced by the program.

<sup>b</sup> The theoretical shifts correspond to the given parameters with the same geometric parameters of the atoms of isborneol as used with CHMSHIFT.

<sup>c</sup> The theoretical carbon shifts were not used.

<sup>d</sup> The values of  $\phi$  and  $\omega$  in this run were restrained to remain  $0.0^\circ$  and the resulting parameters are not included in the averages.

<sup>e</sup> All protons and carbon shifts, save those of C1 and C2.

<sup>f</sup> Did not converge in ten cycles.

<sup>g</sup> With standard deviation from the mean.



constant for lanthanide-substrate complexing is the same for each conformation.

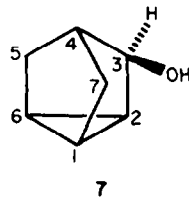
Linear regression analysis for  $C$ ,  $f_1$  and  $f_2$  gave values of  $f_1 = 0.162$ ,  $f_2 = 0.033$ ,  $f_3 = 0.805$  and  $C = 2.28 \times 10^{-3}$ . The correlation coefficient of calculated shifts from these values and the left-hand side of Eq (2) and the experimental values was 0.977 which can be compared to 0.999 for the CHMSHIFT fit with all of the parameters allowed to vary, and 0.999 for ROM = 2.5 Å,  $\angle\text{COM} = 129.5^\circ$ ,  $\theta = 276.4^\circ$  and  $\phi = \omega = 0.0^\circ$ . Fig 10 shows how the fit between observed and calculated shifts compares for the single value of theta and the mixture of three conformations with  $\phi = \omega = 0.0^\circ$  for all. It is interesting that the single value gives quite a bit better fit than is obtained from a mixture of conformations. This could be the result of choosing ROM and  $\angle\text{COM}$  for the conformations on the basis of the single  $\theta$  value fit obtained from CHMSHIFT, or could be because the ideal values of  $\theta$  for the perfectly staggered conformations are not quite correct. Both possibilities have been investigated.

In the first place, exploration over a grid of reasonable  $\angle\text{COM}$  and ROM values showed no combination of conformations with  $\theta = 0, 120$  and  $240^\circ$  which gave as good a correlation as obtained for the single value of  $276.4^\circ$ . Furthermore, a modified CHMSHIFT program, LANCON, was developed which searches for optimal  $\theta$  values and populations\* for three conformations on the basis of specified combinations of  $\angle\text{COM}$  and ROM with  $\phi = \omega = 0^\circ$ . Using the proton shifts alone and starting with  $\theta_1 = 0^\circ$ ,  $\theta_2 = 120^\circ$  and  $\theta_3 = 240^\circ$ , the program converged with correlation coefficients of 0.9940–0.9996 over the range of ROM = 2.5 to 3.25 Å and  $\angle\text{COM} = 120$ – $135^\circ$ . The significant point is that, for all cases, convergence came with predominance of a single conformation to the extent of > 96% within the range of  $259.9$ – $280.8^\circ$  depending on ROM and  $\angle\text{COM}$ . The larger values of  $\angle\text{COM}$  and ROM gave the smaller values of  $\theta$ .

The best LANCON fit with ROM = 2.75 Å and  $\angle\text{COM} = 125.0^\circ$  had a correlation coefficient of

0.9996 and corresponded to essentially 100% of a single conformation with  $\theta = 279.8^\circ$ . Including the carbon shifts, except for those of C1 and C2 where all evidence points to important contact shifts, the same ROM and  $\angle\text{COM}$  values gave the best fit with a correlation coefficient of 0.9988, a RMS deviation of the shifts = 0.51 ppm, and a R value<sup>8</sup> of 0.023. From all of this we conclude that for isoborneol, at least, the single value of  $\theta$  gives a better representation of the actual situation.†

Other less-hindered systems do not necessarily behave in the same way. Thus, application of CHMSHIFT to the  $\text{Pr}(\text{fod})_3$ -induced proton shifts of nortricyclanol (7) gives a reasonable fit with correlation coefficient of 0.9979 and  $\theta = 279.5^\circ$ , but



with  $\angle\text{COM} = 142.8^\circ$ , ROM = 3.49 Å and  $\phi = 2.6^\circ$ . These rather large  $\angle\text{COM}$  and ROM values may stem from the fact that the  $\alpha$ -H and  $\beta$ -C shifts are generally expected to be very nearly independent of  $\theta$  (Fig 6). Now, if there is a mix of conformations, the shifts of the  $\alpha$ -H's (and possibly even some  $\beta$  hydrogens<sup>13</sup>) will be quite constant for the several conformations, but this will not, in general, be true with the other protons which may, in fact, have wrong-way shifts if  $(3 \cos^2 \chi - 1)$  is negative. Contributions of such shifts or other abnormally small shifts resulting from a mix of conformations when CHMSHIFT is seeking a single optimum  $\theta$  value, can act to artificially lengthen ROM and increase  $\angle\text{COM}$  with the result of scaling down the calculated shifts of close-in nuclei relative to those more remote. Evidence for this is provided by a CHMSHIFT fit attempted on a set of calculated proton shifts for 7 assuming ROM = 2.7 Å,  $\angle\text{COM} = 130^\circ$ ,  $\phi = 0^\circ$ , and three equally populated conformations with  $\theta = 0^\circ, 120^\circ$  and  $240^\circ$ . A correlation coefficient of 0.9984 was achieved, but with  $\angle\text{COM} = 176.7^\circ$ , ROM = 3.46 Å,  $\theta = 303.5^\circ$ ,  $\phi = 21.1^\circ$  and  $\omega = 181.2^\circ$ . This is an extreme example, because the conformation with  $\theta = 120^\circ$  is calculated to have three rather large wrong-way proton shifts; however, the finding of large  $\angle\text{COM}$  and ROM values may reflect, besides contributions of contact shifts,‡ the occurrence of more than one important conformation.

A determined effort to ascertain the conformational equilibria with LANCON for 7 was not successful. The problem seems to be that a multiplicity of solutions are possible which differ only slightly in the degree of correlation they achieve, but rep-

\*The only restraints put on the operation of this program were to specify that  $f_1 + f_2 + f_3 = 1$ , and that  $f_n$  values less than -0.1 be rejected as unrealistic. There appear to be families of optimum solutions with one or more large negative  $f_n$  which do not seem physically realistic.

†Because of the possibility that the favored value of  $\theta$  might represent an average over a rather shallow energy minimum, an attempt was made to achieve a better correlation with LANCON by selecting initial  $\theta_1, \theta_2$  and  $\theta_3$  values more or less closely bracketing  $280^\circ$ . No fit nearly as good as that for  $280^\circ$  was found.

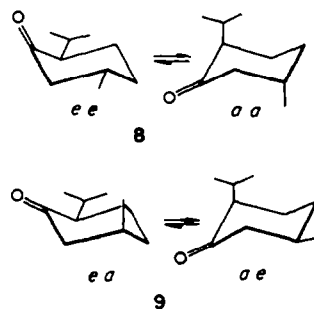
‡Contact shifts can lead to abnormally large (or small) calculated ROM and  $\angle\text{COM}$  values when they augment (or decrease) the dipolar shifts of close-in nuclei relative to those farther away. Increasing (or decreasing) the calculated values of ROM and  $\angle\text{COM}$  tends to correct the overall scale of shifts.

resent either one or two important conformations. The difference between 7 and isborneol in this respect arises from the isborneol Me groups attached to C1 and C7. The calculated shifts of these are especially sensitive to  $\theta$  and provide more definitive conformational information.

A problem arises in conjunction with these same methyl groups as to how the shifts of their hydrogens should be calculated. The simple way is to take an average position for all three hydrogens along an extension of the C-C bond, 0.364 Å beyond the methyl carbon. Alternatively, one can calculate the individual shifts of the hydrogens for the staggered positions of each Me group *vis a vis* its point of attachment and assume these are averaged by rapid Me rotation. These approaches are not equivalent, especially when the lanthanide atom is close to the Me group. Fig 11 shows the difference between the calculated shifts for the Me hydrogens of isborneol for the two procedures as a function of  $\theta$ . When  $\theta$  is 0° or 120°, the lanthanide is rather close to the Me attached to C1 or the *syn*-Me at C7. For this reason, we have used the individual hydrogen locations for staggered methyl conformations in the LANCON treatment.

Another approach to determination of conformational equilibration by lanthanide shifts is to study flexible chains fastened to a rigid core containing the coordination site. Angerman, Danyluk and Victor<sup>16</sup> as well as Willcott and Davis<sup>8</sup> have investigated this kind of system which has the advantage

of permitting the metal location to be established by a CHMSHIFT-type procedure using the shifts of the atoms in the rigid part of the molecule. In subsequent steps, the conformation of the flexible chain can be examined in light of the lanthanide shifts contained therein. Our work on this kind of system has involved the Yb(fod)<sub>3</sub>-induced proton and carbon shifts of methone (8) and isomethone (9)



which entails the additional problem of axial-equatorial equilibria.

Evidence has been presented for the importance of cyclohexanone conformations with a 2-*i*-Pr group axial.<sup>17</sup> However, although a CHMSHIFT analysis shows a better overall correlation for the proton shifts<sup>17</sup> of 9 with *i*-Pr axial (0.9995) than with the *i*-Pr equatorial (0.9920), the difference is not really compelling. It is important to know that these correlations omit the *i*-Pr shifts because of the con-

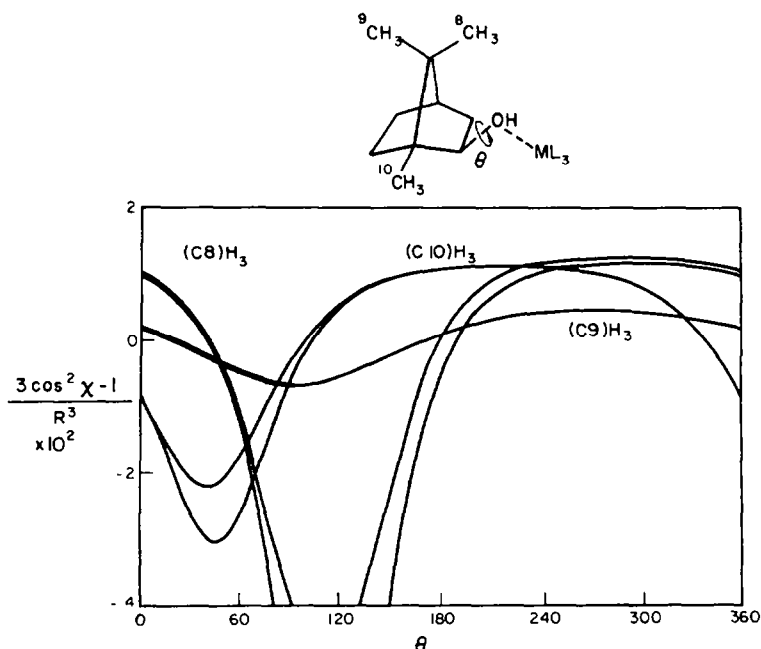
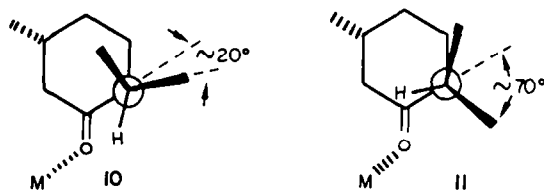


Fig 11. Plots of calculated shifts of isborneol methyl protons using a single average location of the three protons at a point 0.36 Å beyond the methyl carbon along the methyl C—C bond axis (upper line), or the averaged shifts assuming rapid rotation between staggered locations of the methyl protons (lower lines). Other parameters as in Fig 7.

formational uncertainty regarding this group. A modification of CHMSHIFT, designated as CHMSHIFT2, allows an initial fit on the shifts of the rigid part of the molecule to be followed by rotation of desired segments around a specified bond and determination of the optimum correlation of the shifts of the rotated atoms holding the lanthanide geometry constant. The way in which the shifts of the isopropyl atoms change with rotation for an axial i-Pr group is shown in Fig 12.

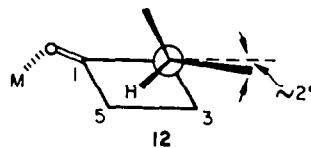
With menthone and CHMSHIFT2, the proton shifts of the nuclei in the rigid part of the molecule could be correlated almost equally well with the i-Pr axial (8 *a, a*) as equatorial (8, *e, e*). What was surprising was that the preliminary results indicate the i-Pr group shifts are fitted very much better with the i-Pr axial.\* With both 8 and 9, there is an ambiguity in the assignments of the shifts of the isopropyl Me protons and carbons. Unfortunately, either assignment leads to a satisfactory fit for the *a, a* arrangements which correspond to the projections 10 and 11 (where we look down on the axial i-Pr group along the C7-C2 bond). The Me's have rather comparable lanthanide shifts, and it will be seen how in 10 and 11, one of the other can be properly oriented with respect to the metal to have a slightly larger shift.

\*However, see V. M. Potapov, G. V. Kirushkina and A. P. Terent'ev, *Dokl. Akad. Nauk SSSR*, **189**, 338 (1969) who suggest from optical rotatory dispersion studies that, in nonpolar solvents, menthone itself may be substantially in the diaxial conformation.



For the *e, e* conformation, the ambiguity is less; either set of assignments to the Me shifts suggests approximately arrangement 12, although not with great confidence because the calculated shift of the isopropyl methine proton is too large.

For isomenthone, good CHMSHIFT2 correlations with rather sharp maxima can be obtained for the



conformation with axial i-Pr, but with the same ambiguity mentioned above and illustrated, for isomenthone, by 13 and 14. These positions correspond to larger differences between the shifts of the isopropyl Me group carbons and hydrogens than observed for menthone. Trials to determine whether 13 and 14 would better be represented as a mixture of i-Pr conformations with perfect, staggered geometries were inconclusive, there being no significant difference in correlation coefficient for either the single value of the torsional angle or of a mix of conformations.

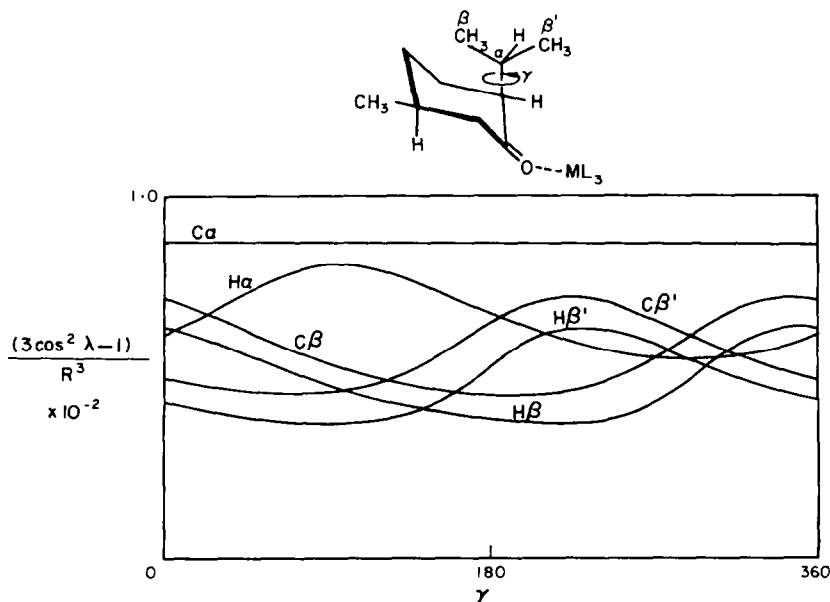
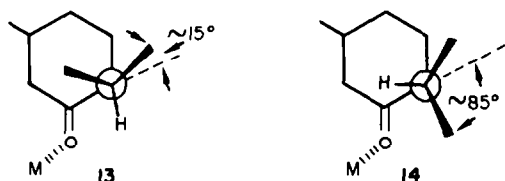


Fig 12. Plot showing sensitivity of the calculated dipolar shifts to magnitude of rotational angle for axial isopropyl group of isomenthone complexed with Yb(fod)<sub>3</sub>. The metal position was taken to be that calculated from the proton shifts of the protons not on the isopropyl group.



It should be clear from the foregoing that the use of lanthanide shifts to determine the fine details of conformational equilibria is by no means simple. Many of the results of the calculations are distressingly insensitive to variations in the quantities which are desired as final output. This is because the sterically preferred lanthanide-substrate geometries are such as to have the interesting atoms as far away as possible from metal, and because the calculated shifts of some of the close-in atoms change more slowly than might be expected qualitatively by fortuitous cancellations in the  $(3 \cos^2 \chi - 1)/r^3$  term. Another hazard is the possibility of multiple solutions which is illustrated here by the axial-equatorial conformational equilibrium of menthone and isomenthone and the torsional angle about the *i*-Pr group.

What can we conclude about the general value of computer analyses, as with CHMSHIFT, of lanthanide-induced NMR shifts? There seems no doubt from earlier studies that for problems involving geometrical isomerism, computer comparison of experimental shifts with the shifts calculated for alternative possible configurations are likely to be highly useful in making assignments even if the coordinates of the metal atom with respect to the substrate have to be treated as additional unknowns. Another helpful application is in assigning NMR resonances to particular atoms when most of the other resonances can be assigned by other means. By way of example, the lanthanide-induced shifts of the proton resonances of nortricyclanol (7) combined with CHMSHIFT gave a set of theoretical  $^{13}\text{C}$  shifts which were scaled and compared with the experimental shifts. Assignments are difficult because four of the seven carbon resonances arise from  $^{13}\text{C}$ -H carbons. In the particular case, only one set of assignments which would fit the calculated lanthanide shifts was possible, and this involved reversing earlier assignments of C1 and C6.

The question of the value of attempting to determine conformational equilibria by lanthanide-induced shifts is, as explained above, not as yet decisively answered. Clearly, more cases need to be studied, but the information obtained here, along with that previously reported, provides considerable optimism for additional research on the problem.

Added in proof—In a very recent paper, K. L. Williamson, D. R. Clutter, R. Emch, M. Alexander, A. E. Burroughs, C. Chua and M. E. Bogel, *J. Am. Chem. Soc.*, **96**, 1471 (1974), report very excellent correlations between

lanthanide shifts for protons and carbons corresponding to particular conformations of a large number of aliphatic alcohols. The analysis, however, did not consider some of the difficulties considered here and elsewhere.<sup>8</sup> As a result, the degree to which the conformational problems presented by the alcohols studied may be regarded as solved may well depend on one's faith in the infallibility of correlation coefficients when these are associated with basically "soft" functions.

**Acknowledgement**—We are pleased to acknowledge helpful suggestions from Professor John I. Brauman (Stanford University).

#### REFERENCES

- <sup>1</sup>Supported by the National Science Foundation and the Public Health Service, Research Grant GM-11072 from the Division of Medical Sciences
- <sup>2</sup>Contribution No. 4791
- <sup>3</sup>C. C. Hinckley, *J. Am. Chem. Soc.* **91**, 5160 (1969)
- <sup>4</sup>P. V. Demarco, T. K. Elzey, R. B. Lewis and E. Wenkert, *Ibid.* **92**, 5734, 5737 (1970)
- <sup>5</sup>*cf.* W. D. Horrocks, Jr., J. P. Sipe, III and J. R. Lubner, *J. Am. Chem. Soc.* **93**, 5258 (1971); W. D. Horrocks, Jr. and J. P. Sipe, III, *Ibid.* **93**, 6800 (1971); and J. Reuben, *Progress in Nuclear Magnetic Resonance Spectroscopy* (Edited by J. W. Emsley, J. Feeney and L. H. Sutcliffe) Vol. 8. Pergamon Press (1972) for reference and discussion
- <sup>6</sup>O. A. Gansow, P. A. Loeffler, R. E. Davis, M. R. Willcott and R. E. Lenkinski, *J. Am. Chem. Soc.* **95**, 3389 (1973); O. A. Gansow, P. A. Loeffler, R. E. Lenkinski, M. R. Willcott and R. E. Davis, *Ibid.* **95**, 3390 (1973)
- <sup>7</sup>G. E. Hawkes, D. Leibfritz, D. W. Roberts and J. D. Roberts, *Ibid.* **95**, 1659 (1973)
- <sup>8</sup>M. R. Willcott, III and R. E. Davis, *Nuclear Magnetic Resonance Shift Reagents* (Edited by R. A. Sievers) pp. 143 and 159 for references and discussion of various approaches to fitting proton and carbon shifts by the dipolar equation. Academic Press, New York (1973)
- <sup>9</sup>See *Nuclear Magnetic Resonance Shift Reagents* (Edited by R. E. Sievers) for references and discussion, especially pp. 1-10, 21-40, 227-244, 247-253, 283-300, 314-318, 341-347. Academic Press, New York (1973)
- <sup>10</sup>G. E. Hawkes, C. Marzin, S. R. Johns and J. D. Roberts, *J. Am. Chem. Soc.* **95**, 1661 (1973)
- <sup>11</sup>C. Marzin, D. Leibfritz, G. E. Hawkes and J. D. Roberts, *Proc. Nat. Acad. Sci. U.S.A.* **70**, 562 (1973)
- <sup>12</sup>S. R. Johns, R. A. Smith, G. E. Hawkes and J. D. Roberts, *Ibid.* **70**, 939 (1973)
- <sup>13</sup>G. E. Hawkes, C. Marzin, D. Leibfritz, S. R. Johns, K. Herwig, R. A. Cooper, D. W. Roberts and J. D. Roberts, *Nuclear Magnetic Resonance Shift Reagents* p. 129 (Edited by R. A. Sievers) Academic Press, New York (1973)
- <sup>14</sup>I. Morishima, K. Okada, T. Yonezawa and K. Goto, *J. Am. Chem. Soc.* **93**, 3922 (1971), and earlier papers cited
- <sup>15</sup>G. E. Hawkes, unpublished research at the University of Liverpool
- <sup>16</sup>N. S. Angerman, S. S. Danyluk and T. A. Victor, *J. Am. Chem. Soc.* **94**, 7137 (1972)
- <sup>17</sup>See discussion by W. D. Cotterill and M. J. T. Robinson, *Tetrahedron* **20**, 765, 775 (1964) and C. Djerassi, *Ibid.* **13** (1961). Lanthanide-shift studies of 2-isopropylcyclohexanone have also recently been reported by K. L. Servis and D. J. Bowler, *J. Am. Chem. Soc.* **95**, 3292 (1973)