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A TOPOLOGICAL APPROACH TO THE INTERACTION OF LANTHANIDE SHIFT REAGENTS WITH THE CARBONYL GROUP

ITS RELEVANCE TO CONFORMATIONAL ANALYSIS

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Abstract—A topological approach to the LIS simulation process of compounds bearing the carbonyl functional group is reported. The Lanthanide was always found to complex in the less hindered position, along the sp^2 lone-pair orbital of the O atom. The relevance to chemistry of such an approach is that only chemical significant positions are considered as feasible sites of complexation of the Lanthanide with the substrate, disregarding all other positions. More important, the results obtained have thrown some light on the factors that may influence the equilibria of conformationally mobile systems, in the presence of LSR.

The reliability of the method employed has been tested in several disparate carbonyl derivatives.

INTRODUCTION

Several hundreds of reports[1] have appeared describing the application of lanthanide shift reagents (LSR) in the NMR analysis of disparate classes of molecules.

Pioneering works have described a simplification of the spectra of complex molecules, by increasing, with the aid of LSR, resolution of signals which appear as "bunched together in featureless clusters[1d]" because of the accidental[2] isochrony involved.

Recently, increasing interest was devoted to simulation of the observed lanthanide induced shifts (LIS) using computational procedures.[1,3-13]

In order to achieve more reliable results the computational procedure involved reached various degrees of sophistication and elaborate programs were designed in the attempt to accomplish the task.[3-13] Furthermore, applications of LSR to the investigation of the conformational equilibria of some molecules is of great interest.[1,3-5] However, such a study may be destined to fail or the results be less valuable if the reasons that may, *or not*, induce conformational changes in the substrate when complexed with the LSR, remain obscure.

A general understanding of these reasons is of great importance to chemistry. In fact, LIS data can be profitably and *directly* used in solving conformational problems, once it can be demonstrated that the interaction of the LSR with the substrate leaves unperturbed the conformational equilibria. In contradistinction, in the case in which the LSR is able to influence such equilibria, the LIS data cannot be used for such purposes but can give useful information on the perturbations of conformational equilibria induced by complexing agents, whose immediate and attractive applications can be found in biological systems.

Although conflicting reports on the influence of LSR on the conformational equilibria can be found in the literature,[4,5,14-17] in our opinion, no systematic analysis of the factors that can lead the substrate to modify its conformation in the presence of LSR has been reported.

In our approach to this problem we considered as relevant only preferential positions of the sites of complexation of the lanthanide with the substrate, disregarding all the other positions but the chemically accessible ones.

This topological simplification was applied to the analysis of the LIS of some carbonyl derivatives with the double purpose of simplifying the computational procedure involved and to throw some light on the factors that can cause some substrates to modify their conformation in the presence of LSR.

Our results indicate that among all the compounds investigated the lanthanide was found to complex with the carbonyl O atom lone-pair in the less hindered position. These findings can explain some conflicting[4,5,14-17] results on the influence of LSR on the conformational equilibria of some of the molecules investigated.

RESULTS AND DISCUSSION

The topological approach

In previous calculations[3-9,11,13] the procedure generally employed in order to obtain a fit between the experimental and calculated LIS was to devise

a computer program in which all the possible spatial locations of the lanthanide ion could be stepwise explored, *i.e.* a *random search* approach.

The optimal location of the lanthanide ion in the space around the coordination site, *i.e.* the location which gave the minimum difference between observed and calculated LIS, was taken as the "time-averaged geometry" of the complex, geometry which can be described by polar coordinates R, φ, and ω, where R is the Ld–O distance, φ the Ld–O–C angle and ω the Ld–O–C–X dihedral angle[3-5]. (Fig 1).

In the present approach a drastic simplification in the calculation procedure was introduced: only chemically significant positions* of the lanthanide site of complexation were thought to contribute to the observed LIS.

For a carbonyl group attached to two different ligands X and Y, (Fig 1) the two oxygen lone-pair reside in diastereomeric environments and consequently two different sites of complexation are, in principle, possible for the lanthanide ion. These diastereomeric positions are represented by values of $\varphi = 120°$ and 240°, respectively.

Deviations from coplanarity of the coordination sites of the Ld ion with the oxygen lone pair main axis were not considered as relevant.†

The relevance to chemistry of such an approach is that only physical significant positions are considered as feasible sites of complexation of the lanthanide with the substrate, disregarding all other positions. Furthermore, this procedure avoids the time-consuming and complex calculations involved in order to explore all the possible, but not necessarely significant, spatial locations of the lanthanide.

α, β-Unsaturated carbonyl compounds

In order to test the validity of the approach we performed, a computer simulation of the LIS in some selected simple molecules, for which a close agreement between observed and calculated LIS has been previously reported by the random search approach[4] (Table 1).

Previous results[4] have shown that molecules in Table 1 exist predominantely in the *s-trans* conformation, which was not altered by addition of the LSR. Consequently the molecules were considered as rigid substrates and in order to calculate the LIS for each proton, the lanthanide was allowed to occupy only sites at $\varphi = 140°$ and $\varphi = 220°$‡ (Fig 1), and the Ld–O internuclear distance was fixed at 3·0 Å, which is the most widely accepted value.[3-6,10-12]

In order to determine the molar fraction of the two diastereomeric complexed substrates a computer program was devised in which the LIS observed for each proton were calculated according to the following formula:

$$\Delta\nu_{i\,obs} = K[(W_{140}G_{140} + W_{220}G_{220})] \qquad (1)$$

where W_{140} and W_{220} are the molar fractions, and G_{140} and G_{220} the geometrical factors corresponding to the forms with the Ld at 140° and 220°, respectively, and K is the pseudocontact constant.

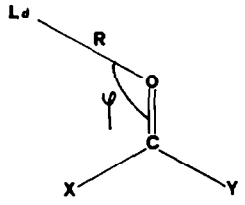


Fig 1.

The geometrical factors can be calculated from the McConnell and Robertson equation[19]:

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

where χ is the O–Ld–H internuclear angle and r is the corresponding Ld–H distance.

Direct analytical solution of Eq 1,[4,5] yields the molar fraction (W_{140}) and the pseudocontact constant (K) which give the best agreement factor (AF) between the observed and calculated LIS.[4,5]

Data in Table 1 reveal that a satisfactory AF between the calculated and experimental LIS was obtained within this hypothesis for the molecules investigated.

More important, in all these compounds only one diastereomeric site of complexation was found to contribute appreciably to the observed LIS. This site is always the less steric demanding, considering the internuclear distances between the lanthanide and the ligands attached to the carbonyl group.

For molecules in Table 2 previous work[4] has

*It is well known that the site of complexation of the lanthanide is generally directed towards the oxygen lone-pairs of the carbonyl group. X-ray data available on related complexes[1c,8,10,18] confirm this hypothesis.

However, no experimental verification is yet available that such directional and preferential location of the lanthanide can be mantained also in solution, although some computational results favor this hypothesis.[3,10,11].

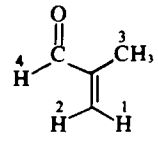
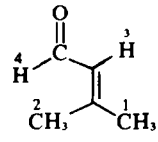
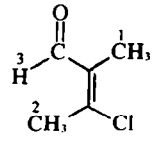
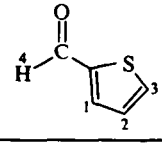
†This assumption may appear as an oversimplification.

However, preliminary trial calculations on several molecules of this type have shown that the calculated LIS values do not vary significantly by varying the dihedral angle ω from 0° (coplanarity) to 40°.

‡The values of $\varphi = 140°$ or 220° came from some preliminary calculations in which φ was varied from 120°–160° or 200°–240°.

In all the compounds investigated the best fit was always obtained for $\varphi = 140°$ or 220°. Thus, the two diastereomeric sites of attack of the Ld were assumed to have this angulation in all cases discussed.

Table 1. Chemical shifts, measured and simulated LIS, and preferred location of Lanthanide for some α,β-unsaturated aldehydes[a]

No	Compound	H-1[b]	H-2[b]	H-3[b]	H-4[b]	K	W_{140}[c]	AF
1[d]		•	•	•	•	1420	100	0·037
		6·0	8·0	13·0	28·0			
		7·01	8·53	12·9	27·63			
2[d]		•	•	•	•	1588	85	0·052
		5·6	6·6	19·4	29·4			
		5·29	7·47	17·98	30·04			
3[f]		•	•	•		4207	88	0·0007
		14·3	32·0	80·0				
		14·36	31·99	79·99				
4		7·63	7·13	7·71	9·80	685	100	0·023
		4·09	2·17	2·58	12·81			
		3·79	2·40	2·55	12·89			

[a] Ligand X (Fig 1) is represented on the left side; consequently for angles $0° \leq \varphi \leq 180°$ the Ld is in *cis* position to this ligand.

[b] Figures in the first row indicate chemical shifts (δ) of undoped spectra; figures in the second row indicate observed molar induced shifts; figures in the third row indicate calculated molar induced shifts.

[c] Molar fraction percent of form with the Lanthanide attached at $\varphi = 140°$

[d] Yb (dpm)$_3$ induced shifts taken from: Z. W. Wolkowski, *Tetrahedron Letters* 821 (1971).

[e] Chemical shift value missing in the original work.

[f] Yb (dpm)$_3$ induced shifts taken from: C. Beautè, Z. W. Wolkowski, J. P. Merda and D. Lelandais, *Ibid.* 2473 (1971).

shown that a mixture of *s-cis* and *s-trans* forms contribute to the NMR spectrum at ambient temperatures.

The finding that in the carbonyl compounds in Table 1 the lanthanide ion can complex only in a preferential position was taken as the starting hypothesis in order to calculate the *s-cis* and *s-trans* rotamer ratio in molecules represented in Table 2. Consequently, the lanthanide was located according to the results summarized in Table 1, and the molar ratio of the two rotamers was thus calculated.[4]

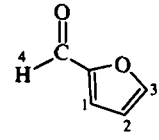
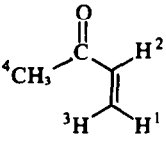
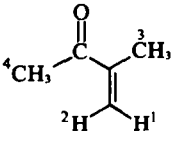
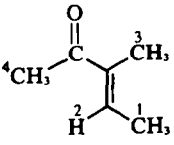
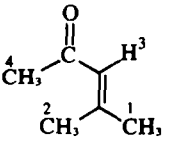
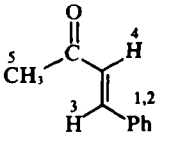
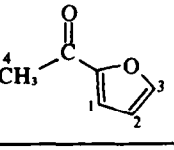
Pertinent values of the population ratio of these forms were in close agreement with the estimate of previous authors[4] (Table 2). This result indicates that the topological approach can be used with a high degree of confidence, and can throw some light on the influence of the LSR on the conformational equilibria of mobile systems.

In fact, for molecules in Tables 1 and 2 the *s-cis*/*s-trans* population ratio was found to be the same whether determined in the presence or absence of lanthanide. In particular, because in the presence of lanthanide the calculated *s-cis*/*s-trans* ratio reflects the ratio of the two conformers in the complexed substrate, it may appear fortuitous that such a ratio is exactly equal to that found for the non-complexed molecule.

However, inspection of Tables 1 and 2 reveals that the coordination site of the lanthanide in such molecules is always far enough to leave essentially unperturbed the complexed molecule. It is immaterial for the Ld, which attacks in such a position, to complex a substrate *s-cis* or *s-trans* so that no chemical reason can be envised which forces the molecule to undergo changes in conformation.

The only factor which eventually can lead to a rotamer ratio different from that one expected in the absence of a complexating agent would be that the pseudocontact constants for the two forms

Table 2. Chemical shifts, measured and simulated LIS, and preferred conformation for some α,β-unsaturated Aldehydes and Ketones[a]

No	Compound	H-1[b]	H-2[b]	H-3[b]	H-4[b]	H-5[b]	K	AF	%s-*cis*
1		7·17	6·55	7·60	9·53		496	0·083	66
		4·43	2·03	2·55	8·99		513[c]	0·095[c]	56[c]
		4·33	1·78	1·76	9·24				
2[d]		•	•	•			1874	0·011	21
		10·0	14·0	20·0			1830[c]	0·007[c]	27[c]
		9·72	14·09	20·07					
3[f]		•	•	•	•		1732	0·016	11
		9·0	11·8	15·0	18·0		1770[c]	0·005[c]	12[c]
		8·75	11·76	14·81	18·30				
4[f]		•	•	•	•		1609	0·017	15
		5·9	11·5	13·8	16·8		1686[c]	0·001[c]	18[c]
		6·16	11·36	13·55	16·99				
5		1·85	2·11	6·00	2·11		909	0·175	74
		3·96	9·12	6·35	11·80		903[c]	0·173[c]	72[c]
		3·84	9·84	8·13	9·60				
6		7·42[g]	7·42[h]	6·71	7·51	2·33	1092	0·130	69
		3·09[g]	1·21[h]	11·99	9·55	12·89	1137[c]	0·064[c]	63[c]
		5·19	1·97	11·92	9·96	11·54			
7		7·21	6·55	7·63	2·45		732	0·094	54
		5·70	2·10	1·90	8·10		780[c]	0·014[c]	33[c]
		5·78	2·55	2·26	7·64				

[a] Ligand X (Fig 1) is represented on the left side; consequently for angles $0° \leq \varphi \leq 180°$ the Ld is in *cis* position to this ligand.

[b] Figures in the first row indicate chemical shifts (δ) of undoped spectra; figures in the second row indicate observed molar induced shifts; figures in the third row indicate calculated molar induced shifts.

[c] K, AF and percent of *s-cis* taken from ref. 4.

[d] Yb (dpm)$_3$ induced shifts taken from; C. Beauté, S. Cornuel, D. Lelandais, N. Thoai, and Z. W. Wolkowski, *Tetrahedron Letters* 1099 (1972).

[e] Chemical shift value missing in the original work.

[f] Yb (dpm)$_3$ induced shifts taken from: Z. W. Wolkowski, *Ibid.* 821 (1971).

[g] *Ortho* protons of the phenyl ring.

[h] *meta* and *para* protons of the phenyl ring.

differ appreciably. Once again, because of the existence of this preferential site of attack, it is difficult to believe that this situation can arise. Consequently the previous findings[4] that the conformational equilibria of such α, β-unsaturated compounds is not influenced by the LSR can be

rationalized under this, more general, topological approach.

Amides

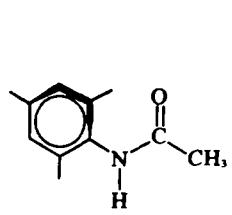
These compounds are one of the most versatile substrates for investigating the influence of the complexating agent on the conformational equilibrium. In fact, in an amide molecule with two different ligands attached to the N atom, due to kinetically restricted rotation around the C–N amide linkage, two diastereomers are possible which will feature, at ambient temperatures, separate signals in the NMR. Consequently, in such substrates any change in population caused by the LSR can be easily detected.[14-16]

We investigated nineteen amides (Table 3) in which the steric congestion around the carbonyl group was allowed to vary.

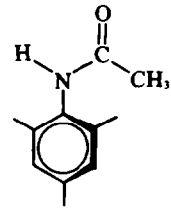
Computer simulation of the observed LIS (Table 3), revealed that in this class of molecules the preferential site of complexation of the lanthanide occurs at the less sterically hindered position; accordingly, among the various conformers the lanthanide selects the form with less demanding steric congestion around the complexation site. If this conformer, is *not* the only one populated, conformational changes can be observed in the NMR spectrum, by increasing the lanthanide concentration. The only condition required is that the free energy of complexation should be greater than the energy required for modifying the substrate conformation.

Among all the compounds investigated only the secondary amides **11–16** of Table 3 were shown to undergo significant changes in population by further addition of LSR.[14-16]

For example, in compound **15**, in absence of LSR both forms **15a** and **15b** contribute to the ^{1}H–NMR spectrum, at ambient temperatures.



15a



15b

In $CDCl_3$ the isomer ratio **15a/15b** was found to be *ca* 74:26 in absence of LSR.[20] Increasing the concentration of lanthanide, diastereomer **15b** increases significantly, and its signals are seen to be shifted to low field a great deal faster than the corresponding ones of **15a** (Fig 2). In addition, the LIS for the signals of the *cis* isomer (**15b**) show appreciable curvature even at low values of the ratio [Ld]/[Substrate], at variance with that observed for the *trans* isomer **15a** (Fig 3) in which the LIS are linear up to *ca* 0·35 LSR/substrate molar ratio.

These observations indicate that complexation of the lanthanide with the *cis* form must occur much more easily with respect to the *trans* rotamer. Indeed, rotation of the *trans* to the *cis* form allows the lanthanide to complex the carbonyl oxygen in position *cis* to the hydrogen attached at the nitrogen which is, without doubt, the less steric demanding site. If the nitrogen hydrogen is substituted by different ligands of greater size, this particular situation is no longer possible and consequently no changes in population are expected. In fact, in compounds **2, 3, 6–8, 17–19** (Table 3) no changes in populations were observed, even at equimolar ratio of [lanthanide]/[substrate].

In particular, for compound **3** in Table 3, as well for **6–8**, only one diastereomeric form contributes to the NMR spectrum at ambient temperatures.[21]

Table 3. Chemical shifts, measured and simulated LIS, and preferred location of Lanthanide for some amides[a]

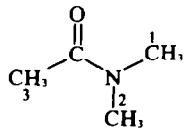
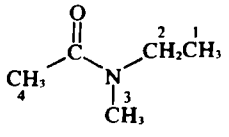
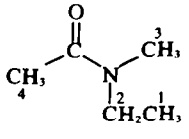
No	Compound	H-1[b]	H-2[b]	H-3[b]	H-4[b]	H-5[b]	H-6[b]	K	$W_{1/2}$[c]	AF
1		3·06 10·2 10·8	3·16 5·2 6·24	2·17 11·4 10·92				1033	99	0·072
2a		1·06 6·63 5·70	3·33 11·67 12·35	2·87 5·83 7·18	1·98 13·38 12·34			1178	100	0·104
2b		1·14 3·62 4·01	3·21 5·75 7·00	2·80 10·89 10·62	1·98 13·00 12·40			1180	90	0·080

Table 3 (*continued*)

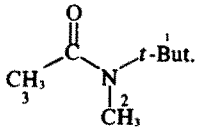
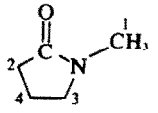
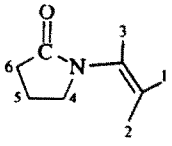
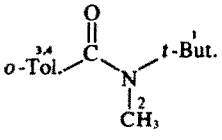
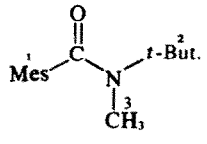
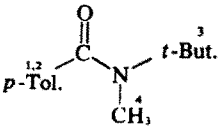
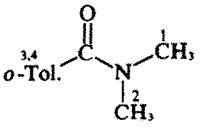
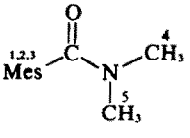
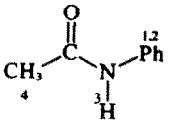
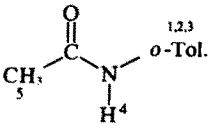
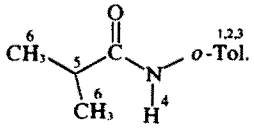
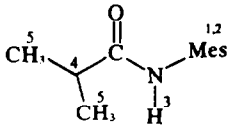
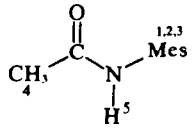
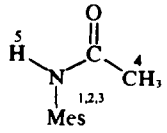
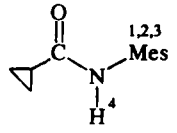
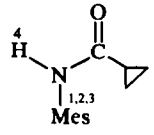
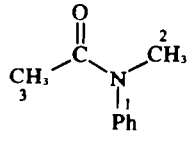
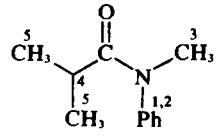
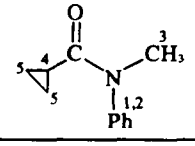
No	Compound	H-1[b]	H-2[b]	H-3[b]	H-4[b]	H-5[b]	H-6[b]	K	W_{140}[c]	AF
3		1·35 6·66 6·49	2·80 7·26 9·54	1·98 18·52 17·33				1646	75	0·123
4		2·83 8·15 7·97	2·33 11·10 10·48	3·38 3·39 4·92	2·06 3·88 3·95			893	100	0·113
5		4·30 3·02 3·06	4·48 3·45 4·42	7·22 15·21 13·87	3·48 5·58 6·12	2·13 4·65 5·15	2·45 12·67 13·29	1136	89	0·089
6		1·47 4·32 4·39	2·62 5·01 5·04	2·03[d] 5·61[d] 4·47	6·87[e] 4·26[e] 5·16			858	84	0·150
7		2·06[f] 3·26[f] 3·59	1·47 4·00 4·06	2·60 4·69 4·36				738	87	0·067
8		7·08[g] 6·02[g] 5·90	6·82[h] 0·40[h] −0·12	1·42 5·74 5·56	2·73 5·43 5·72			967	89	0·064
9		3·05 9·72 9·48	2·75 5·13 5·77	7·03[e] 5·50[e] 5·28	2·23[d] 4·56[d] 4·49			956	100	0·055
10		2·06[f] 3·41[f] 4·34	6·56[i] 1·11[i] −0·48	2·16[j] 0·50[j] −1·04	2·99 9·69 8·43	2·65 4·80 5·55		935	99	0·247
11		7·15[k] 7·53[k] 7·47	6·93[l] 1·75[l] 1·22	8·15 3·95 5·85	2·00 8·72 7·36			662	100	0·195
12		7·40[e] 2·65[e] 3·41	6·80[m] 1·15[m] 0·21	2·05[d] 2·59[d] 3·25	7·13 6·60 5·98	1·93 7·67 7·56		682	84	0·140
13		7·33[e] 4·29[e] 4·39	6·83[m] 0·50[m] 0·29	2·10[d] 1·81[d] 1·40	7·33 4·29 3·48	2·45 3·82 5·03	1·15 2·81 2·08	397	88	0·219

Table 3 (*continued*)

No	Compound	H-1[b]	H-2[b]	H-3[b]	H-4[b]	H-5[b]	H-6[b]	K	W_{140}[c]	AF
14		1·96[f] 1·73[f] 1·59	2·13[f] 0·31[f] 0·34	6·85 1·99 2·57	2·42 3·49 3·70	1·14 2·07 1·49		291	98	0·191
15a		2·04[f] 1·66[f] 1·84	2·15[f] 0·26[f] 0·34	6·58[i] 0·66[i] 0·52	2·10 4·25 4·18	6·66 —		377	99	0·054
15b		2·04[f] [n]	2·04[f]	6·66[i]	1·63	6·66				
16a		2·16[f] 0·0	2·05[f] 0·0	6·56[i] 0·0	6·93 0·0			—	—	—
16b		2·16[f] [n]	2·16[f]	6·66[i]	6·93					
17		7·05[k] 2·68[k] 4·73	3·13 9·66 9·13	1·83 11·26 10·80				973	89	0·144
18		7·08[k] 4·89[k] 6·19	7·08[l] 2·53[l] 2·02	3·10 14·22 12·67	2·48 8·42 9·97	0·95 7·50 5·44		1290	100	0·183
19		7·03[k] 4·91[k] 5·89	7·03[l] 2·26[l] 1·88	3·17 11·94 11·12	1·33 7·28 8·96	0·97 10·39 9·21		1283	79	0·134

[a] Ligand *X* (Fig 1) is represented on the left side; consequently for angles $0° \leq \varphi \leq 180°$ the Ld is in *cis* position to this ligand.

[b] Figures in the first row indicate chemical shifts (δ) of undoped spectra; figures in the second row indicate observed molar induced shifts; figures in the third row indicate calculated molar induced shifts.

[c] Molar fraction of form with the Lanthanide attached at $\varphi = 140°$.

[d] Tolyl ring *ortho* methyl group.

[e] Tolyl ring *ortho* proton.

[f] Mesityl ring *ortho* methyls.

[g] *p*-Tolyl ring *ortho* protons.

[h] *p*-Tolyl ring *meta* protons.

[i] Mesityl ring *meta* protons.

[j] Mesityl ring *p*-methyl.

[k] Phenyl ring *ortho* protons.

[l] Phenyl ring *para* proton.

[m] *o*-Tolyl ring *para* proton.

[n] Deviates from linearity in the $\Delta\nu$ *vs.* [Ld]/[S] plot (Fig 3).

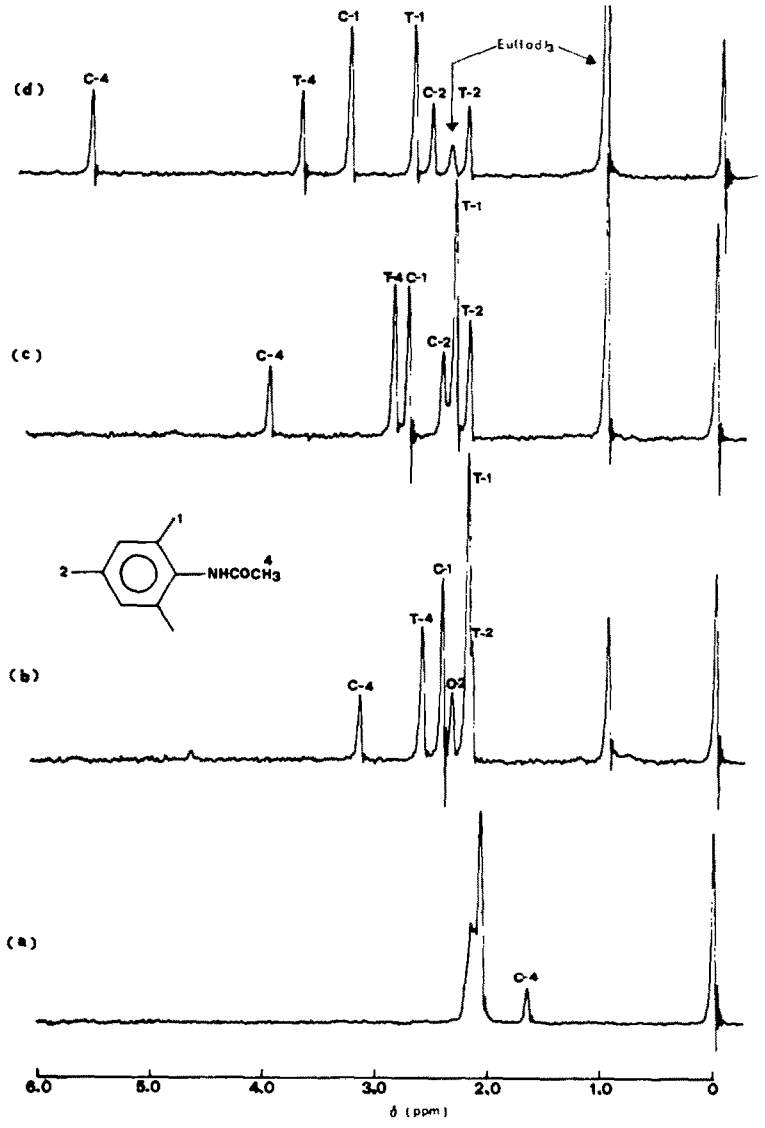


Fig 2. 60-MHz ^{1}H-NMR spectra (methyl region) of compound **15** as a function of the concentration (mole/mole) of [Ld]/[Substrate] (a) = 0; (b) = 0·092; (c) = 0·153; (d) = 0·337, in $CDCl_3$ and TMS as internal reference, at 38°. Peaks labelled *C* and *T* refer to the *cis* and *trans* isomer, respectively (see text).

Table 4. Physical and Chemical Characteristics of the Amides Unreported in the Literature

Compound[a]	b.p./mmHg or m.p.(°C)	Recrystallization solvent	Formula	Analysis Calcd. C	H	N	Found C	H	N
6	68–69	Petroleum ether	$C_{13}H_{19}NO$	76·05;	9·33;	6·82	76·25;	9·18;	6·90
7	76–77	Petroleum ether	$C_{15}H_{23}NO$	77·20;	9·94;	6·00	77·30;	9·87;	6·03
8	79–80	Petroleum ether	$C_{13}H_{19}NO$	76·05;	9·33;	6·82	76·18;	9·27;	6·75
10	160/18	—	$C_{12}H_{17}NO$	75·35;	8·96;	7·32	75·17;	9·02;	7·26
14	151–52	EtOH	$C_{13}H_{19}NO$	76·05;	9·33;	6·82	76·28;	9·20;	6·95
16	170–71	EtOH	$C_{13}H_{17}NO$	76·81;	8·43;	6·89	77·01;	8·29;	6·93

[a] See Table 3 for identification of the amides.

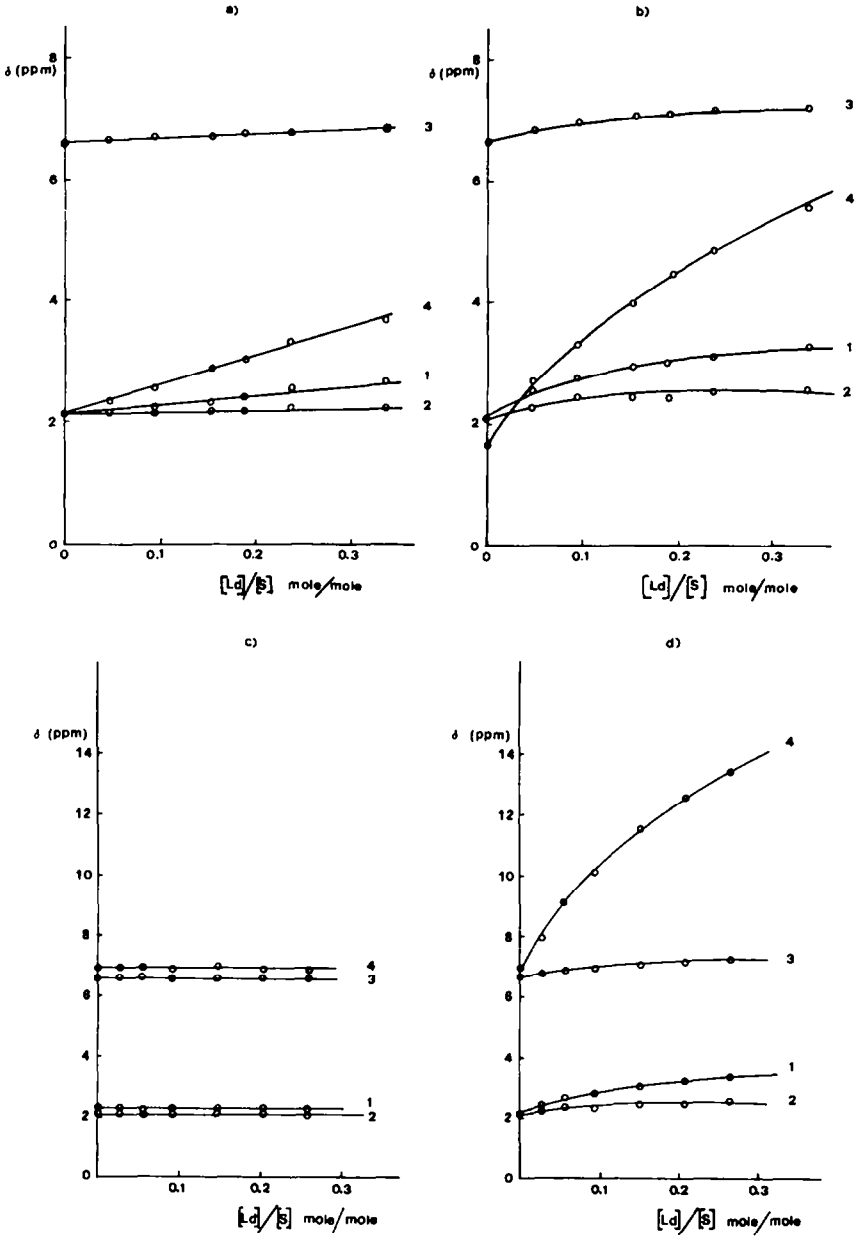


Fig 3. Variation of induced shifts with molar ratio [Eu(Fod)$_3$]/[Substrate] for compounds **15** and **16** in Table 3. (a) LIS for **15a** (*trans* isomer); (b) LIS for **15b** (*cis* isomer); (c) LIS for **16a** (*trans* isomer); (d) LIS for **16b** (*cis* isomer). See Table 3 for the numbering system of the signals.

This form, according to the data from the LIS simulation process, is the one with the t-Bu group *cis* to the carbonyl group. Thus, the less steric demanding site of complexation for the lanthanide is *cis* to the acetyl methyl group (Table 3).

Rotation around the N–C amide bond, although it will bring the N–CH_3 group *cis* to the carbonyl is not expected to leave more "space" for the lanthanide. In fact, as proved by the results obtained with dimethylacetamide (**1**), the attack of the lanthanide in position *cis* to the carbonyl methyl group is still the more favored. In light of this analysis no changes in rotamer population are expected and found for **3**. Similar arguments can be adduced to explain analogous experimental results found for all the N-methyl anilides investigated (compounds **17–19**, Table 3), in which the LIS simulation process indicates that the only dias-

tereomer which contributes to the spectrum is the one with the N-Me group biased in a conformation *cis* to the carbonyl group.

For compound **2** in which the two diastereomeric forms do not differ appreciably in steric congestion around the carbonyl group both forms contribute in nearly equal weight to the NMR spectrum.[21] As expected, addition of LSR, does not produce appreciable variation of the population ratio of the two forms.

CONCLUSIONS

In our opinion, the results obtained indicate that the topological approach can be a simple and useful method for investigating the problem of the interaction of LSR with organic substrates.

Here we have tested this approach for substrates bearing the carbonyl functional group and the results have thrown some light on the factors that may influence the equilibria of conformationally mobile systems.

Work on similar lines has been recently reported for the analysis of the interaction of LSR with the sulfoxide group by Wing *et al*[10] and with the cyano group by Willcott *et al.*[22] Other functional groups can be tested in an analogous manner and such analysis can be extended as a convenient way to analyse the problem, still unsolved, of the interaction of LSR with di- and poly-functional molecules.

Such an extension may be of help in analyzing complex biological systems since the use of LSR is one of the most powerful tools for simplifying the complex NMR absorption pattern of these substrates.

Added in proof: A similar approach has been described for the carbonyl group by: R. H. Newman, *Tetrahedron* **30**, 969 (1974)

EXPERIMENTAL

Lanthanide induced shifts measurements were performed with $Eu(fod)_3$. Spectra of about 5% $CDCl_3$ solns (TMS as internal reference), containing 0–1·0 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, 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, up to a value of *ca* 0·4 mole/mole. 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 a CDC-6600 digital computer.

For compounds in which the phenyl ring possesses a C_2 axis coincident with its bond to the central atom, calculations of the coordinates of the *ortho* and *meta* ligands were performed by positioning the Ld–O–C plane perpendicular to the aryl ring. When the aryl ring lacked such an axis the angle between the aryl ring and the Ld–O–C plane was stepwise varied (10° increment) until the best fit of the data was obtained. For compounds **6** and **12** (Table 3) such an angle was found to be *ca* 90°; in derivative **9** the *o*-tolyl ring is coplanar with the carbonyl group and the methyl group is *trans* to the O atom. In compound **13** the *o*-tolyl ring deviates of *ca* 40° from the coplanarity with the N-H group and the methyl group is *cis* to the N-hydrogen.

In molecules bearing an isopropyl group the best fit between the observed and calculated LIS was obtained positioning the two methyl groups *cis* to the carbonyl group and bisecting the Ld–O–C plane, while the methine hydrogen was placed in this plane and opposite to the carbonyl oxygen.

For derivatives possessing a t-Bu group the calculated LIS were obtained averaging the geometrical factors of the three Me groups. Both rotamers, possessing one of the Me groups in the Ld–O–C plane (one has this Me group *cis* and the other *trans* to the carbonyl oxygen) were thought to contribute in equal weight to the averaged spectrum.

Methods for calculating the geometrical factors of the methyl and cyclopropyl groups were described previously.[3-5]

Synthetic. Most of the compounds used in this study were commercial products purified by standard procedures or were synthesised and characterised according to the literature. Some amides (unreported in the literature) were prepared in this Laboratory according to the general procedure described below.

0·1 mole of the acid chloride, dissolved in dry ether or benzene, were added dropwise to an equimolar mixture of amine and triethylamine, at room temp under stirring. After 10 min the mixture was poured onto water, and the organic layer was extracted with $CHCl_3$. The solvent was removed under reduced pressure and the crude product was distilled under vacuum or recrystallized from a suitable solvent. In Table 4 are summarized the physical and chemical characteristics of these amides.

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