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SIMULATION OF THE LANTHANIDE INDUCED SHIFTS

DESCRIPTION OF A COMPUTER METHOD AND ITS APPLICATIONS TO CONFORMATIONAL EQUILIBRIA OF SIMPLE SYSTEMS

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Abstract—A computer method to simulate the observed Lanthanide Induced Shifts (LIS) is described and its applications to the study of the conformational equilibria in solution for simple systems are reported. Starting from structurally rigid systems, it is shown that the LIS simulation process allows mistaken assignment to be corrected by systematic permutation of signals with uncertain assignments.

Some examples of structurally flexible systems with an internal rotation angle are studied (2-carbonyl derivatives of furan and thiophene, N-vinylpyrrolidone, cyclopropanecarboxyamides), and the results allow the structures actually present in the conformational equilibrium to be determined.

It has been also found that it is possible to estimate the population ratio between *s-cis* and *s-trans* conformers in a number of α,β-unsaturated systems.

Lanthanide shift reagents (LSR) have received widespread attention since their discovery in 1969[1] and, as a result of the intensive efforts of numberous workers,[2] the phenomenon of LIS appears now reasonably understood.[3-8]

The theoretical background necessary to account for the pseudocontact shifts was developed in 1958,[9] so that is is possible to investigate the molecular geometry of the lanthanide complexes with several ligands by matching the observed shifts and those calculated according to the McConnell and Robertson equation.[9] The latter strictly holds only for metal complexes with axially symmetrical ligand fields,[2,9] but it has been assumed to be generally valid.

Computer simulation of the LIS of structurally rigid systems has been reported.[5, 6, 10-13] We have now developed computing techniques suitable to study flexible systems and describe the application of the LIS technique to the study of the conformational equilibria of simple systems.

LIS simulation process

The LIS simulation process is best described when applied to a structurally rigid molecule (atomic coordinates are fixed and can be deduced from pertinent solid-state data or measured on Dreiding models).

The interaction lanthanide-substrate is thought[2] to be entirely or predominantly of a pseudocontact nature, usually expressed by the McConnell and Robertson equation:[9]

$$\Delta\nu = K(3\cos^2\chi - 1)\,r^{-3} \qquad (1)$$

where χ is the O–Ld–H internuclear angle and r is the corresponding Ld–H distance. It has been common practice among workers in the field to assume the observed LIS proportional to the intrinsic LIS ($\Delta\nu$ in Eq 1). The validity of this assumption has received full support in a recent[7] exacting study of the equilibria taking place between the lanthanide shift reagent and the substrate.

For structurally rigid molecules with a single coordination site (i.e. oxygen) the molecular geometries of the lanthanide complexes can be obtained determining the optimal location of the lanthanide ion in the space around the coordination site.[10] A computer program is most useful to explore all the possible lanthanide spatial locations, defined in Fig 1 by polar coordinates R, φ, ω where R is the Ld–O distance, φ is the Ld–O–C angle, and ω is the Ld–O–C–C dihedral angle.

Input data are the atomic coordinates and the observed LIS for each proton in the molecule. In step 1 the geometrical factor $(3\cos^2 x - 1)r^{-3}$ corresponding to each proton in the molecule is analytically calculated for a given set of R, φ, ω values.

Step 2 performs a least squares minimization of the observed LIS *vs* the geometrical factors corresponding to each proton. In this way the pseudocontact constant (K, Eq 1) is obtained, and the theoretical LIS can be calculated according to Eq 1 (Step 3). In Step 4, the difference between observed and calculated LIS for a given set of R, φ, ω values (i.e.

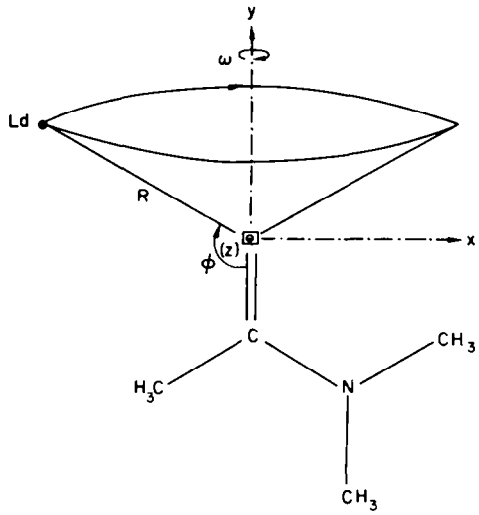


Fig 1. Possible locations of the Lanthanide (Ld) ion in the space around the oxygen atom. R represents the Ld–O distance; φ is the Ld–O–C internuclear angle; the dihedral angle Ld–O–C–C, ω, is zero for the configuration indicated in Figure. Varying R, φ, ω all the Ld possible spatial locations can be explored. The internal coordinate system is also shown.

for each lanthanide spatial location) is expressed* in terms of error by means of Hamilton agreement factor (A.F.):

$$\text{A.F.} = \sqrt{\frac{\sum_i (\text{LIS}_{\text{obs}\,i} - \text{LIS}_{\text{calcd}\,i})^2}{\sum_i \text{LIS}^2_{\text{obs}\,i}}}. \qquad (2)$$

Steps 1–4 are repeated for all the possible sets of R, φ, ω values. The agreement factors (A.F.) corresponding to each molecular geometry of the lanthanide-substrate complex are obtained as output in a square matrix format (φ *vs* ω, at constant R). The minimum value of A.F. is assumed to determine the most likely molecular geometry of the complex.

In practice only φ and ω were allowed to vary and the Ld–O distance (R, Fig 1) was kept constant at 3·0 Å. We have verified, in fact, that the minimum A.F. value is not displaced by varying R in the 2·5–3·5 Å range, and that is a very flat function of R in that range.

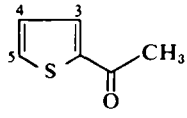
As an example, in Table 1 are reported the results of a LIS simulation performed on the dimethylacetamide–Eu(fod)$_3$ complex by varying the Eu–O distance in the range 2·0–3·4 Å.

Table 1. Effect of the Eu–O distance (R) on the LIS simulation results for the DMA–Eu(fod)$_3$ complex

R(Å)	φ	ω	A.F.
2·0	110°	100°	0·044
2·2	110°	100°	0·037
2·4	110°	100°	0·030
2·6	110°	100°	0·023
2·8	110°	100°	0·016
3·0	110°	100°	0·010
3·2	110°	100°	0·008
3·4	110°	110°	0·005

It can be seen that the Eu position in the complex appears unaffected by the variation of R and that the corresponding A.F. values denote an excellent degree of LIS simulation over the range of R explored.

The accuracy of the (time-averaged) molecular geometry of the lanthanide-substrate complex determined by LIS simulation depends on the accuracy of atomic coordinates and observed LIS for each proton in the molecule. Uncertainties in signal assignments may result in serious errors in the final optimal geometry of the complex. We have found it useful to exchange signals with uncertain assignment and to compare the A.F. corresponding to the optimal geometries thus obtained. Higher A.F. are invariably obtained in cases of mistaken assignments. Signal permutation is automatically performed in our program through the activation of a subroutine. Several stereochemical problems can be handled in this way. For instance, the chemical shifts assignments of protons 3 and 5 in 2-acetylthiophene (known[15] to exist preponderantly in the *s-trans* form 1) until recently have been somewhat controversial.[16]



1

In Table 2 are reported the results of two LIS simulations performed by permuting the signals corresponding to protons 3 and 5 in form 1.

Clearly, the results in Table 2 are in favor of assignment A, which is believed[16] to be the correct one.

Simulation of LIS in flexible molecules

So far we have described the LIS simulation process as applied to structurally rigid molecules. In

*Computer simulation of the LIS proton spectra has been reported several times,[5, 6, 10–13] but relatively little computing details have been given. A notable exception is that of Willcott *et al.*[5] who have described their method in some detail, and have proposed to adopt the Hamilton[14] agreement factor (A.F.) as a measure of the error in the LIS simulation and as a significant testing criterion. Accordingly, we have tested the use of Hamilton[5,14] A.F. and have adopted it.

Table 2. Effect of the signals permutation in the LIS simulation process for the 2-acetyl-thiophene-Eu(fod)$_3$ complex

	3	4	5	CH_3	A.F.	φ	ω
A[a]	2·79	1·83	5·44	9·66			
	2·84	1·76	5·46	9·65	*0·007*	90°	120°
B[a]	5·44	1·83	2·79	9·66			
	1·56	0·45	2·59	10·36	*0·361*	90°	110°

[a]Numbers on the first row are the observed LIS, in the second row are the calculated LIS.

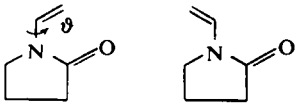
general, however, flexible molecules need to be considered.

In order to explore a given range of molecular geometries for molecules with one internal rotation angle, we activated in our program a subroutine operating through a standard rotation matrix. For each torsional angle selected, a new set of molecular coordinates would thus replace the initial input coordinates. Plots of the minimum A.F. values corresponding to each torsional angle explored, could be obtained in this way.

These plots are very informative since from them it can be inferred how well a *single structure* does simulate the conformational equilibrium, therefore allowing the structures actually present in the equilibrium to be determined. The case of the N-vinyl pyrrolidone illustrates how the method is applied.

The energy barrier to internal rotation about the C—N amide bond has been found considerably lowered by N-vinyl substitution.[17] This suggests that overlapping of the nitrogen lone pair and of the vinyl π-electrons takes place, so that the vinyl group successfully competes with the electronegative oxygen for the unshared nitrogen electrons and the double bond character of the C—N bond is reduced.[17] Accordingly, it would be expected that the vinyl group is not free-rotating in N-vinyl amides, but rather tends to adopt a preferred conformation, lying coplanar with the amide linkage. Two planar forms (**2** and **3**) can be written in the case of N-vinyl pyrrolidone, so that one is faced with the problem of finding out if a planar form is actually preferred over other non-planar and, if this is the case, to establish whether the conformational equilibrium is best represented by only one form or by a mixture of forms **2** and **3**.

Starting from the planar form **2**, all the non-planar forms necessary may be generated by varying the torsion angle ϑ.



2

3

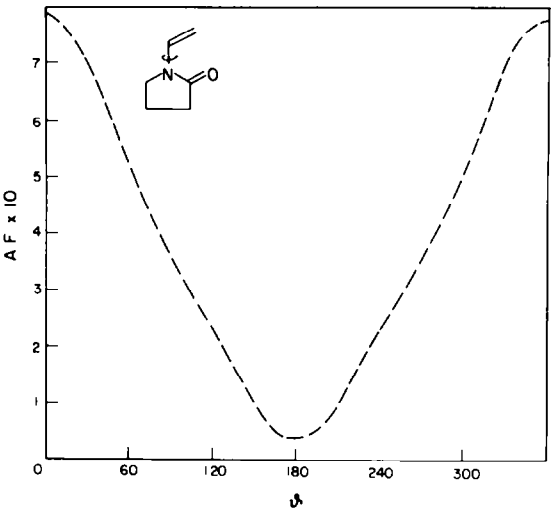


Fig 2. Plot of the minimum agreement factor values (A.F.) corresponding to each torsional angle (ϑ) explored. The starting conformation for the N-vinyl pyrrolidone is shown and ϑ is measured counterclockwise.

In Fig 2 is reported the curve obtained plotting the minimum A.F. values *vs* ϑ.

The curve is symmetrical with a single minimum centered at 180°, indicating that the planar conformation **3** is the one preferred (the Eu ion location corresponds to R = 3·0 Å; φ = 125°; ω = 70°). The high A.F. ratio between the values corresponding to forms **2** and **3** also indicates that the conformational equilibrium is completely shifted towards form **3** in the N-vinyl pyrrolidone.

However, in other cases where the A.F. ratio between conformers participating in the equilibrium is relatively low, other methods (see below) are required in order to obtain quantitative population estimates.

An example which illustrates this situation and also shows an important limitation of the method, is given by 2-formyl-thiophene (**4**) and 2-formyl-furan (**5**).

Recent studies from various techniques[15, 16, 18-21] indicate that **4** exists largely in the *s-trans* form, while mixtures of *s-cis* and *s-trans* forms are reported[15, 22-26] in the case of **5**. Deviations from planarity may be considered a minor problem here, so that the formyl group and the heterocyclic ring can be regarded as always coplanar in **4** and **5**. In the case of the thiophene derivative **4**, the curve in Fig 3 shows a single broad minimum centered on the (planar) *s-trans* form.

Instead, in the case of the furan derivative **5**, the curve in Fig 3 shows two symmetrical minima shifted by ± 120° from the planar *s-trans* form. Since this minimum cannot be interpreted as corresponding to *a non-planar s-trans* (or *s-cis*) form, it has to be concluded that this minimum is an

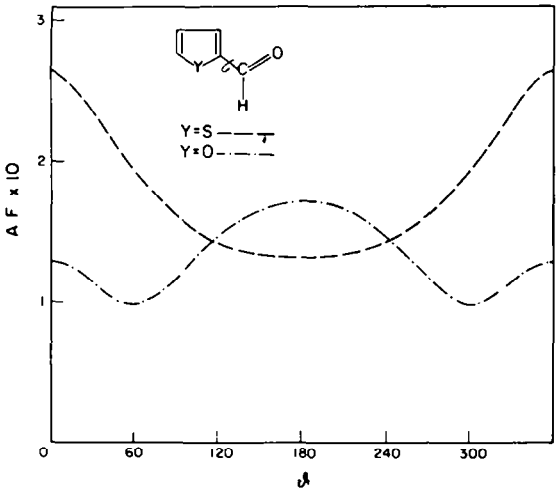


Fig 3. Plot of the minimum agreement factor values (A.F.) corresponding to each torsional angle (ϑ) explored. The starting conformations for thiophene-2 and furan-2-carboxyaldehydes are shown and ϑ is measured counterclockwise.

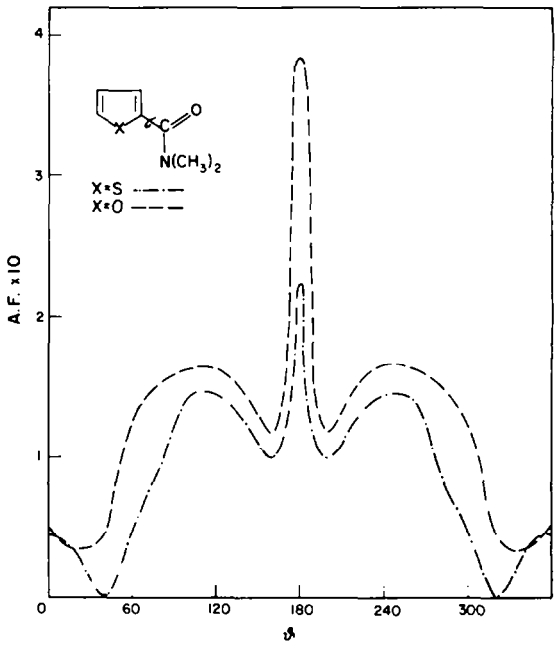


Fig 4. Plot of the minimum agreement factor values (A.F.) corresponding to each torsional angle (ϑ) explored. The starting conformations for the thiophene-2 and furan-2-carboxyamides are shown and ϑ is measured counterclockwise.

artefact due to low A.F. ratio between the values corresponding to the *s-cis* and *s-trans* forms in compound **5**. More specifically, the low A.F. ratio indicates that the two forms are both populated at the equilibrium, although not allowing a quantitative estimate. The minimum A.F. value for a non-planar form merely indicates that this form simulates the conformational equilibrium better than any other *single structure.*

Sometimes, however, the A.F. minima for non-planar forms can be interpreted as corresponding to physical identity.

Curves in Fig 4 show *two non-planar s-cis* and *s-trans* forms in furan-2- (**6**) and thiophene-2-N, N-dimethylcarboxyamide (**7**). The planar states corresponding to these forms appear to have considerably higher A.F. values, suggesting that steric hindrance might cause deviations from planarity in these molecules and the inspection of molecular models confirms this interpretation.

Population estimates at the equilibrium

In the foregoing section we have seen that it would be desirable to have a method allowing quantitative population estimates in the case of molecules which exist as mixtures of several conformations.

In order to apply the LIS simulation process to such molecules, the McConnell and Robertson equation[9] (1) can be rewritten in the general form:

$$\Delta\nu_i = K(\sum_j w_j G_{ij}) \qquad (2)$$

*Complete expression for coefficients K and w_j in Eq (3) will appear separately.

where $\Delta\nu_i$ are the LIS corresponding to the ith spectral signal, w_j are the molar fractions of the j conformations eventually present, and G_{ij} the geometrical factors corresponding to the ith spectral signal for all the j forms.

When two conformations in equilibrium, e.g. to determine the population ratio between *s-cis* and *s-trans* forms in the systems seen above, Eq (2) becomes:

$$\Delta\nu_i = K[w_1 G_{i1} + (1 - w_1)G_{i2}]. \qquad (3)$$

Since G_{i1} and G_{i2} can be calculated for each lanthanide spatial location in the complex, w_1 is the only unknown quantity and Eq (3) can be analytically solved by least squares minimization. In fact, coefficients K and w_1 can be obtained by partial derivation with respect to K and w_1, and then resolving the systems of the two equations obtained.*

When G_1 and G_2 corresponding to all the protons in a molecule have been calculated for a given lanthanide spatial location in the complex, Eq (3) yields the values of K and w_1, thus allowing the theoretical $\Delta\nu$ for each proton to be evaluated.

This procedure is extended to all the possible lanthanide locations, and the location corresponding to the best LIS simulation identifies the most likely molar fraction w_1.

With this method we have investigated a number

Table 3. Population ratio data for α,β-unsaturated derivatives and some related compounds

Compound	% *s-cis*	Compound	% *s-cis*
$CH_2{=}C(CH_3){-}CHO$	0	$CH_2{=}C(CH_3){-}CO{-}N(CH_3)_2$	10
$C(CH_3)_2{=}CH{-}CHO$	1	$CH(Ph){=}CH{-}CO{-}N(CH_3)_2$	95
$CH(CH_3){=}C(CH_3){-}CHO$	10	$CH_2{=}CH{-}CO{-}NC_5H_{10}$	91
$CH(CH_3){=}CH{-}CHO$	9	$CH(Ph){=}CH{-}CO{-}NC_5H_{10}$	89
$CH_2{=}CH{-}COCH_3$	27	2-formyl-thiophene	1
$CH_2{=}C(CH_3){-}COCH_3$	12	2-formyl-furan	56
$CH(CH_3){=}C(CH_3){-}COCH_3$	18	2-acetyl-thiophene	18
$C(CH_3)_2{=}CH{-}COCH_3$	72	2-acetyl-furan	33
$CH(Ph){=}CH{-}COCH_3$	63	thiophene-2-N,N dimethyl-carboxyamide	99
$CH_2{=}CH{-}CONH_2$	64	furan-2-N,N dimethyl-carboxyamide	91
$CH_2{=}CH{-}CO{-}N(CH_3)_2$	82		

of α,β-unsaturated aldehydes, ketones, and amides, determining the population ratio between *s-cis* and *s-trans* conformers in these compounds. In Table 3 the figures obtained are summarized.

As the literature on the subject is extensive it is not easy to discuss each case in detail, but should be stressed that the population data in Table 3 are in general agreement with those available in the literature.[27]

We have chosen to illustrate here only a few cases concerning the α,β-unsaturated amides.

In the case of acrylamide the experimental LIS of the three vinyl signals are available.[46]

Data in Table 4 show the results of the LIS simulation performed by systematic signal permutation for each of the twelve combinations which arise assuming the acrylamide as a rigid molecule existing completely in the *s-cis* or in the *s-trans* form.

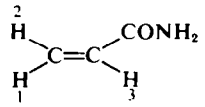
The minimum A. F. value (0·166) is obtained for a *s-cis* conformation in which the assignments are identical with those originally reported[46] but this value is rather high, and furthermore it is close to A.F. values of other combinations in Table 4.

In order to ascertain if the conformational equilibrium is better represented by a mixture of *s-cis* and *s-trans* forms, calculations according to Eq (3) were performed. The results in Table 5 show that at the equilibrium 64% of the acrylamide is in the *s-cis* form. The A.F. value is now very low (0·00006), so that the LIS calculated are coincident with the experimental ones.

Deviations from planarity may be considered minor in α,β-unsaturated aldehydes but the inspection of molecular models shows that this might not be the case with the corresponding amides. Recent[47] crystal data on *p*-bromcinnamamide show that the amide group is rotated 15° out of the *s-cis* conformation with respect to the rest of the conjugated system.

Remarkably, the four amides in Fig 5 follow a

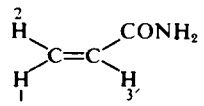
Table 4. Effect of signals permutation in the LIS simulation process for the acrylamide-Eu(fod)$_3$ complex



	1	2	3	A.F.	φ	ω
s-trans	C	B	A	0·585	155°	180°
s-trans	C	A	B	0·294	135°	180°
s-trans	B	A	C	0·417	140°	180°
s-trans	A	C	B	0·204	160°	180°
s-trans	B	C	A	0·596	150°	180°
s-trans	A	B	C	0·338	160°	180°
s-cis	C	B	A	0·251	90°	180°
s-cis	A	B	C	0·166	130°	180°
s-cis	A	C	B	0·297	125°	180°
s-cis	B	C	A	0·375	95°	180°
s-cis	C	A	B	0·534	120°	180°
s-cis	B	A	C	0·546	120°	180°

$\Delta\nu_{obs}$: A = 31·6; B = 66·4; C = 57·4.
Original literature assignment[46] A = 1; B = 2; C = 3.

Table 5. LIS simulation results for the Acrylamide-Eu(fod)$_3$ complex



	1	2	3
$\Delta\nu_{obs}$	31·6	66·4	57·2
$\Delta\nu_{calcd}$	31·6	66·4	57·2

Simulation results: R = 3·0 Å; φ = 120°; ω = 160°; A.F. = 0·00006; % *cis* 64.

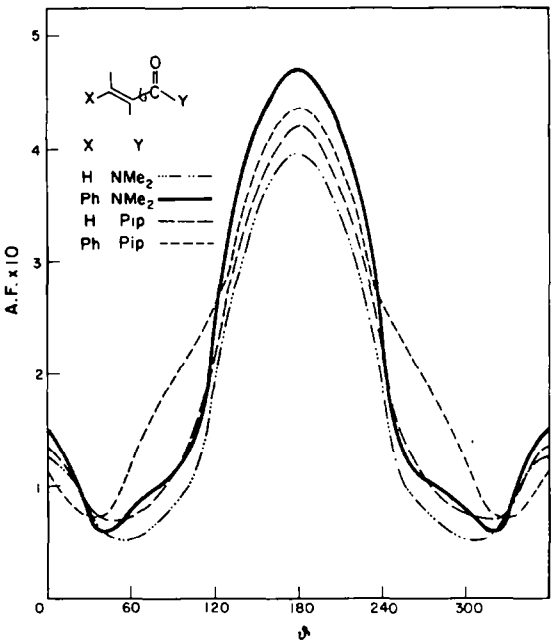


Fig 5 Plot of the minimum agreement factor values (A.F.) corresponding to each torsional angle (ϑ) explored. The starting conformations for α,β-unsaturated amides are shown and ϑ is measured counterclockwise.

common pattern, and the minimum A.F. values are 20–50° displaced from the planar *s-cis* conformation.

Although this result might be regarded as valid evidence that non-planar *s-cis* forms are actually preponderant at equilibrium, the possibility of an artefact cannot be absolutely ruled out on this point.

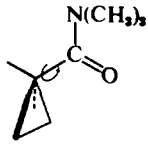
Averaging effects in symmetrical molecules

The conformational systems examined possess a symmetry such that averaging of the protons chemical shifts cannot possibly occur. In fact, in α,β-unsaturated compounds any value of the torsion angle (ϑ) different from zero or π generates two enantiomeric molecular conformations, but no averaging of the protons chemical shifts occurs as a consequence of the exchange between the two enantiomeric forms.

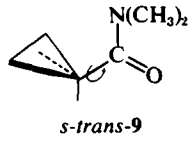
This is not the general case, however, since averaging of the protons chemical shifts (*and therefore of LIS*) is quite common in symmetrical molecules.

In order to illustrate this point, we have studied the conformational equilibria of some cyclopropanecarboxyamides (CPCA). The problem of the conformational preference of CPCA is in fact very similar to that of α,β-unsaturated amides. It is generally agreed[48–51] that cyclopropanecarboxyaldehyde exists preferentially in a conformation where the endo orbitals of the cyclopropane ring overlap with the adjacent π orbital of the carbonyl group, so that the latter exactly bisects the cyclopropane ring.

In the case of CPCA, however, if it is still true that the geometrical arrangement with the amide unit bisecting the cyclopropane ring meets the Walsh[52] requirements for maximum overlap of cyclopropyl and carbonyl orbitals, the nonbonded atoms interactions are unfavorable.[53] There are two geometrical arrangements (forms **8** and **9**) in which the amide unit bisects the cyclopropane ring. Since the nonbonded interactions are unfavorable for both conformers, it is conceivable that *gauche* forms (with torsional angles different from the bisecting one) may become populated.[53]



s-cis-**8**



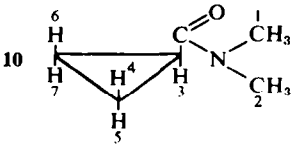
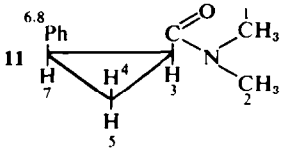
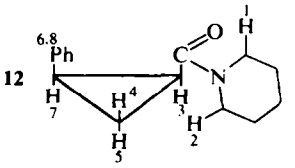
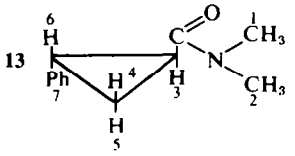
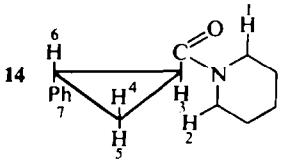
s-trans-**9**

For the unsubstituted CPCA (compound **10**, Table 6), any *gauche* form exists in two enantiomers, and their exchange causes the averaging of the protons chemical shifts and LIS. This implies that ring protons lying in symmetric positions *must* show identical LIS independently from the conformational preference of the molecule (Table 6). In this situation the best LIS simulation will always be obtained for a bisecting conformation, and there is no obvious way to avoid this artefact.

Three minima are found for compound **10** in the curve reported in Fig 6. The deepest minimum corresponds to form **8**, largely favored with respect to form **9**. The remaining two minima may identify two enantiomeric *gauche* rotamers whose averaging generates, totally or in part, the minimum corresponding to form **8**.

Only two minima are seen in Fig 6 for the curve corresponding to the *cis*-2-phenyl CPCA derivative (compound **11**, Table 6). Both are removed from the bisecting position (now sterically hindered by the interaction between amide and phenyl

Table 6. Chemical shifts and LIS data for CPCA[a]

		1	2	3	4	5	6	7	8
10		3·02 15·49	3·02 8·86	1·74 9·46	0·95 15·40	0·75 6·91	0·95 15·40	0·75 6·91	
11		2·72 7·99	2·97 3·54	2·20 4·75	1·85 8·40	1·42 2·96	7·19[b] 4·31[b]	2·47 3·03	7·19[c] 1·21[c]
12		3·48 10·50	3·48 3·54	2·28 6·23	1·75 10·94	1·24 3·47	7·18[b] 4·29[b]	2·28 6·23	7·18[c] 2·10[c]
13		3·10 10·93	3·10 5·06	2·08 5·31	1·63 10·54	1·07 3·96	2·65 8·95	7·20[b] 1·22[b]	
14		3·57 9·26	3·57 4·24	2·07 5·09	1·75 8·79	1·27 3·47	2·32 8·06	7·21[b] 0·98[b]	

[a] Figures in the first row indicated chemical shifts (δ) of undoped spectra; figures in the second row indicate observed molar induced shifts.
[b] Ortho protons of the phenyl.
[c] Meta and para protons of the phenyl.

groups) and correspond approximately to the *gauche* rotamers present in the curve corresponding to the unsubstituted CPCA (Fig 6). No averaging effects are expected in the *cis*-2-phenyl derivative, so that the two minima should be regarded as corresponding to conformers actually populated. One of these conformers is largely preferred over the other (Fig 6), and the inspection of molecular models shows that this preference is due to a less hindered molecular conformationn.

Averaging may again take place between the ring protons in *cis* position with respect to the amide group in the *trans*-2-phenyl CPCA derivative (compound **13**, Table 6). Three minima are seen in Fig 6 for the curve corresponding to compound **13**, and it is not easy to discern if the minimum corresponding to the bisecting conformation **8** is due to an artefact or not. However, one of the two *gauche* forms is *stabilized* by the presence of the *trans* phenyl ring, while the other is *destabilized*, with respect to the unsubstituted CPCA (Fig 6).

If one reflects that in the stabilized *gauche* form the amide group lies *quasi* coplanar with the phenyl ring,* it is conceivable to attribute this stabilization to the transmission of electronic effects from the phenyl ring to the amide group through the cyclopropane ring.[53]

In summary the analysis of the two substituted CPCA derivatives (compounds **11**, **13**) seems to support the hypothesis[53] that *gauche* conformers

*It is known[54] that the preferred conformation of the phenyl group in phenylcyclopropane is that in which the phenyl bisects the cyclopropane ring.

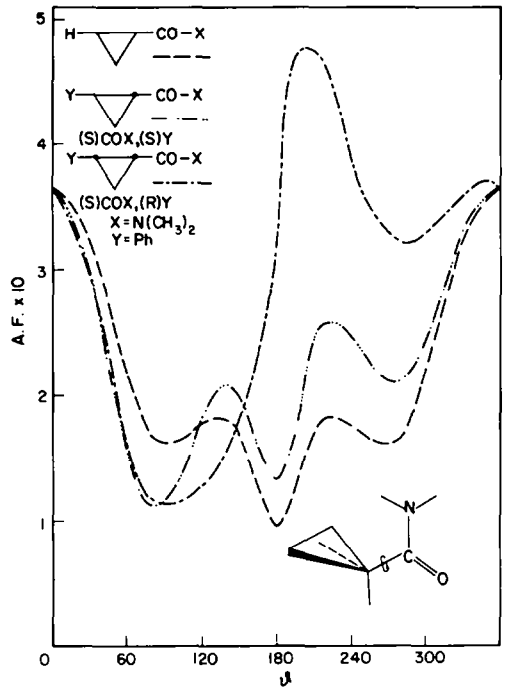


Fig 6. Plot of the minimum agreement factor values (A.F.) corresponding to each torsional angle (ϑ) explored. The starting conformations for cyclopropanecarboxyamides are shown and ϑ is measured counterclockwise.

are populated in CPCA, but the question of their relative stability with respect to the bisecting *s-cis* form **8** remains unsettled.

CONCLUSIONS

The results reported here should illustrate the power of the LIS simulation technique in conformational analysis.

The LIS analysis is meaningful and its results are reliable only if the conformational equilibria in the substrate molecule are not perturbed by the lanthanide addition.[5,10] At least for the important classes of compounds considered here, no sensible perturbation of the conformational equilibria occur, as shown by the general agreement of our results with the data from other techniques. In this respect it should be noted that, in spite of the considerable amount of data existing on the systems studied, our results have often provided additional information, which is not in conflict with the salient facts previously ascertained.

However, the LIS simulation method presented here, in spite of its obvious utility, is far from being definitive, and in some instances does not lead to univocal conclusions. It is likely that further work in this field may overcome these drawbacks, and it is therefore worthwhile to continue the investigation of simple systems with the long-range goal to proceed from small to large molecules.

EXPERIMENTAL

Compounds used in this study were synthesised and characterised according to the literature. Lanthanide induced shifts measurements were performed with Eu(fod)$_3$. Spectra of about 5% $CDCl_3$ solns (TMS standard), containing 0–0·15 mole of ligand (L) per mole of substrate (S), were obtained at 60 MHz (Varian A 60-D analytical spectrometer). The lanthanide shift reagent was added stepwise from a stock soln (0·32 M), with the help of a 50 μl microsyringe. Each signal was followed in the spectra and the LIS were found directly proportional to the [L]/[S] ratio present. A least squares fit of the experimental points was used to obtain the observed LIS. Calculations relative to the simulation of the experimental LIS data were performed on an CDC-6600 digital computer.

We will be glad to provide our program listings (Fortran IV) to anybody who may desire them.

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REFERENCES

[1]C. C. Hinckley, *J. Am. Chem. Soc.* **91**, 5160 (1969)
[2]For a review of the subject see: R. von Ammon and R. D. Fischer, *Angew. Chem.* Internat. Edit **11**, 675 (1972)
[3]Some pertinent papers are listed in Refs 4–8
[4]J. K. M. Sanders, S. W. Hanson and D. H. Williams, *J. Am. Chem. Soc.* **94**, 5325 (1972)
[5]M. R. Willcott, R. E. Lenkinski and R. E. Davis, *Ibid.* **94**, 1742 (1972); R. E. Davis and M. R. Willcott, *Ibid.* 1744 (1972)
[6]P. V. Demarco, B. J. Cerimele, R. W. Crane and A. L. Thakkar, *Tetrahedron Letters* 3539 (1972)
[7]B. L. Shapiro and M. D. Johnston, Jr, *J. Am. Chem. Soc.* **94**, 8185 (1972)
[8]N. S. Angerman, S. S. Danyluk and T. A. Victor, *Ibid.* **94**, 7137 (1972)
[9]H. M. McConnell and R. E. Robertson, *J. Chem. Phys.* **29**, 1361 (1958)
[10]G. Montaudo and P. Finocchiaro, *J. Org. Chem.* **37**, 3434 (1972)
[11]F. A. Hart, J. Briggs, G. H. Frost, G. P. Moss and M. L. Stainforth, *Chem. Comm.* 1506 (1970)
[12]G. P. Moss, J. Briggs, F. A. Hart and E. N. Randall, *Ibid.* 364 (1971)
[13]S. Farid, A. Ateya and M. Maggio, *Ibid.* 1285 (1971)
[14]W. C. Hamilton, *Acta Crystallogr.* **18**, 502 (1965)
[15]J. M. Angelelli, A. R. Katritzky, R. F. Pinzelli and D. R. Topsom, *Tetrahedron* **28**, 2037 (1972), and Refs therein
[16]M. L. Martin, C. Andrieu and G. J. Martin, *Bull. Soc. Chim. Fr.* 698 (1968)
[17]D. G. Gerhing and W. A. Mosher, *J. Org. Chem.* **31**, 3436 (1966)
[18]C. Andrieu and Y. Mollier, *Bull. Soc. Chim. Fr.* 831 (1969)
[19]H. Lumbroso, D. M. Bertin and P. Cagniant, *Ibid.* 1720 (1970)
[20]L. Kaper and Th. J. De Boer, *Rec. Trav. Chim.* **89**, 825 (1970)
[21]F. Mönnig, H. Dreizler and H. D. Rudolph, *Z. Naturforsch.* A, **20**, 1323 (1965)
[22]L. Arlinger, K. I. Dahlqvist and S. Forsén, *Acta Chem. Scand.* **24**, 662 (1970)
[23]M. L. Martin, J. Roze, G. J. Martin and P. Fournari, *Tetrahedron Letters* 3407 (1970)

[24]D. J. Chadwick, J. Chambers, G. D. Meakins and R. L. Snowden, *Chem. Commun.* 624 (1971)
[25]B. R. Larsen, F. Nicolaisen and J. T. Nielsen, *Acta Chem. Scand.* **26**, 1736 (1972)
[26]K. I. Dahlqvist and A. B. Hornfeldt, *Tetrahedron Letters* 3837 (1971)
[27]For α,β-unsaturated Aldehydes, see Refs 28–34; for Ketones, 35–44; for Amides, 45; for Thiophene and Furan derivatives, see Refs 15, 16, 18–26.
[28]R. Wagner, J. Fine, J. W. Simmons and J. H. Goldstein, *J. Chem. Phys.* **26**, 634 (1957)
[29]F. A. Cherniak and C. C. Costain, *Ibid.* **45**, 104 (1966)
[30]K. Kuchitsu, T. Fukuyama and Y. Morino, *J. Mol. Structure* **1**, 463 (1967)
[31]M. Traetteberg, *Acta Chem. Scand.* **24**, 373 (1970)
[32]M. Suzuki and K. Kozima, *Bull. Chem. Soc. Japan* **42**, 2183 (1969)
[33]Z. W. Wolkowski, *Tetrahedron Letters* 821 (1971)
[34]C. Beauté, Z. W. Wolkowski, J. P. Merda and D. Lelandais, *Ibid.* 2473 (1971)
[35]D. D. Faulk and A. Fry, *J. Org. Chem.* **35**, 364 (1970) and Refs therein
[36]C. Beauté, S. Cornuel, D. Lelandais, N. Thoai and Z. W. Wolkowski, *Tetrahedron Letters* 1099 (1972)
[37]A. R. Katritzky, R. F. Pinzelli and D. R. Topsom, *Tetrahedron* **28**, 3449 (1972)
[38]J. Ronayne, M. V. Sargent and D. H. Williams, *J. Am. Chem. Soc.* **88**, 5288 (1966)
[39]C. J. Timmons, *Chem. Commun.* 576 (1965)
[40]R. L. Erskine and E. S. Waight, *J. Chem. Soc.* 3425 (1960)
[41]E. Baldwin, *J. Org. Chem.* **30**, 2423 (1965)
[42]K. Noack and R. N. Jones, *Canad. J. Chem.* **39**, 2201 (1960)
[43]M. Kronenberg and E. Havinga, *Rec. Trav. Chim.* **84**, 17 (1965)
[44]T. K. Khanmamedov, A. D. Aliev, B. A. Krentsel, *Izv. Akad. Nauk SSSR, Ser. Khim.* **9**, 2040 (1970); *Chem. Abstr.* **73**, 131378 (1970)
[45]C. Kruk and K. Spaargaren, *Spectrochim. Acta* **27A**, 77 (1971)
[46]C. Beauté, Z. W. Wolkowski and N. Thoai, *Chem. Commun.* 700 (1971)
[47]M. A. M. Meester and H. Schenk, *Rec. Trav. Chim.* **90**, 508 (1971)
[48]L. S. Bartell, B. L. Carroll and J. P. Guillory, *J. Chem. Phys.* **43**, 647 (1965)
[49]G. J. Karabatsos and N. Hsi, *J. Am. Chem. Soc.* **87**, 2864 (1965)
[50]R. Hoffmann, *Tetrahedron Letters* 3819 (1965)
[51]M. Pelissier, A. Serafini, J. Devanneaux, J. F. Labarre and J. F. Tocanne, *Tetrahedron* **27**, 3271 (1971), and Refs therein
[52]A. D. Walsh, *Trans. Faraday Soc.* **45**, 179 (1949)
[53]G. Montaudo and C. G. Overberger, *J. Org. Chem.* **38**, 804 (1973)
[54]G. L. Closs and R. A. Moss, *J. Am. Chem. Soc.* **86**, 4042 (1964)