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A SIMPLE METHOD FOR SIMULATING LANTHANIDE INDUCED SHIFTS IN BIFUNCTIONAL SUBSTRATES.

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Recently we reported a simple topological approach to the computer simulation of Lanthanide Induced Shifts (LIS) in some substrates containing a carbonyl group.[1] This approach revealed that the Lanthanide complexed with the substrate only in certain preferred positions. More importantly,the results threw some light on the factors that influence the equilibria of conformationally mobile systems when complexed with Lanthanide Shift Reagents (LSR).[1] Furthermore,we predicted that this simple approach could be readily extended to become a very convenient way to analyze the general problem,still unsolved,of the interaction of LSR with bi- and poly-functional substrates.[1,2]

We now wish to report some preliminary results which show the reliability and utility of this approach to the interaction of LSR with bifunctional substrates. As a first step in our analysis we investigated the three bifunctional amides in Table I : N,N'-diacetylpiperazine(**1**), 2,5-*trans*-dimethyl-N,N'-diacetylpiperazine (**2**) and N,N'-diacetylpirazolidine(**3**). In all these derivatives,when rotation of the acetyl group is kinetically restricted on the nmr time scale, several diastereomeric forms are possible,which can be demonstrated by complexation with LSR.[3]

Under our topological approach we allowed the Lanthanide to complex only with the two lone-pairs of the carbonyl oxygen atom. The distance Lanthanide-Oxygen was always taken equal to 3.0 Å.[1] In the more general case,*i.e.*,in molecules in which the carbonyl group is attached to two different ligands,the two oxygen lone-pairs reside in diastereomeric environments,which are represented by values of the C-O-Ld internuclear angle (φ) of 140° and 220°,respectively.[4] In derivatives **1**-**3** of Table I a φ value of 140° indicates a position of the Lanthanide *cis* to the acetyl methyl group; on the other hand a φ value of 220° stands for the Lanthanide *cis* to the nitrogen atom (positions *A* and *B*,respectively, in Figure 1).

Consequently, dealing with two carbonyl groups within each molecule, as in the present case, the possible combinations of sites in which the Lanthanide can complex are three: AA, AB, and BB, where AA stands for a complexed molecule in which the two Lanthanide ions are both directed towards the acetyl methyl groups. The significance of positions AB and BB are thus obvious.[5]

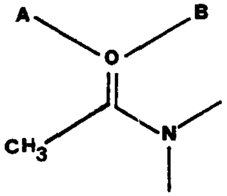


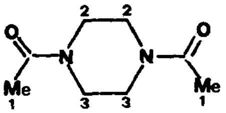
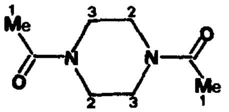
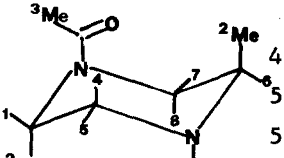
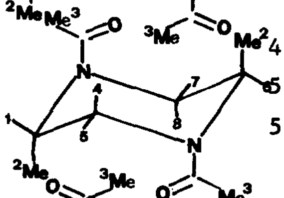
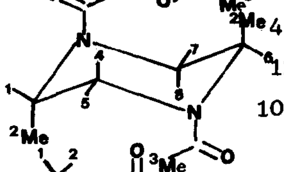
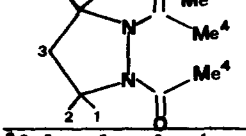
Figure 1

Data in Table I reveal that a satisfactory agreement factor(AF) between the calculated and experimental LIS was obtained within this approach for the molecules investigated. For derivative **3** it has been shown[8] that, at ambient temperatures, only diastereomer **3a** contributes appreciably to the nmr spectrum and that both acetyl groups are not coplanar with the $N{-}N{-}C_{carbonyl}$ plane. Due to kinetic restricted rotation around the N-N bond,[9] protons 1 and 2 in **3a**(see Table I) are diastereotopic and the use of LSR coupled with simulation of the observed LIS allowed us to further support the finding that only form **3a** exists at room temperature. In fact, the calculated LIS for the other two possible diastereomeric forms of **3** are too far away to be reconcilied with the experimental values.

In all these compounds only one diastereomeric site of complexation(AA) was found to contribute appreciably to the observed LIS. This site is always the less steric demanding, as judged by considering the internuclear distances between the Lanthanide and ligands attached to the carbonyl group, and these findings parallel what was already found in the LIS simulation process of some monofunctional amides.[1] *Thus the relevance to chemistry of such approach is that the LIS simulation process can be easily done positioning the Lanthanide ion only in the less steric demanding site. Consequently, the investigation of bi- and poly-functional substrates becomes a much simpler task.*

Acknowledgement. We thank Dr. G.Montaudo for the gift of a sample of compound **3** and for stimulating our interest on this work.

Table I. Chemical shifts,measured and simulated LIS for some bifunctional amides.

No.	Compound	H-1[a]	H-2[a]	H-3[a]	H-4[a]	H-5[a]	H-6[a]	H-7[a]	H-8[a]	AF^b_{AA}	AF^b_{AB}	AF^b_{BB}	K^c
1a		2.30	3.70	3.70						.063	.169	.551	1722
		11.9	13.8	7.7									
		10.9	14.6	7.6									
1b		2.30	3.70	3.70						.030	.238	.583	2189
		13.5	18.1	10.4									
		14.0	17.6	10.6									
2a		4.03	—	2.20	3.45	3.45	4.90	4.37	2.95	.155	.359	.369	1156
		5.2		6.5	5.8	5.8	12.5	12.8	5.8				
		5.5		7.4	5.5	5.7	11.0	10.8	8.0				
2b		4.03	—	2.20	3.05	4.23	4.03	4.23	3.05	.112	.276	.583	1073
		5.2		6.5	5.8	10.9	5.2	10.9	5.8				
		5.7		6.9	6.7	9.7	5.7	9.7	6.7				
2c		4.90	—	2.20	3.45	3.45	4.90	3.45	3.45	.147	.250	.558	1191
		12.5		6.5	5.8	5.8	12.5	5.8	5.8				
		10.7		7.7	6.8	6.3	10.7	6.3	6.8				
3a		4.12	3.03	2.05	2.10					.111	.703	.793	1355
		11.0	8.3	4.5	11.1								
		9.0	8.1	5.2	11.8								

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[a] Only clearly detectable signals are reported;figures in the first row indicate chemical shift(δ) of undoped spectra;figures in the second row indicate observed molar induced shifts;figures in the third row indicate calculated molar induced shifts only for the complexed form which gave the best agreement factor,i.e., form with the Lanthanide in position AA.

[b] The agreement factor refersto forms with the Lanthanide in positions AA, AB, and BB,respectively.

[c] Pseudo-contact constant calculated only for form with the Lanthanide in position AA.

[d] In this form both acetyl groups were considered twisted 20°,in opposite directions, around their N-C bonds.

References and Footnotes

1) P.Finocchiaro,A.Recca,P.Maravigna and G.Montaudo,*Tetrahedron*,**30**,0000(1974).
2) A.F.Cockerill,G.L.O.Davies,R.C.Harden,and D.M.Rackham,*Chem.Rev.*,**73**,553(1973) and references cited therein.
3) G.Montaudo and P.Finocchiaro,*J.Org.Chem.*,**37**,3434(1972).
4) These values came out from a best fitting of calculated and observed LIS in some related monofunctional amides : see reference 1 for a detailed discussion of the subject. The molecular geometry of the compounds investigated was inferred from pertinent structural data on closely related molecules and the computer program employed for the calculations is a modification of that one described in reference 1.
5) It may appear that in this analysis we are considering *each* carbonyl group complexed with a Lanthanide molecule in a sort of 2:1 complex,where two Lanthanide ions complex *simultaneously* with one diamide molecule. Although this situation can probably occur at very high molar concentrations of Lanthanide/ Substrate it is obvious that in solutions with a molar deficiency of LSR this kind of 2:1 complex is very unlikly. What we really mean,by our notation, is that in the time-averaged geometry of the complexed molecule the Lanthanide occupies such relative positions. In fact,it can be easily demonstrated that a 2:1 or a 1:1 complexes can be both analyzed in the same way,at least on the nmr time scale at ambient temperatures in which the exchange of Lanthanide ion is a fast process,and the doped spectrum represents an averaged spectrum of free and complexed substrate.[6] The only remarkable difference would be observed in the numerical value of the pseudo-contact constant (*K*) of the McConnell and Robertson equation[7]: if both carbonyl groups are considered bound to one Lanthanide ion (2:1 complex) the *K* value would be one half of the value determined under the hypothesis of 1:1 complex.
6) J.Briggs,F.A.Hart and G.P.Moss,*Chem.Commun.*,1506(1970).
7) H.M.McConnell and R.E.Robertson,*J.Chem.Phys.*,**29**,1361(1958).
8) G.Montaudo,S.Caccamese,P.Finocchiaro and P.Maravigna,to be published.
9) G.J.Bishop,B.J.Price and I.O.Sutherland,*Chem.Commun.*,672(1967).