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Limitations of Lanthanide Shift Reagents for Determination of Conformation of Nonrigid Molecules¹

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Abstract: Studies on the correlation of observed lanthanide-induced shifts (LIS) in the ^1H , ^{13}C , and ^{19}F NMR spectra with those calculated by application of the McConnell equation in order to determine configuration and conformation in solution have been made on two sets of diastereomeric compounds: **1**, **2**, **3** and **4**, **5**. This correlation method was applied to diastereomers **1** and **3** using LIS from all hydrogen and ^{13}C atoms in the molecule. These diastereomers differ in exo vs. endo configuration in the rigid portion of the molecule. No significant difference in calculated LIS for the correct vs. incorrect diastereomeric structures was noted when unit weights were used in determining the R values (a measure of the degree of correlation). However, when LIS values were weighted according to the inverse of the magnitude of the shift, a significant correlation with the correct configuration was found. Even then the magnitude of the difference was small considering the major stereochemical difference in the structures of **1** and **3**. Diastereomers **1** and **2** as well as **4** and **5**, which differ in configuration at the nonrigid portion of the molecule, showed no significant correlation of observed and simulated LIS with the correct diastereomer even when using inverse weights in determining the R values. These results indicate that extreme caution should be used in assigning configurations to nonrigid molecules based on this method and that, with the possible exception of very carefully selected examples, solution conformations derived from such studies are of dubious value at this time.

In 1969, Hinckley³ demonstrated that the addition of the dipyridine adduct of tris(2,2,6,6-tetramethyl-3,5-heptanedionate)europium(III), $\text{Eu}(\text{dpm})_3$, resulted in downfield shifts of the proton signals of cholesterol, which were proximal to the OH function. Following Hinckley's discovery, the literature flourished with reports further delineating this phenomenon and the application of it to chemical problems.

The lanthanide-induced shifts (LIS) arising from the

presence of a paramagnetic complex have been expressed as a sum of terms for contact and dipolar (or pseudocontact) interactions. The contact term is the result of the Fermi contact interaction.⁴ This is a "through-bond" interaction which takes place only if there is a finite probability of finding an unpaired electronic spin on the atomic s orbital of the nucleus being observed. The LIS resulting from dipolar interaction was first described in detail by McConnell and Robertson.⁵ Assuming

axial symmetry, it is described by the following equation:

$$\text{LIS} = C[3 \cos^2 \theta - 1/r^3] \quad (1)$$

where LIS is the lanthanide-induced shifts, r is the distance between the metal and the nucleus being observed, θ is the angle which the principal magnetic axis makes with a line drawn from the metal to the nucleus, and C is a proportionality constant for a given complex.

Briggs et al.,^{6,7} with their work on the rigid molecule borneol, were the first to attempt to fit LIS to eq 1. With the positions of all the atoms known and the magnetic axis assumed to be along the metal-oxygen bond, the only variable was the metal position. By varying the assumed metal position and comparing the calculated to the observed LIS for borneol, they found a position which gave a good correlation between the calculated and the observed shifts induced by $\text{Pr}(\text{dpm})_3$. Several other investigators⁶⁻¹⁴ also showed that, in rigid molecules, the form of the dipolar equation given in eq 1 served fairly well to account for the observed shifts.

Willcott and Davis¹⁵ then went further and used LIS to distinguish between two geometric possibilities in conformationally rigid substrates. In these and other early quantitative applications of lanthanide shift reagents (LSR), the LIS were used to locate the metal position using a rigid, known structure. Some measure of the correspondence of the observed vs. the calculated LIS was then employed to determine how satisfactory a physical model had been used as a basis for the calculations. These types of calculations have been reported to be useful in distinguishing between structural isomers in rigid molecules.¹⁵⁻²⁰

Barry, Williams et al.²¹⁻²³ were the first to apply quantitative calculations of LIS to conformationally flexible molecules. They used LIS to study the solution conformation of adenosine-5'-monophosphate (AMP) in deuterium oxide and in dimethyl sulfoxide in the presence of europium(III) ions (Eu_2O_3). Recently, many investigators have carried out studies involving the calculations of solution conformations consistent with LIS^{14,21-40} and most have indicated a high degree of success. It has been assumed that the correspondence between observed LIS and those calculated based on a conformational model is a valid criterion for equating the actual conformation of the molecule in solution with the conformational model. The analogy has been drawn between x-ray crystallography for determination of solution conformation.⁴¹

Unfortunately, there are no currently available methods for evaluating to what extent the LIS calculated conformations correspond to those of the actual molecules in solution (cf. also ref 42). The present investigation attempts to evaluate the confidence which can be placed on such solution conformational determinations made on partially flexible systems. The particular compounds (1-5) which served as the basis for these studies were chosen because they combined a rigid bicyclic moiety joined through rotatable ester bonds to the other half of the molecule. The rigid bicyclic portion could be used with some confidence to locate the position of the lanthanide; then the other half of the ester could be used for testing the ability of this method to determine the major conformational orientation of the ester bond and the relationship of the two halves of the molecule with respect to each other. Although the actual major conformation (or conformations) of these compounds in solution is not known, the results can be analyzed for the extent that one conformation is preferred over others, based on the simulation of the LIS using the McConnell-Robertson equation, and its reasonableness, based on physical models and chemical information.^{42,43} Furthermore, in the case of the three diastereomeric α -methoxy- α -trifluoromethylphenyl acetate esters (MTPA esters, compounds 1-3), extensive NMR configurational correlations have been made based on models for

the conformation in solution.^{44,45} These models would serve as an additional check on the conformations arrived at by the LIS method.

So the initial rationale of these studies was to prepare diastereomers 1, 2, and 3, determine their respective LIS, and then by application of the McConnell-Robertson equation to these data calculate the "solution conformation" of each diastereomer. A measure of the reliability of the method could be obtained by comparing how well the data for one diastereomer could be correlated with a conformation of the correct structure vs. one of the alternate incorrect diastereomeric structures.

The use of eq 1 to simulate the shift induced by lanthanides makes two assumptions: (1) that the shifts are due to dipolar interactions with no contribution from contact interactions; and (2) that a single stoichiometric species predominates in solution. A number of investigators^{20,42,46-51} have shown that the use of Yb(III) as the lanthanide minimized the amount of contact shift observed, thereby giving observed shifts which are in most cases primarily due to the dipolar term. For this reason, in the present investigation, the quantitative calculations are carried out with shifts induced by Yb(III). If the observed LIS are an average of two or more complex species in solution with different geometries, one geometric model may not give calculated LIS corresponding to the observed time-averaged LIS. Shapiro et al.,⁵²⁻⁵⁴ Armitage et al.,⁵⁵⁻⁵⁷ and Kelsey⁵⁸ have carried out analyses of the equilibria and stoichiometry of the LSR-substrate complexes. Their results at higher shift reagent to substrate molar ratios are best interpreted in terms of the presence of both 1:1 and 1:2 LSR-substrate complexes. To avoid complications resulting from two complexes in solution, LSR-substrate ratios below 0.4 have been used in these studies. Under these conditions, generally only one major complex should be involved. A test that this is indeed so is to determine the ratio of all the LIS at each LIS-substrate ratio with respect to the LIS of one standard nucleus (in the same molecule) at that LSR-substrate ratio. These shift ratios should remain constant over the range of LSR-substrate molar ratios being employed if only one complex is being observed. If two (or more) species are present a change in the LSR-substrate molar ratio should change the relative amounts of each species, thereby changing the ratios of the LIS to each other (unless of course both species had the same LIS).

Results

Compound 1. The LIS results for compound 1, 4-amino-2-[(*R*)- α -methoxy- α -trifluoromethylphenylacetyl]-1-(*S*)-4-(*R*)-isoborneol (Figure 1), will be discussed first. The data obtained for 1 in the presence of $\text{Yb}(\text{dpm})_3$ were analyzed for the presence of more than one species by dividing the shifts at each LSR-substrate molar ratio by the shift of C_8 at that molar ratio. The ratios that were obtained all varied by less than 1.5% for LSR-substrate ratios from 0.05 to 0.40. This confirms that the assumption of a single complex is valid under these conditions.

It was next shown that the complexation of $\text{Eu}(\text{dpm})_3$ with 1 was centered at least 99% at the primary amine.¹ This was determined by a competition experiment with two model compounds having an MTPA ester and a primary amine in two separate molecules. It can be seen from Dreiding models that the separation of the ester and methoxy moieties from the amine precludes any cooperative binding to the LSR. Since the LSR is binding to a site spatially separated from the freely rotating portion of the molecule, the binding of the LSR should have little effect on the solution conformation. Table I contains the LIS data obtained with $\text{Eu}(\text{dpm})_3$ and $\text{Yb}(\text{dpm})_3$ as well as the chemical shifts with no LSR present.

The lanthanide position and the direction of the magnetic axis were calculated using the program CHMSHIFT¹² and the

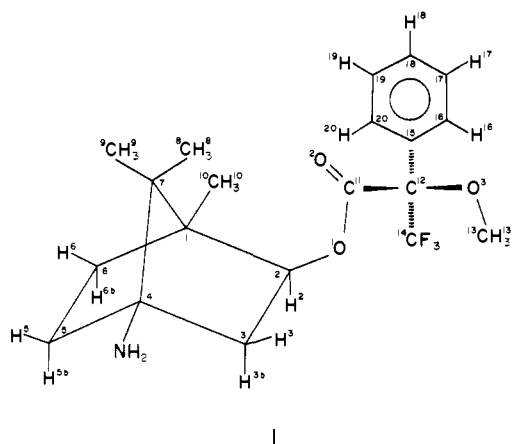


Figure 1. 4-Amino-2-[(*R*)- α -methoxy- α -trifluoromethyl- α -phenylacetyl]-1-(*S*)-4-(*R*)-isborneol (**1**).

Table I. Chemical Shifts for Compound **1** Alone and with LSR

Atom	Chemical ^a shift	LIS ^b with Eu(dpm) ₃	LIS ^b with Yb(dpm) ₃
C ₁ (s) ^c	49.32	11.76	35.32
C ₂ (d)	81.06	12.25	32.46
C ₃ (t)	44.69	25.12	73.87
C ₄ (s)	63.75	69.98	151.99
C ₅ (t)	34.07	27.47	76.79
C ₆ (t)	32.03	12.65	33.59
C ₇ (s)	47.27	-11.56	56.67
C ₈ (q) ^d	16.55	14.58	39.90
C ₉ (q) ^d	16.94	15.31	40.56
C ₁₀ (q)	12.66	4.81	18.12
C ₁₁ (s)	165.75	3.29	9.26
C ₁₃ (q)	55.14	1.21	3.06
C ₁₄ ^e	123.32	1.62	4.47
C ₁₅ (s)	132.38	1.56	3.91
C _{16,20} (d)	127.12	0.99	2.61
C _{17,19} (d)	128.11	0.35	0.92
C ₁₈ (d)	129.29	0.22	0.55
H ₂	4.96	6.97	19.86
H ₃		20.40 ^f	55.00 ^f
H _{3b}	2.13	19.20	52.00
H ₅		20.40 ^f	55.00 ^f
H _{5b}		20.40 ^f	55.00 ^f
H ₆		8.25	23.60
H _{6b}		7.17	20.50
H ₈ ^g	0.72	11.33	33.22
H ₉ ^g	0.70	11.62	33.93
H ₁₀	0.79	5.07	15.23
H ₁₃	3.53	1.09	2.90
H _{16,20}		1.21	3.12
H _{17,19}		0.01	-0.18
H ₁₈		0.05	-0.18
F	7.68	1.60	4.17

^a ¹H and ¹³C chemical shifts are in parts per million downfield from internal Me₄Si. ¹⁹F chemical shift is in parts per million downfield from external TFA. The sample was 0.65 M substrate in CDCl₃-2% Me₄Si. Atoms numbered as in Figure 1. ^b LIS calculated as discussed in Experimental Section. ^c ¹³C multiplicities are from the ¹H coupled spectrum (s = singlet, d = doublet, t = triplet, q = quartet). ^d The signals for C₈ and C₉ were never differentiated. ^e The signal for C₁₄ was a quartet due to coupling from fluorine (*J* = 289 Hz). There was no coupling due to protons. ^f These are only approximate values, since H₅, H_{5b}, and H₃ shifted as a broad lump. ^g The signals for H₈ and H₉ were never differentiated.

LIS of all hydrogen and ¹³C atoms in the rigid portion of the molecule. The weighted *R* value (*WR* value; cf. Experimental Section) for this position was 2.3% (*R* value, 1.9%; correlation coefficient, 0.9995), indicating very good agreement between

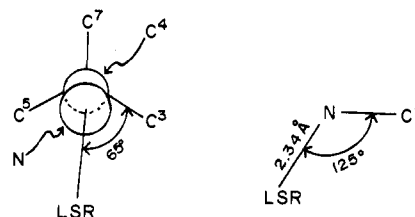


Figure 2. Lanthanide position obtained for **1**. LSR stands for lanthanide shift reagent.

Table II. Lanthanide Position Parameters^a Obtained from CHMSHIFT for Compound **1**

ROM	2.75 Å
ANGCOM	125.1°
THETA	245.0°
PHI	8.2°
XOMEGA	182.0°

^a ROM is the lanthanide-donor bond and ANGCOM is the angle between the lanthanide, nitrogen, and C₄. This value of 245° for THETA puts the lanthanide 5° out of trans coplanarity with the nitrogen, C₄, and C₇. PHI and XOMEGA are the two polar coordinates defining the direction of the magnetic axis with PHI being the deviation of the magnetic axis from colinearity with the metal-donor bond; see also ref 12.

the calculated and observed LIS. The metal position is shown in Figure 2 and the parameters given in Table II. Next the program MAXI (cf. Experimental Section) was used to determine which conformation gave the best calculated fit to the experimental data. The appropriate groups in the molecule were rotated around each of the three bonds between atoms C₂-O₁, O₁-C₁₁, and C₁₁-C₁₂ (cf. Figure 1; C₂-O₁ refers to the bond between carbon-2 and oxygen-1, etc.) in 30° increments (a total of 131 conformations). For this determination of the approximate calculated conformation, the LIS were included for atoms C₁₁, C₁₄, C₁₅, C₁₈, H₁₈, and F. The survey of all of these conformations showed that the *WR* value reached several minima. Therefore, when MAXI was used to minimize the *WR* value, it was run several times, starting near the different minima uncovered during the preliminary calculations. The *WR* value was minimized by rotating about five bonds, now including C₁₂-C₁₅ and C₁₂-O₃. The LIS of atoms affected by these two new bond rotations were also included, namely C₁₃, C₁₆, C₁₇, C₁₉, C₂₀, H₁₃, H₁₆, H₁₇, H₁₉, and H₂₀.

This use of the program MAXI gave three distinct minima for **1**, having *WR* values of 3.5, 3.7, and 4.5%. The three calculated conformations found were not slight variations of the same general conformation, but different from each other by significant rotations about all bonds (see Table III). Dreiding models showed that the three calculated conformations were all physically reasonable, i.e., there was no unreasonable steric crowding. Use of the Hamilton^{59,60} *R* value ratio test of significance showed that the three *WR* values were not statistically different. Therefore, it seems that the LIS study has not revealed much more concerning the solution conformation than could be surmised by observing the sterically uncrowded conformations of molecular models.

The next experiment was to use the observed LIS for **1**, but a model of compound **2** (Figure 3) for the calculated LIS. Compound **2** is a stereoisomer of **1** in which only the configuration at C₁₂ is reversed. The calculated conformation for a model of **2** using the observed LIS of **1** was determined in the same manner as for the calculated conformation of **1**. This time two minimum *WR* values, 4.4 and 4.5%, were found with quite different calculated conformations. Thus, one can correlate

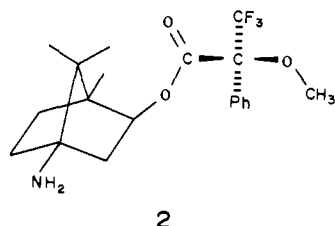


Figure 3. 4-Amino-2-[(*S*)- α -methoxy- α -trifluoromethyl- α -phenylacetyl]-1-(*S*)-4-(*R*)-isoborneol (**2**).

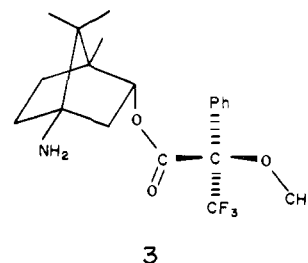


Figure 4. 4-Amino-2-[(*R*)- α -methoxy- α -trifluoromethyl- α -phenylacetyl]-1-(*S*)-4-(*R*)-borneol (**3**).

Table III. Dihedral Angles Defining the Calculated Conformations of Structures **1** and **2**

Bond ^a	Dihedral angle ^b of conformation giving <i>WR</i> value				
	Structure 1		Structure 2		
	3.5%	3.7%	4.5%	4.4%	4.5%
C ₃ -C ₂ -O ₁ -C ₁₁	159.4	154.4	128.4	171.1	155.8
C ₂ -O ₁ -C ₁₁ -C ₁₂	236.9	211.9	180.2	244.2	324.4
O ₁ -C ₁₁ -C ₁₂ -C ₁₅	321.6	352.9	39.8	100.9	220.9
C ₁₁ -C ₁₂ -C ₁₅ -C ₁₆	247.4	272.0	253.0	229.0	18.0
C ₁₁ -C ₁₂ -O ₃ -C ₁₃	51.9	7.9	60.0	358.6	113.0

^a Atom numbers refer to Figure 1. "O₁" refers to oxygen-1 and "O₃" refers to oxygen-3. ^b The four atoms define the four-member chain whose dihedral angle is given. The middle two atoms define the bond being rotated. By standard convention, a dihedral angle is positive in sign when the fourth atom is torsionally displaced clockwise from the first by the absolute value of the angle (in degrees) and negative when counterclockwise (while looking down the bond such that the first atom is nearer to the observer).

the LIS observed for **1** with the calculated LIS based on the wrong diastereomeric structure **2**, with only slightly poorer *WR* values (two conformational minima, *WR* = 4.4 and 4.5%) than for the structure of the correct diastereomer **1** (three conformational minima, *WR* values 3.5, 3.7, and 4.5%). These differences are not large enough so that one could place any confidence in a configurational assignment based on this method.

Compound **2** was synthesized and its LIS experimentally determined in the presence of Yb(dpm)₃. Although the LIS for the rigid bicyclic portion of the molecule were almost identical with those for **1**, those for the atoms in the flexible portion of the molecule varied by an average of approximately 25% (Table IV). Therefore, the reason for the inability of the LIS method to discriminate effectively between these two diastereomeric structures was *not* that they had very similar LIS. It appears that this LIS-structure correlation method as reported here is not sensitive enough to discern the difference between stereoisomeric structures such as **1** and **2**. The reason for this is not revealed by these studies.

The stereochemical difference between diastereomers **1** and **2** lies in the nonrigid portion of their structures; namely, they are epimeric at the α position of the acid moiety. Because of the possibility of free rotation at this α position, the resulting NMR differences are more subtle than if the stereochemical variation had been of the *cis*-*trans* type in the rigid portion of the structure. Therefore, a study was made of compound **3** (Figure 4), the borneol vs. isoborneol diastereomer of **1** which is epimeric at C₂ (*exo* vs. *endo*). Thus, a comparison of the observed LIS of **1** with the simulated LIS of diastereomers **1**, **2**, and **3** should give added basis for evaluating the utility of this technique for calculating "solution conformations".

Table IV. Observed LIS for Compound **2**

Atom ^a	LIS ^b	Atom ^a	LIS ^b
C ₁	35.34	C ₁₈	1.85
C ₂	32.45	H ₂	19.60
C ₃	73.23	H ₃	54.60
C ₄	152.67	H _{3b}	51.40
C ₅	77.84	H ₅	54.60
C ₆	33.87	H _{5b}	54.60
C ₇	56.93	H ₆	23.32
C ₈	39.94	H _{6b}	20.49
C ₉	40.88	H ₈	32.63
C ₁₀	18.20	H ₉	33.55
C ₁₁	9.21	H ₁₀	15.21
C ₁₃	2.24	H ₁₃	1.96
C ₁₄	4.41	H _{16,20}	3.82
C ₁₅	4.61	H _{17,19}	1.23
C _{16,20}	3.68	H ₁₈	1.23
C _{17,19}	2.23	F	4.18

^a Compound **2** is numbered the same as **1**, Figure 1. ^b These are the observed LIS obtained as discussed in the Experimental Section.

Using the experimentally determined LIS of **1**, an attempt was made to fit the data to some conformation of the wrong diastereomer **3**. The conformation was calculated in the same manner as previously outlined. The lanthanide position found for the rigid portion of the molecule gave a *WR* value of 2.9% (*R* value, 2.2%; correlation coefficient, 0.9993). The program MAXI was then used to minimize the *WR* value by rotating around five bonds, as was done on the earlier compounds. The minimum *WR* value obtained was 5.3% (*R* value, 2.4%; correlation coefficient, 0.9995). The statistics for the conformations calculated for structures **1**, **2**, and **3** are given in Table V.

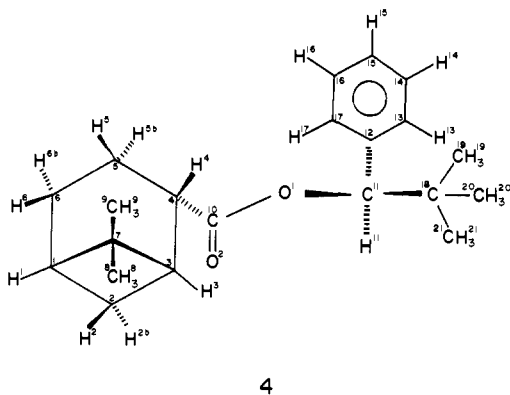
According to the Hamilton^{59,60} *R* value ratio tests for significance, the difference between the *WR* values of 3.5 and 5.3% is statistically significant at approximately the 99% confidence level. Therefore, the stereochemical change represented by the difference between structures **1** and **3**, namely *endo* vs. *exo*, is discernible by this technique. Nonetheless, the difference in *WR* values is small, considering the major difference in these structures, and one would not be completely confident of a structural assignment based on a difference of this magnitude. It should be emphasized that using the regular unit weight *R* values, only a 90% confidence level was attained. Thus the use of weighted *R* values appears to contribute a significant improvement in this method.

Compound 4. The fourth compound studied during this investigation was (*R*)-phenyl-*tert*-butylcarbonyl *trans*-myrtaenoate (**4**) (Figure 5). The LIS for all hydrogen and ¹³C atoms were determined in the presence of Yb(fod)₃ [tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium(III)] along with the chemical shifts in the absence of any LSR. These data are summarized in Table VI. The LIS data were first checked to see if one predominant lanthanide-substrate

Table V. Statistics for Calculated Conformations of Compounds **1**, **2**, and **3**

	1^a			2^b		3^c
Correlation coefficient	0.99964	0.99964	0.99962	0.99959	0.99961	0.99953
<i>R</i> value, %	2.11	2.10	2.17	2.23	2.18	2.41
<i>WR</i> value, ^d %	3.47	3.69	4.49	4.39	4.49	5.31

^a These are the values for the three calculated conformations found for structure **1** (Figure 1). ^b These are the values for the two calculated conformations found for structure **2** (Figure 3). ^c These are the values for the calculated conformation found for structure **3** (Figure 4). ^d See Experimental Section for the method of determining weighted *R* values (*WR* values).

**Figure 5.** (*R*)-Phenyl-*tert*-butylcarbinyl *trans*-myrtanoate (**4**).

complex was being observed. Dividing the observed LIS at each molar ratio by the shift of C₃ at that molar ratio gave numbers which varied by less than 2% for LSR-substrate ratios from 0.02 to 0.35, thus indicating one predominant LIS-substrate species in solution.

The same approach was used to calculate the conformation of **4** which best simulated the observed LIS as was used for **1**. The lanthanide position and the direction of the magnetic axis were arrived at using the program CHMSHIFT, with the LIS of the atoms in the rigid portion of the molecule. The minimum *WR* value obtained was 6.8% (*R* value = 2.5%), indicating that the calculated LIS for these atoms were in fairly good agreement with the observed values. Next, using this position for the lanthanide and the LIS for all of the carbon and hydrogen atoms in the molecule, the program MAXI was used to minimize the *WR* value by rotating about all four freely rotatable bonds, namely, C₄-C₁₀, C₁₀-O₁, O₁-C₁₁, and C₁₁-C₁₂ (cf. Figure 5). Then, using this best conformation, the program CHMSHIFT was used again to relocate the lanthanide and the direction of the magnetic axis, still using all 30 LIS. Using this new lanthanide position, the program MAXI was used to minimize the *WR* value by rotating about the four bonds again. At this point the lanthanide position and conformation had converged to their best values in terms of simulating the observed LIS (*WR* value, 15.7%; *R* value, 9.3%; correlation coefficient, 0.991).

The final lanthanide position (Table VII) and conformation (Table VIII) seemed reasonable. The lanthanide was centered 2.3 Å from the carbonyl oxygen and the conformation seemed to have a minimum of steric interactions, as seen from Dreiding models. The direction of the magnetic axis deviates only 11° from a line drawn between the carbonyl oxygen and the lanthanide. This seems to reinforce the calculated conformation found, since the magnetic axis was in no way constrained to be directed toward the carbonyl oxygen and the carbonyl group was free to rotate. Whether or not the calculated solution conformation has any basis in reality is moot, but it does appear to be physically reasonable.

The next test was to determine whether or not this method could distinguish between two diastereomeric myrtanoate

Table VI. Chemical Shifts and LIS of Atoms in Compound **4**

Atom ^a	Chemical shift, δ ^b	LIS ^c
C ₁	40.10 (d) ^d	9.24
C ₂	24.34 (t)	16.01
C ₃	43.53 (d)	25.47
C ₄	41.67 (d)	56.32
C ₅	16.98 (t)	27.87
C ₆	23.93 (t)	9.98
C ₇	38.99 (s)	8.26
C ₈	26.53 (q)	1.93
C ₉	20.28 (q)	1.59
C ₁₀	174.73 (s)	134.6
C ₁₁	82.24 (d)	54.50
C ₁₂	138.47 (s)	30.04
C _{13,17}	127.48 (d)	16.47
C _{14,16}	127.28 (d)	4.58
C ₁₅	127.12 (d)	2.60
C ₁₈	35.10 (s)	23.78
C _{19,20,21}	26.09 (q)	15.68
H ₁		4.88
H ₂		7.87
H _{2b}		19.72
H ₃	2.21	22.99
H ₄	2.96	37.30
H ₅		16.08
H _{5b}	2.13	32.43
H ₆		4.88
H _{6b}		6.68
H ₈	1.25	0.74
H ₉	0.89	-0.29
H ₁₁	5.51	72.16
H _{13,17}	7.25	14.63
H _{14,16}	7.25	0.06
H ₁₅	7.25	-1.10
H _{19,20,21}	0.92	13.74

^a Atom numbers refer to Figure 5. ^b Chemical shift in parts per million downfield from internal TMS Me₄Si in CDCl₃ with no LSR present. ^c LIS in the presence of Yb(fod)₃ determined as discussed in Experimental Section. ^d Multiplicities are from the ¹H coupled spectrum (s = singlet, d = doublet, t = triplet, q = quartet).

esters prepared from (*R*)-(-)- and (*S*)-(+)-phenyl-*tert*-butylcarbinol. This was done by the same procedure used in studying compound **1**, namely, trying to find a conformation for the ester from the (*S*)-(-) alcohol **5**, which would give calculated LIS which correspond to the observed LIS for the alternate diastereomer **4**.

The best calculated conformation and metal position for structure **5** (Figure 6) gave a *WR* value of 15.9% (*R* value, 10.9%; correlation coefficient, 0.988), which is essentially the same as that found for **4** (*WR* value, 15.7%). Thus this method cannot distinguish between diastereomers **4** and **5**. Again, the possible explanation that both diastereomers indeed have similar observed LIS was inapplicable, since the LIS for the protons for compounds **4** and **5** differ by an average of approximately 17%. One could calculate the LIS for two or more conformations and assign them weighted averages in order to

Table VII. Lanthanide Position Parameters^a Obtained from CHMSHIFT for Compound **4**

ROM	2.34 Å
ANGCOM	121.7°
THETA	253.6°
PHI	11.0°

^a ROM is the lanthanide-donor (O₁) bond length and ANGCOM is the angle between the lanthanide, O₁, and C₁₀. This value of 253.6° for THETA puts the lanthanide 73.6° out of trans coplanarity with O₁, C₁₀, and C₄. PHI is the deviation of the magnetic axis from collinearity with the lanthanide-donor bond; see also ref 12. The actual calculations used C₁₀ as the origin and these parameters were determined only for reference.

Table VIII. Dihedral Angles of Bonds in the Final Conformations of Compounds **4** and **5**

Bond ^a	Dihedral angle, ^b deg	
	4	5
C ₃ -C ₄ -C ₁₀ -O ₁	96.5	97.6
C ₄ -C ₁₀ -O ₁ -C ₁₁	139.0	143.6
C ₁₀ -O ₁ -C ₁₁ -H ₁₁	-11.3	16.8
O ₁ -C ₁₁ -C ₁₂ -C ₁₃	92.9	75.8

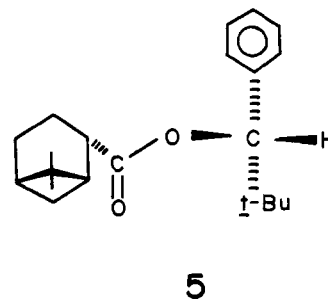
^a Atom numbers refer to Figure 5. "O₁" refers to oxygen-1. ^b Angle in degrees as defined in Table III.

try to describe the real situation. However, adding new variables would only make the system less well defined. In summary, one set of observed LIS was used to find calculated solution conformations for two diastereomers **4** and **5**. Neither gave a statistically better fit than the other and both calculated conformations were physically reasonable.

Conclusions

The correlation of observed LIS with calculated values simulated by application of the McConnell equation (eq 1) has been studied in two sets of diastereomers. In the case of diastereomers **1** and **3**, the correlation of the observed with the calculated LIS based on the best fit to some conformation of the known correct structure was slightly better than the fit based on the wrong diastereomeric structure **3** when inverse weights were used in the *R* value calculation (cf. Experimental Section). This difference was much less significant when unit weights were used to calculate the *R* values. Diastereomers **1** and **3**, which were being compared, were epimeric in the rigid portion of the molecule and bore an *exo*-*endo* relationship to each other. In view of the major stereochemical difference between **1** and **3**, the rather marginal difference in the correlation of observed and simulated LIS values is anything but impressive.

Furthermore, by this method the observed LIS of **1** could be correlated almost as well with calculated LIS derived from either the correct structure **1** or incorrect diastereomeric structure **2**. These diastereomers are epimeric at the α carbon in the freely rotating acid moiety of the ester rather than in the rigid portion of the molecule. Clearly this LIS method cannot be relied upon to distinguish between these two diastereomers. This LIS method also failed to discriminate between structures **4** and **5**, which are epimeric in the freely rotating portion of the molecule. This lack of ability to discriminate between structures **1** and **2** or **4** and **5** was not a result of indistinguishable LIS, which were found to be quite distinct. These results reinforce the conclusion that this use of LIS in its present state of refinement generally *cannot* be relied upon to discriminate between such diastereomers, which differ in configuration in

**Figure 6.** (*S*)-Phenyl-*tert*-butylcarbonyl *trans*-myrtanoate (**5**).

the freely rotating portion of the structure. Furthermore, the marginal ability of this method to discriminate between diastereomers **1** and **3**, which differ in *endo*-*exo* configuration in the rigid portion of the molecule, indicates that great caution should be exercised in applying this method to such cases.

This study did not give a direct answer to the reliability of the LIS technique for the determination of solution conformations. However, the severe limitations of this method for discriminating between the *configuration* of diastereomeric structures indicate that at this time not much reliance can be placed on it for use in determining the predominant solution conformation of molecules except in special cases. This is reinforced by the finding that the observed data for **1** could be simulated satisfactorily by three conformations and that of **2** by two conformations. These conformations were not slight variations, but differed in bond rotations from 20 to 120°. There may be carefully selected cases where this method will be of value in determining solution conformations where one is trying to discriminate between two very different conformations, but the results should be analyzed with caution. These conclusions appear to contrast with the optimistic evaluations suggested by others.^{14,21-23,38,40,41,64}

Experimental Section

Materials for NMR Studies. The organic compounds used in these studies had the correct analyses. They were synthesized and their configurations were determined by known methods.¹ The details will be published elsewhere.

Eu(fod)₃ was purchased from Ventron Co. and sublimed at 150 °C (0.001 mm) before use. Yb(fod)₃ was purchased from Willow Brook Labs, Inc., and sublimed at 110 °C (0.001 mm). Eu(dpm)₃ and Yb(dpm)₃ were purchased from Willow Brook Labs, Inc., and sublimed at 155 °C (0.01 mm). After sublimation, all LSR were stored over P₂O₅ at 60 °C (0.1 mm) prior to use.

The CDCl₃ used in the NMR studies was washed twice with a saturated solution of NaHCO₃, once with H₂O, dried over Na₂SO₄ (4 h), and distilled. The first one-fourth of the distillate was not used and the remainder stored over 3A molecular sieves for at least 24 h prior to use. The tetramethylsilane (Me₄Si) used was washed once with concentrated H₂SO₄, once with H₂O, twice with a saturated solution of NaHCO₃, once with H₂O, dried over Na₂SO₄ (4 h), and distilled. The first one-fourth of the distillate was not used and the middle one-half collected and stored over 3A molecular sieves before use. The NMR sample tubes used were dried at 110 °C for 2 days prior to use.

NMR Studies in the Presence of LSR. The NMR experiments were carried out using the dilution method of Shapiro et al.,^{52,53} keeping the substrate concentration constant and varying the LSR concentration. Stock solutions were prepared by weighing the substrate into a volumetric flask, which was then filled with CDCl₃-2% Me₄Si. The initial samples were prepared by weighing into an NMR sample tube the substrate and enough LSR to give the maximum molar ratio desired. The tube was then filled with CDCl₃-2% Me₄Si to a mark, giving 0.25 ml of solution. Subsequent molar ratios were obtained by adding aliquots of the stock solution to the NMR tube. The amount added was determined gravimetrically. The ¹³C, ¹H, and ¹⁹F NMR spectra were run on each sample before proceeding to the next molar ratio. This was done to obtain the ¹³C, ¹H, and ¹⁹F data on exactly the

same samples to avoid the errors involved in preparing two separate samples for determinations on the different nuclei.

All spectra were run on a Varian XL-100 NMR spectrometer⁶¹ in 5-mm sample tubes at 32 ± 2 °C. The samples used to carry out the NMR studies on **4** and **5** with Yb(fod)₃ were 1.0 M in substrate and involved molar ratios (LSR–substrate) up to 0.36. The samples used for the studies on **1** and **2** with Yb(dpm)₃ were 0.65 M in substrate and involved molar ratios up to 0.40.

Determination of LIS. The LIS used for the quantitative calculations in this study were the slopes of the chemical shifts vs. the molar ratios (LSR–substrate) at molar ratios of 0.4 and lower (including the chemical shifts with no LSR present). A linear least-squares analysis⁶² was carried out to determine the best straight line through each set of data. The slope from this least-squares line was then used as the LIS. Due to the definition of “slope”, these LIS represent the changes in chemical shifts extrapolated to a molar ratio of 1.0. The numbers are not, however, intended to represent “bound chemical shifts”, “limiting chemical shifts”, nor any prediction of what the total change in chemical shifts would be at a molar ratio of 1.0. The standard deviation of the slope from the least-squares analysis was used as the standard deviation of the LIS. The correlation coefficients for the least-squares lines were greater than 0.999 in all cases, except where the induced shifts were small enough so that errors in line position determination were significant.

Computation Model. The method used here determines a single metal position and a single molecular conformation which gives calculated LIS from eq 1 which best agree with the observed LIS. The position of the methyl protons is assumed to be a point at the average position. The method involves first locating the position of the lanthanide and the direction of the magnetic axis using the computer program CHMSHIFT¹² (modified to minimize the weighted *R* value; see below) and the LIS of the atoms whose positions are rigid and known. This leaves only the variables defining the lanthanide position and the direction of the magnetic axis. Once the position of the lanthanide is known, the conformation of the flexible portion of the molecule is varied using the computer program MAXI (see below) and the LIS of all of the atoms. After determining the conformation which gives the best calculated LIS for all of the atoms in the molecule, it is sometimes desirable to use CHMSHIFT again to find a new lanthanide position, this time using the conformation found and the LIS of all of the atoms. If the position of the lanthanide has changed significantly, then MAXI can be used again with this new lanthanide position. The lanthanide position and conformation obtained in this manner are assumed to be the best in terms of reproducing the observed LIS.

The Computer Program MAXI. The computer program MAXI was developed by the author to vary the conformation of a molecule to determine which single conformation gives the best calculated LIS. The program requires a preset metal position (usually obtained from CHMSHIFT), an initial set of coordinates for the molecule, and the observed LIS. The conformation is varied by rotation about single bonds specified by the user. It can be run in two modes. The first is “brute force”, where the molecule is taken through all possible conformations within the limits preset by the user. The second mode starts with the input rotation values and optimizes by the method of steepest descent. In practice, it is usually best to survey all of the possible conformations by rotating about all of the freely rotating bonds by 360° in 30° increments. Then the optimization mode can be started with approximately the best conformation (± 20 – 30°).

Weighting Scheme for LIS. Both CHMSHIFT and MAXI were run such that the weighted *R* value was minimized. The weight assigned to each LIS was the inverse of the magnitude of the shift, except for shifts below 3.0 where an upper limit of 0.33 was set on the weights. Unit weights were not used because they tend to discriminate against smaller shifts. This can be easily demonstrated with the equation for calculating *R* values.^{59,60}

$$R = [\sum(\text{expt LIS} - \text{calcd LIS})^2 / \sum(\text{expt LIS})^2]^{1/2}$$

Note that the following two sets of calculated LIS will have exactly the same influence on the *R* value.

Experimental: expt LIS₁ = 4.0 expt LIS₂ = 40.0

Situation 1: calcd LIS₁ = 4.5 calcd LIS₂ = 45.0

Situation 2: calcd LIS₁ = 9.0 calcd LIS₂ = 40.5

Situation 1 is clearly more desirable than 2, yet the unit weight *R* value cannot tell them apart. The weighting scheme was therefore set up to help remedy this discrimination. This type of weighting scheme is not without precedent.⁶³ In x-ray crystallography, the weight used is $1/\sigma^2$, where $\sigma = (F_{\text{obsd}})^{1/2}$ and F_{obsd} is the magnitude of the observed reflection. In effect, the weight is the inverse of the absolute magnitude of the reflection's intensity.

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- (62) P. R. Bevington, "Data Reduction and Error Analysis for the Physical Sciences", McGraw-Hill, New York, N.Y., 1969, Chapter 6.
- (63) G. A. Stout and L. H. Jensen, "X-ray Structure Determination", Macmillan, New York, N.Y., 1968, p 454.
- (64) NOTE ADDED IN PROOF: It has been reported that LIS could be used to quantitatively determine the solution equilibrium of conformers in the conformationally mobile *cis*-8-oxabicyclo[4.3.0]non-3-ene series. However, if one reevaluates the Hamilton *R* value ratio statistics test using the correct number of observations, it can be seen that virtually any ratio of conformers gives calculated LIS which are within reasonable statistical limits of the observed LIS. D. J. Bennett, A. C. Craig, B. P. Mundy, G. W. Dirks, and K. B. Lipkowitz, *J. Org. Chem.*, **41**, 469 (1976).

Conformational Analysis of Carbocyanine Dyes with Variable-Temperature Proton Fourier Transform Nuclear Magnetic Resonance Spectroscopy

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Abstract: The conformational properties of a series of meso-substituted carbocyanine dyes have been investigated by means of variable-temperature proton Fourier transform NMR spectroscopy. At equilibrium, the dyes in acetone-*d*₆ exist in varying proportions of two conformations differing in geometry about one of the 8-9 bonds in the connecting chain. The *cis* conformation is favored by meso substitution, the free-energy differences being 0.42 ± 0.1 (-9°C), 0.65 ± 0.2 (-26°C), and 0.70 ± 0.2 kcal/mol (-28°C), respectively, for 3,3'-diethyl-9-methyloxacarbocyanine perfluorobutyrate, 3,3',9-triethylthiacarbocyanine perfluorobutyrate, and 3,3'-diethyl-9-methylselenacarbocyanine perfluorobutyrate, with estimated errors indicated. The free energies of activation for conversion of the *cis* into the *trans* forms of the above three dyes were 14.6 ± 0.1 (12°C), 12.6 ± 0.1 (-32°C), and 12.2 ± 0.2 kcal/mol (-28°C), respectively. For the sulfur- and selenium-containing dyes, exchange of the nonequivalent protons on the connecting chain occurred rapidly by means of a path not involving the *trans* conformation as an intermediate. The very strained di-*cis* conformation, which is *cis* at both bonds 8-9 and 8-9' in the connecting chain, is proposed as an alternative intermediate. The free-energy barriers for conversion of the *cis* into the di-*cis* conformation are 8.4 ± 0.2 (-103°C) and 8.0 ± 0.3 kcal/mol (-103°C) for the sulfur- and selenium-containing dyes. The barrier is raised to 14.7 ± 0.1 kcal/mol (12°C) for the oxygen-containing dye. A phenyl group is an effectively smaller substituent in 3,3'-diethyl-9-phenylthiacarbocyanine perfluorobutyrate than are the alkyl groups in the other dyes, the free-energy difference between the *cis* and *trans* conformations being 1.00 ± 0.30 kcal/mol (-27°C). The free-energy barrier for the *cis* to di-*cis* process is much greater for the phenyl-substituted dye than for the other compounds. It is apparently larger even than the barrier for the *cis* to *trans* exchange of 13.8 ± 0.5 kcal/mol (-5°C) and, thus, cannot be determined accurately. Correspondingly, very bulky meso substituents lower the barrier for conversion of the *cis* into the di-*cis* form through an increase of the energy of the ground-state conformations. The low barrier for 3,3'-dimethyl-9-*tert*-butylthiacarbocyanine perchlorate results in its having a temperature-independent NMR spectrum between 35 and -100°C .

Cyanine dyes play an important role in the photographic process by sensitizing the silver halide emulsion to appropriate wavelengths of light.¹ In the simplest sense, any compound with the general structure I may be considered a cyanine, but the photographically important materials are terminated with heterocyclic rings as in II. Those dyes, such as II, containing a three-carbon bridge, are referred to as carbocyanines.

Space-filling models indicate that steric interactions are minimized in the extended or "all-*trans*" conformation of unsubstituted carbocyanine dyes and x-ray crystallography has shown 3,3'-diethylthiacarbocyanine (IIa) to be in the all-*trans* conformation in the solid state.² A general discussion of the relative stability of the various conformations of carbocyanine dyes has been given by West, Pearce, and Grum.³ Dyes

substituted in the 9-position show steric interaction of the substituent with the two heteroatoms in the "all-*trans*" (or simply *trans*) conformation. The interaction with one of the heteroatoms is removed by conversion of the dye into the "mono-*cis*" (or simply *cis*) conformation, although it is replaced by crowding involving the 8-proton. Carbocyanine dyes with 9-substituents have been found in both the *trans*⁴ and *cis*⁵ conformations in the solid state. Absorption spectroscopy has indicated that 9-substituted carbocyanine dyes exist in solution as a mixture of conformations;⁶ the equilibrium can be shifted by irradiation into the absorption bands of either the *cis* or the *trans* form.³ Even unsubstituted carbocyanines can be partially converted into the *cis* conformation in solution,⁷ and the rate of *cis*-*trans* interconversion has been measured in a number