Tetrahedron Vol. 38, No. 22, pp. 3245 to 3254, 1982
Printed in Great Britain.

0040-4020/82/223245-10$03.00/0
Pergamon Press Ltd.

CONFORMATIONAL ANALYSIS-V.[+]

A LANTHANIDE INDUCED SHIFT (L.I.S.) N.M.R. INVESTIGATION OF CONFORMATIONAL ISOMERISM IN AROMATIC ALDEHYDES AND KETONES

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(*Received in UK 28 September* 1982)

Abstract - An L.I.S. N.M.R. investigation of conformational isomerism in meta-nitrobenzaldehyde and furan- and thiophene-3-aldehydes, and of the conformation of acetophenone has been carried out. With the diamagnetic (complexation) contributions to the observed shifts removed by means of experiments with La $(fod)_3$ and the application of our previously-described lanthanide ion complexing model, the pseudo-contact shifts have been used to obtain the precise conformational preferences of the aldehydes. They exist to the extent of 45%, 100% and 80% respectively in the O-trans conformation, findings which are in good agreement with previously-reported values. The L.I.S.'s for acetophenone are in best agreement with a planar molecule, although the definition is not as good in this case. These examples suggest that the L.I.S. technique is of general applicability in the determination of conformer populations and the conformations of aromatic aldehydes and ketones.

INTRODUCTION

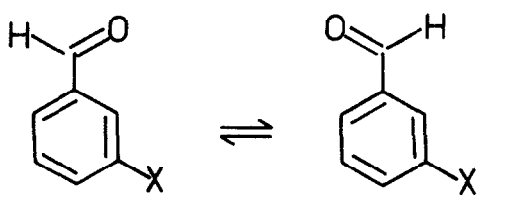
In a recent paper,[2] we have shown that by the simultaneous use of ^{1}H and ^{13}C L.I.S.'s, with the ^{13}C diamagnetic complexation shifts removed by use of La $(fod)_3$ and a chemically appropriate model for the lanthanide ion binding, it is possible to obtain precise agreement between observed and calculated shifts in benzaldehyde and furan- and thiophene-2-aldehydes. This level of agreement allows the deduction of the conformational preference of furan-2-aldehyde where an equilibrium consisting of appreciably-populated, non-equivalent forms occurs.

In the work presented here, we consider whether our approach to the utilisation of the L.I.S. technique[2] is a general method for the investigation of conformational equilibria in unsymmetrically-substituted, aromatic aldehydes and we extend our field of study to include an aromatic ketone. We take, as examples, meta-nitrobenzaldehyde and furan- and thiophene-3-aldehydes, and the simplest aromatic ketone, acetophenone.

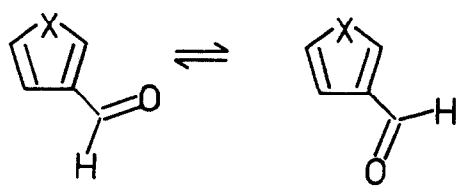
Conformational isomerism in unsymmetrically-substituted benzaldehydes was investigated originally in the N.M.R. studies of Karabatsos and Vane.[3] They used the stereospecificity of the $^{5}J_{HH}$ coupling of the aldehyde proton to the anti-oriented meta proton of the aromatic ring, via the well-known, planar, zig-zag path, to deduce the conformational preferences of a number of substituted benzaldehydes. Assuming that the value of this coupling in salicylaldehyde (0.7Hz) corresponds to the O-cis conformer and that the

[+] for Part IV see reference 1.

coupling to the cis-oriented meta proton is zero, they obtained a value of ca. 60% O-trans from the observed coupling of 0.45-0.50Hz for meta-nitrobenzaldehyde , (see Scheme 1 for the nomenclature). Recently, more precise values of the conformer populations have been determined by the observation of the separate spectra of the conformers at ca.-150°C.[4,5] Conformer populations of 100% O-trans for the ortho-chloro-, -fluoro-and -t-butyl-benzaldehydes, ca. 50% for the ortho- and meta-methylbenzaldehydes, and 41%, 35% and 26% for the meta-bromo-,-chloro-, and -fluorobenzaldehydes are reported.



O - cis O - trans



O - cis O - trans

Scheme 1

Chemical shift correlations[6] and L.I.S. studies[7] have also been used in the determination of the conformer preferences of substituted benzaldehydes. However, the L.I.S. study suffers from the same drawbacks that we have highlighted previously. The use of only ^1H induced shifts furnishes too little data for a well-determined analysis and in consequence a chemically-unreasonable model (lanthanide ion binding along the C=O bond axis) was adopted.

The substituted furans and thiophenes have also been extensively investigated. The measurement of both the $^4J_{HH}$ and $^5J_{HH}$ couplings in furan- and thiophene-3-aldehydes allowed Roques and co-workers[8] to determine the conformer populations in these molecules as 100% and 80% O-trans respectively (see Scheme 1 for the nomenclature). These results contrast with the theoretical predictions of Radom and co-workers who, in a series of investigations,[9,10,11] calculated $E_{trans}-E_{cis}$ to be 0.15[9] and 0.01[10] kcal mole^{-1} for furan-3-aldehyde and -0.08[11] kcal mole^{-1} for thiophene-3-aldehyde.

L.I.S.'s have been used by Gacel *et al.*[12] to determine the conformer populations in furan-and thiophene -3-aldehydes. Once again, however, only the ^1H L.I.S.'s were obtained, giving four observables (and hence equations) from which five unknowns (one normalisation factor, three coordinates for the lanthanide ion position and the conformer ratio) need to be determined. Even with the additional assumption made that the La--O distance equals 3.0Å , the system is still not overdetermined and the values of the conformer ratios thus obtained are not definitive.

Nagata *et al.*[13] used coupling constants, carbonyl shielding effects and solvent shifts to deduce the conformer preferences of thiophene-3-aldehyde and 3-methoxycarbonylthiophene. Their results suggested the preference for a twisted (non-planar) O-trans conformer (which these authors describe as the S-cis form). This non planar conformer has not been invoked by any other investigators.

In acetophenone there is no conformational isomerism but the precise conformation of the side-chain is of interest. The results of ab-initio (STO-3G) calculations predict an energy difference ($E_{orthogonal}-E_{planar}$) of 4.4 kcal mole^{-1},[14] which compares with the experimental value of the barrier height of 3.1 kcal mole^{-1}.[15] However, there is no direct experimental evidence for the planar conformation in solution.

RESULTS

The pseudo-contact shifts given in Tables 1-4, corrected for the effects of complex formation ($\Delta M - \Delta D$), have been used along with the program LIRAS-3 (described previously[3]) to obtain the required conformational information. As we have repeatedly stressed, in all such studies the major problem is the necessity for an over-determined set of equations. We use the model derived previously[16] of four-site lanthanide ion complexation in which the lanthanide position is reflected in the xy and yz planes. (This is equivalent, of course, to the two-site model for a planar substrate). Furthermore the percentage population of the lanthanide ion exo and endo to the carbonyl is allowed to vary. Thus, five unknowns need to be determined to fix the lanthanide complexation, (one normalisation factor, three lanthanide ion co-ordinates and the percentage population). The additional information required is the conformer population in the aromatic aldehydes and the side-chain torsional angle in acetophenone, making a total of six unknowns in each case. In each molecule, sufficient information is provided to obtain these data: it is convenient to consider each system separately.

meta-Nitrobenzaldehyde. Twelve pseudo-contact shifts have been measured (Table 1): thus, the system is considerably over-determined, although there is some uncertainty over the question of the extent of a contact shift contribution to the induced shift at the carbonyl carbon.[2] The benzaldehyde geometry of reference 2 was used and the search for the best fit between calculated and experimental shifts was conducted over a range of conformer populations, both including and excluding the carbonyl carbon shift. The results are shown in Figure 1 in which the agreement factor (A.F. or R cryst) displays a minimum very clearly at 42 ($\pm$ 5) % O-trans conformer. Inclusion of the carbonyl carbon shift leads to a slightly better A.F., but the position of the minimum is unchanged. The lanthanide positions at the minima are given in Table 5 and will be considered with the other values later.

The percentage of the O-trans conformer found compares (at first sight) unfavourably with that predicted by Karabatsos and Vane[3] (ca. 60%). However, their measurements relied on accurate values of the H-H coupling constants in systems which are often strongly coupled and in which the observed splittings may not equal the couplings: thus it was felt sensible to re-measure the appropriate data at 250 MHz. At this frequency meta-nitrobenzaldehyde displays a first-order ^{1}H-coupling pattern and gives J (CHO-H_5) 0.47 Hz. in precise agreement with ref. 3. Furthermore, the ^{1}H spectrum of benzaldehyde at 250 MHz gives three, well-separated, ring resonances in which the meta protons show clearly the aldehyde proton coupling of 0.43 ($\pm$ .01) Hz. This is significantly greater than the observed splitting of the triplet aldehyde resonance (ca. 0.35 Hz) due, probably, to further unresolved couplings of the aldehyde proton to the other ring protons. The long-range coupling in meta-nitrobenzaldehyde is therefore not appreciably greater than that in benzaldehyde (in which the conformer

Table 1. Observed Shifts (δ), L.I.S.'s (Δ M) Diamagnetic Shifts (Δ D) and Pseudo Contact Shifts ($\Delta M - \Delta D$) p.p.m. for meta-Nitrobenzaldehyde

	C=O	C_1	C_2	C_3	C_4	C_5	C_6	CHO	H_2	H_4	H_5	H_6
δ [a]	189.81	137.48	124.38	148.84	128.59	130.48	134.76	10.15	8.71	8.50	7.81	8.28
ΔM [b]	92.03	32.12	21.98	12.78	10.56	10.99	21.88	49.72	21.97	6.54	6.30	20.09
ΔD [c]	7.99	-0.84	1.26	0.74	2.21	0.64	2.21					
$\Delta M - \Delta D$	84.04	32.96	20.72	12.04	8.35	10.35	19.67					

[a] $[S]_o$ 1.049 ML^{-1} in $CDCl_3$.

[b] from three additions of Yb(fod)$_3$, ρ 5.08, 8.49, 11.13 x 10^{-2} ML^{-1}, all corr. coeff. > 0.997.

[c] $[S]_o$ 0.784 ML^{-1}, ρ 12.27 x 10^{-2} ML^{-1}.

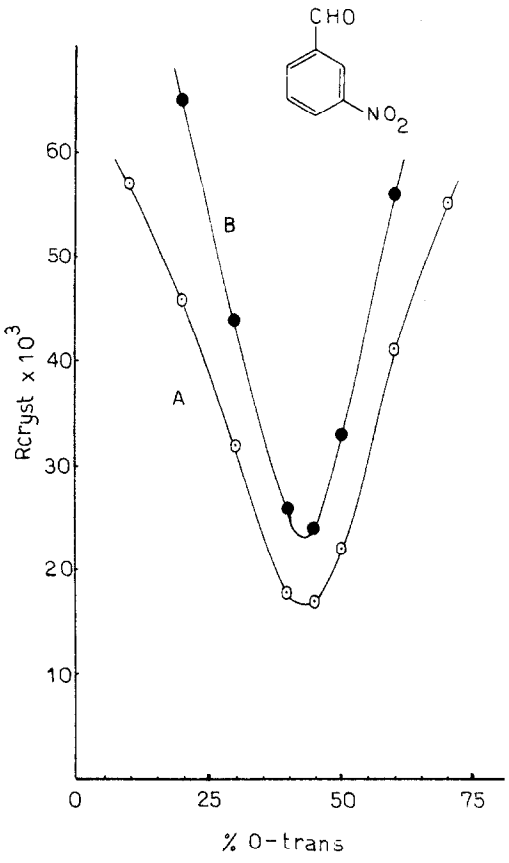


Figure 1. The agreement factor (R_x) versus the % O-cis conformer for meta nitrobenzaldehyde a) with and b) without the inclusion of the carbonyl carbon.

population must be 50:50). Thus, the results of the long-range coupling measurements and of the L.I.S. determination are in reasonable agreement, with the latter being of somewhat greater accuracy.

Furan- and Thiophene-3-Aldehydes. It is convenient to discuss these systems together, as the data were treated in an identical manner. In both cases there are nine, observed, pseudo-contact shifts, including the carbonyl carbon, and six, unknown parameters. The geometry was derived from that of the corresponding 2-aldehydes of reference 2 by simply moving the aldehyde group to the 3-position. Again, the search for the best agreement was conducted over a range of conformer populations, both including and excluding the carbonyl carbon, and the results are presented graphically in Figures 2 and 3 and numerically in Table 5. In furan-3-aldehyde, the best agreement is always observed for 100% of the O-trans isomer (Figure 2) whereas in thiophene-3-aldehyde, the best fit is found with ca. 80-85% O-trans (Figure 3). In both cases, the definition of the A.F. curves is good, and it is particularly encouraging that these results (which have been obtained without any ad hoc assumptions about the conformational preferences), agree with other experimental determinations of the conformer populations. For example, Roques et al.[8] obtain 100% O-trans and 80% O-trans respectively for furan- and thiophene-3-aldehydes from coupling

Table 2. Observed Shifts (δ), L.I.S.'s (ΔM), Diamagnetic Shifts (ΔD) and Pseuso contact Shifts ($\Delta M - \Delta D$) (p.p.m.) for Furan-3-Aldehyde

	C = O	C_2	C_3	C_4	C_5	CHO	H_2	H_4	H_5
δ^a	184.43	151.37	128.77	107.04	145.01	9.95	8.09	6.79	7.48
ΔM^b	123.65	26.52	45.45	30.98	17.34	65.84	17.23	29.93	10.54
ΔD^c	9.35	4.81	-1.23	0.48	1.28				
$\Delta M - \Delta D$	114.30	21.71	46.68	30.98	16.06				

[a] $[S]_o$ 0.927 ML^{-1} in $CDCl_3$.

[b] from three additions of Yb $(fod)_3$, ρ 4.89, 8.51 and 12.61 x 10^{-2} ML^{-1}, all corr. coeff. > 0.998.

[c] from three additions of La $(fod)_3$ ($[S]_o$ 1.00 ML^{-1}), ρ 4.29, 8.78 and 12.61 x 10^{-2} ML^{-1}, all corr. coeff. for significant shifts (>1.0°) > 0.99.

Table 3. Observed Shifts (δ), L.I.S.'s (ΔM), Diamagnetic Shifts (ΔD) and Pseudo contact Shifts ($\Delta M - \Delta D$) p.p.m. for Thiophene-3-Aldehyde

	C = O	C_2	C_3	C_4	C_5	CHO	H_2	H_4	H_5
δ^a	184.85	136.58	143.14	125.51	127.41	9.93	8.12	7.54	7.36
ΔM^b	134.17	31.09	48.18	32.79	17.36	72.20	22.02	33.63	11.27
ΔD^c	9.34	6.97	-2.11	1.50	0.64				
$\Delta M - \Delta D$	124.83	24.12	46.07	31.29	16.72				

[a] $[S]_o$ 1.089 ML^{-1} in $CDCl_3$.

[b] from three additions of Yb $(fod)_3$, ρ 3.85, 7.53 and 11.09 x 10^{-2} ML^{-1}, all corr. coeff. > 0.999.

[c] from three additions of La $(fod)_3$, $[S]_o$ 1.09 ML^{-1}, ρ 3.65, 7.36 and 13.14 x 10^{-2} ML^{-1}, all corr. coeff. for significant shifts (>1.0) > 0.96.

constant data, in precise agreement with the results obtained here. The agreement further demonstrates the need for caution in equating the results of M.O. calculations [9,10,11] to the solution conformational equilibria of multi-polar molecules.

Acetophenone. There is no conformational equilibrium in acetophenone: the question does arise, however, as to the precise conformation of this molecule, i.e. the orientation of the acetyl side-chain with respect to the phenyl ring. Because of the rapid rotation about the phenyl-carbonyl group bond on the N.M.R. time scale, and as a result of the accidental equivalence of the meta and para proton chemical shifts, there are nine, observed, pseudo-contact shifts including that due to the carbonyl carbon (Table 4) and six parameters to be determined.

The geometry of acetophenone was taken from the crystal studies of acetophenone at 154°K[17] and of para-nitroacetophenone[18]. The results of the two studies are in good agreement and give the resultant geometry shown in Scheme 2. The benzene ring is effectively a regular hexagon of side 1.397Å with the side-chain dimensions shown.

The search for the best A.F. was conducted over a range of side-chain torsional angles, again both including and excluding the carbonyl carbon shift, with the results shown graphically in Figure 4 and numerically in Table 5. A number of different models were used for the methyl protons. As these protons are very close to the complexed lanthanide ion, they show large pseudo-contact shifts and are also sensitive to the precise model used. We considered a three-fold axis of rotation of the methyl group with a) one proton eclipsing the carbonyl group and b) staggered with respect to the carbonyl and also

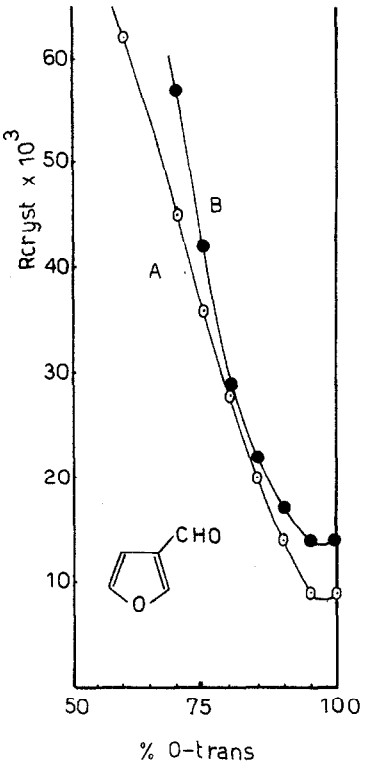


Figure 2. The agreement factor (R_x) versus the % O-cis conformer for furan-3-aldehyde a) with and b) without the inclusion of the carbonyl carbon.

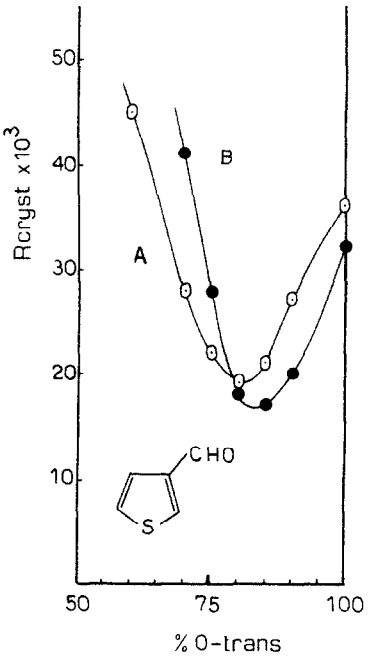


Figure 3. The agreement factor (R_x) versus the % O-cis conformer for thiophene-3-aldehyde a) with and b) without the inclusion of the carbonyl carbon.

Table 4. Observed Shifts (δ), L.I.S.'s (ΔM), Diamagnetic Shifts (ΔD) and Pseuso-contact Shifts ($\Delta M - \Delta D$) p.p.m. for Acetophenone

	C = O	C_1	$C_{2,6}$	$C_{3,5}$	C_4	C(Me)	$H_{2,6}$	$H_{3,4,5}$	H(Me)
δ [a]	198.00	137.20	128.34	128.59	133.10	26.55	7.95	7.48	2.58
ΔM [b]	119.20	48.07	30.94	14.48	13.14	51.29	31.06	7.47	33.81
ΔD [c]	13.50	-2.17	2.58	0.31	3.21	-0.99			
$\Delta M - \Delta D$	105.70	50.24	28.36	14.17	9.93	52.28			

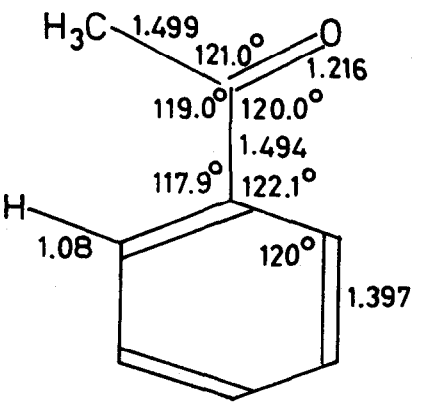
[a] $[S]_o$ 0.945 ML^{-1} in $CDCl_3$.

[b] from three additions of Yb $(fod)_3$, ρ 4.47, 7.87 and 11.27 x 10^{-2} ML^{-1}, all corr. coeff. > 0.995.

[c] $[S]_o$ 0.683, ρ 10.00 x 10^{-2} ML^{-1}.

c) a six-fold axis of rotation. The lowest agreement factor was obtained for case b) and the results for this model are given in Figure 4.

Figure 4 shows clearly that, as expected, the preferred conformation of the acetyl group is in the plane of the phenyl ring. However, the



Scheme 2. Acetophenone geometry.

definition of the A.F. versus dihedral angle curve is much less good than in the analogous conformer population graphs (Figure 1-3). This is perhaps not surprising since the nuclei in the 2,6 and 3,5 pairs are each equivalenced by the rapid internal rotation and yet these are the only nuclei whose L.I.S.'s are sensitive to the phenyl-carbonyl group torsional angle. (It would be of interest to consider an analogous system in which equivalence due to rapid rotation does not occur: this is under investigation). Nonetheless, Figure 4 does prove clearly that the L.I.S. technique can determine side-chain conformations in solution for such molecules. We note that the A.F. curve shows much better definition when the carbonyl carbon shift is excluded, even though the value of the A.F. at 0° is higher. The reason for this can be deduced from the data in Table 5. The R.M.S. error (observed-calculated shifts) is less when the carbonyl shift is excluded. The contrasting behaviour of the A.F. and the R.M.S. error is simply due to the very large value of the

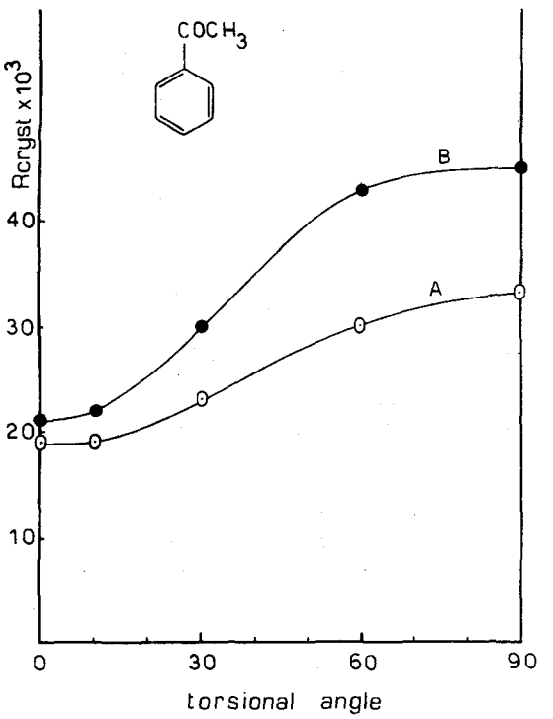


Figure 4. The agreement factor (R_x) versus the torsional angle of the acetyl group w.r.t. the phenyl ring for acetophenone a) with and b) without the inclusion of the carbonyl carbon.

Table 5. Results of Analyses of L.I.S. Shifts.

	A.F. (Rcryst)	R.M.S.	Lanthanide Co-ordinates				
			r (Å)	ϕ°	ψ°	Pop.(%)	% O-trans
Meta-nitrobenzaldehyde							
a) -C = O	.0240	0.54	2.75	65	135	100	45
b) All nuclei	.0165	0.54	2.65	75	130	100	45
Furan-3-aldehyde							
a) -C = O	.014	0.48	2.60	65	145	100	100
b) All nuclei	.009	0.47	2.55	65	145	100	100
Thiophene-3-aldehyde							
a) -C = O	.017	0.63	3.20	55	140	100	85
b) All nuclei	.019	1.03	2.60	75	130	100	80
Acetophenone							
a) -C = O	.021	0.64	2.95	55	145	85	-
b) All nuclei	.019	0.85	3.10	65	140	80	-

pseudo-contact shift at the carbonyl carbon, which appears in the denominator for the A.F. but not in the R.M.S. error.

The effects of the inclusion of the carbonyl carbon shift are also seen in the geometry of the best solutions (Table 5). In the aldehydes, the Yb--O bond length always decreases, as was found previously,[2] but in the ketone (in contrast) the bond length increases. In this case, however, the lanthanide population is very different from that in the aldehydes due, presumably, to greater steric repulsions. In the aldehydes, the population is 100% exo, i.e. towards the aldehyde proton, exactly as expected on steric grounds. In the ketone it is ca. 80% exo (i.e. towards the methyl carbon). All the complex geometries found are consistent with our original postulate[19] of co-ordination with the carbonyl lone-pairs, though it should be noted that the lanthanide position is not restricted in the computational search procedure.

CONCLUSIONS

The major finding which emerges from these studies is that the L.I.S. technique, when due consideration is given both to the removal of diamagnetic shifts and to a chemically acceptable model of lanthanide complexation, may be used reliably in the determination of both conformer populations and, to some extent, the conformations of aromatic aldehydes and ketones. The degree of definition obtained is very acceptable for the conformer population studies and compares favourably with most other N.M.R. methods apart from the absolute measurement of the intensities of signals due to the separate conformers at low temperatures. In principle it is possible to combine the L.I.S. and low temperature measurements to obtain both ΔH° and ΔS° for the conformational equilibrium studied; one recent example of this application has been given.[1]

The degree of definition found in the determination of the orientation of the acetophenone side-chain is less good and the probable reason for this has been suggested. However, there would appear to be no objection, in principle, to greater refinement of this procedure given a suitable example. Indeed, provided the system is suitably over-determined, this technique should be applicable to the determination of both conformer populations and geometries in suitable cases.

EXPERIMENTAL

The ^1H and ^{13}C spectra for L.I.S. analysis were recorded at 80 and 20 MHz respectively on the same samples with a Varian FT-80 spectrometer, at a probe temperature of ca. 25°C. Some spectra were also run on a Brücker WM 250 spectrometer. All spectra were measured on solutions in $CDCl_3$ which had been stored over molecular sieves and passed through a dried Al_2O_3 column immediately before use. Commercial lanthanide shift reagents were dried in vacuo over P_4O_{10} for 24 hrs.

Commercial m-nitrobenzaldehyde was recrystallised from benzene (m.p. 57-58°C). Commercial acetophenone and thiophene-3-aldehyde were distilled in vacuo the day before their use. Furan-3-aldehyde was prepared from the corresponding primary alcohol according to ref.[20] and distilled in vacuo the day before its use.[24]

The results of the L.I.S. experiments with $Yb(fod)_3$ (incremental weighing method) are given in Tables 1-4. The proton and carbon assignments follow from the literature.[21,22,23] The experimental points were all obtained with a molar ratio $\rho = [L]_o / [S]_o$ in the range between 0.00 and 0.13. Both the correlation coefficients ($\geq .997$ with one exception) and the intercepts (which are identical to the unshifted spectra) demonstrate the accurate linearity of these plots.

$La(fod)_3$-induced shifts on carbon signals are reported in Tables 1-4 (protons did not display any meaningful shifts). Obviously agreement factors are good only when variations in chemical shifts are not too small. However, even in such cases, the intercepts are identical to the unshifted spectra, thus demonstrating the linearity of these plots.

Acknowledgements.

We thank the British Council for a Substantive Award, the S.E.R.C. for support, Miss L. Pardo for technical assistance and Professor C. Dell'Erba for assistance and support.

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24. This preparation was performed by Miss L. Pardo supervised by Professor C. Dell'Erba and Dr. M. Novi.