

Conformational analysis. Part 29.¹ The conformational analysis of 2-substituted fluoro- and trifluoromethyl-benzaldehydes, acetophenones and methyl benzoates by the lanthanide induced shift (LIS) technique



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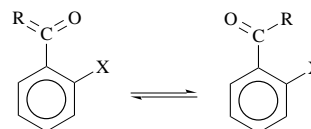
An improved LIS technique, using, Yb(fod)₃ to obtain the paramagnetic induced shifts of all the spin $\frac{1}{2}$ nuclei in the molecule, together with complexation shifts obtained by the use of Lu(fod)₃ has been used to investigate conformational isomerism in 2-fluorobenzaldehyde 1, 2-fluoroacetophenone 2, methyl 2-fluorobenzoate 3 and the corresponding 2-trifluoromethyl compounds 4, 5 and 6. The use of fluorine LIS in these molecules was first established by analysis of the LIS in 4-fluorobenzaldehyde 7 and 4-trifluoromethylbenzaldehyde 8 in which conformational isomerism is not possible and confirmed in subsequent analyses. It is shown that ¹⁹F LIS may be used with the same degree of confidence as the corresponding ¹H and ¹³C LIS in these molecules. Analysis of the LIS data was considered together with *ab initio*, modelling and solvation calculations to provide a comprehensive account of the conformer geometries and energies for these compounds in a variety of solvents. The 2-fluoro compounds are all planar, with the *trans* (C=O...F) conformer always more stable, in 1 and 2 predominating in all but very polar solvents. In the corresponding 2-trifluoromethyl compounds both the *cis* and *trans* conformers of the aldehyde 4 are planar with the *trans* form predominating, but the ketone 5 is essentially in one orthogonal conformation and the ester 6 interconverting between two nonplanar conformations with the *trans* conformer predominant.

Introduction

Previous investigations in this series have demonstrated the importance and the utility of the LIS method in determining the structures and conformations of a variety of molecules in solution²⁻⁷ and the essential conditions necessary for successful LIS studies have been given. Amongst these are the determination of only one or two molecular parameters (*e.g.* a torsional angle or conformer ratio) and both the quality and the comprehensiveness of the experimental data. In particular, the diamagnetic complexation shift (ΔD) must be subtracted from the experimental paramagnetic shifts (ΔM) to obtain the required pseudo-contact shift ($\Delta M - \Delta D$). Very recently it has been shown that diamagnetic complexation shifts measured using Lu(fod)₃ gave consistently better results when used with the paramagnetic shifts obtained with Yb(fod)₃ than the more common La(fod)₃ reagent.^{2,3} This is probably due to the greater similarity of Yb *vs.* Lu as compared to Yb *vs.* La.

This technique thus provides a means of obtaining accurate and comprehensive LIS data and it has been used recently to determine the conformer ratios in substituted acetophenones and acetylnaphthalene and also to directly test the molecular geometries, either calculated or experimental, for benzaldehyde, acetophenone, methyl benzoate and their 2,6-dimethyl and 2,6-difluoro derivatives.^{2,3} It was found that the calculated (*ab initio* or molecular mechanics) geometries did not reproduce the experimental data for the 2,6-difluoro compounds, probably due to the difficulty of accurately reproducing the F...O interactions in these compounds. Thus, it was of some interest to determine whether this improved LIS technique could be applied to the determination of the molecular geometries and conformer energies of similar fluorinated compounds with more than one possible conformation in solution and here we apply this method to the investigation of the conformational

analysis of some 2-fluoro and 2-trifluoromethyl substituted benzaldehydes, acetophenones and methyl benzoates. These molecules can exist in the *O-cis* and *O-trans* forms (Scheme 1)



Scheme 1 Conformational isomers in 2-substituted aromatic carbonyl compounds, X = F, CF₃; R = H, Me, OMe

and the relative energy of the two forms is a sensitive measure of the F...O=C and F...R interactions. Furthermore, as the interactions of the fluorine substituent are of a major significance in the conformational analysis and the fluorine nucleus is also an excellent NMR-active nucleus it was also of interest to determine whether the ¹⁹F LIS could be used with the same degree of certainty in the analysis as the ¹H and ¹³C LIS.

The conformations of fluoro and trifluoromethyl substituted acetophenones, benzaldehydes and benzoates have been the subject of numerous investigations.⁹⁻¹⁷ The conformational preference of 2-fluorobenzaldehyde was investigated using the observed dipole moment to estimate the conformational equilibrium *via* calculated dipole moments of the individual *cis* and *trans* forms from INDO calculations¹⁰ to give 73% of the *trans* conformer in benzene solution. However, the dipole moment in CCl₄ solution has been interpreted as evidence for the *trans* form to be exclusively favoured.¹³ Schaefer and Wasylishen,^{9,12} used the stereospecific ⁵J_{HH} coupling between the aldehyde proton and the aromatic H5 proton to determine the percent of the *cis* and *trans* forms in CS₂-C₆D₁₂ and acetone solvents as 96 and 86% *trans* corresponding to free energy differences of 1.82

Table 1 C–F couplings (Hz) in fluoro and trifluoromethyl aromatic carbonyl compounds

Compound	C=O	C-1	C-2	C-3	C-4	C-5	C-6	CH ₃	CF ₃
1	6.7	8.0	256.6	20.5	9.1	3.7	1.9	—	—
2	3.5	12.7	254.8	23.8	8.5	3.4	2.5	7.0	—
3	3.7	10.1	259.8	22.5	9.0	4.2	1.2	—	—
4	2.7	1.5	32.5	5.5	<i>a</i>	1.1	<i>a</i>	—	274.4
5	<i>a</i>	2.0	32.4	5.1	<i>a</i>	1.0	<i>a</i>	<i>a</i>	272.1
6	<i>a</i>	2.1	32.4	5.5	<i>a</i>	1.0	<i>a</i>	<i>a</i>	273.1
7	<i>a</i>	2.5	9.7	22.3	256.7	22.34	9.7	—	—
8	<i>a</i>	<i>a</i>	<i>a</i>	3.8	32.7	3.8	<i>a</i>	—	272.9

^a The coupling is less than the digital resolution (0.35 Hz).

Table 2 Observed carbon, proton and fluorine chemical shifts (δ), LIS values (ΔM), diamagnetic shifts (ΔD) and pseudo-contact shifts $\Delta M(\text{PC})$ for the 4-substituted compounds

4-Fluorobenzaldehyde 7										
	C-1	C-2,-6	C-3,-5	C-4	C=O	H-2,-6	H-3,-5	F	Ald.	
Shift	132.99	132.26	116.37	166.54	190.56	7.92	7.22	59.38	9.98	
ΔM^a	47.08	31.55	15.63	14.05	135.42	30.40	10.10	12.03	72.62	
ΔD^b	-1.42	2.22	0.72	1.77	7.23	-0.06	-0.07	5.05	-0.20	
$\Delta M(\text{PC})$	48.50	29.33	14.91	12.28	128.19	30.40	10.10	6.98	72.82	
4-Trifluoromethylbenzaldehyde 8										
	C-1	C-2,-6	C-3,-5	C4	C=O	CF ₃	H-2,-6	H-3,-5	CF ₃	Ald.
Shift	138.76	129.96	126.17	135.69	191.07	123.50	8.01	7.81	98.61	10.11
ΔM^c	50.81	33.65	16.72	15.32	149.20	7.54	32.21	10.89	6.09	81.47
ΔD^d	-1.21	1.57	0.49	1.87	7.26	-0.07	-0.01	-0.05	-0.31	-0.11
$\Delta M(\text{PC})$	52.02	32.08	16.23	13.44	141.94	7.54	32.21	10.89	6.40	81.58
Intercept	138.71	129.93	126.16	135.67	190.90	123.50	7.98	7.80	98.61	10.02

^a Yb(fod)₃, S_0 0.41 mm. $\rho \times 10^{-2}$ 2.47, 4.11, 5.60, corr. coef. >0.9988. ^b Lu(fod)₃, S_0 0.37 mm. $\rho \times 10^{-2}$ 2.73, 4.46, 6.29, corr. coef. >0.9993. ^c Yb(fod)₃, S_0 0.27 mm. $\rho \times 10^{-2}$ 2.05, 4.33, 6.18, corr. coef. >0.9999. ^d La(fod)₃, S_0 0.33 mm. $\rho \times 10^{-2}$ 1.40, 3.31, 4.97 corr. coef. >0.995.

and 1.08 kcal mol⁻¹ (1 cal = 4.184 J) respectively. Extrapolation of the liquid phase data gave an estimate of the vapour phase energy difference as 2.75 kcal mol⁻¹ in favour of the *trans* form in good agreement with the theoretical value of 2.20 kcal mol⁻¹.

In 2-fluoroacetophenone the observed dipole moment in CCl₄ and benzene solution was interpreted as arising from *ca.* 90% *O-trans* form from INDO calculations¹⁴ (see below), whereas that of 2-trifluoromethylacetophenone was interpreted on the basis of one orthogonal conformation with a 90° CO–ring dihedral angle. These conclusions were supported by NMR evidence, particularly from the ⁵J_{CH₃-F} coupling. This 'through space' coupling in 2-fluoroacetophenone is only possible in the *trans* conformer. In CCl₄ deuteriotoluene and acetone the coupling is 5.2, 4.8 and 4.5 Hz and this decrease was interpreted as due to an increase in the population of the more polar *cis* conformer with increasing solvent polarity.¹⁵⁻¹⁷ This coupling is only 0.4 Hz in 2-trifluoromethylacetophenone¹⁴ which is consistent with the proposed orthogonal conformation.

Experimental

All samples were obtained commercially (Aldrich and Fluorochem), except the methyl 2-fluoro and 2-trifluoromethyl benzoates which were prepared from the corresponding acids by standard procedures.¹⁸ The aldehydes needed to be distilled prior to use, the others were used directly for the LIS experiments. The solutions were made up as 0.5 M in deuteriochloroform which had been stored for at least 24 h over molecular sieves prior to use. The shift reagent Yb(fod)₃ is available commercially and Lu(fod)₃ was prepared following Springer *et al.*¹⁹ The shift reagents were dried *in vacuo* over P₂O₅ at *ca.* 35 °C for 24 h, and maintained *in vacuo* over P₂O₅ between successive additions to the sample. Three additions of shift reagent (*ca.* 15–20 mg) were weighed directly in the NMR tube. The plots of chemical shifts *vs.* ρ , the ligand/substrate ratio, were checked for

linearity (all correlation coefficients >0.999) and for the intercept at the origin (a good test for any impurities). The diamagnetic shifts (ΔD) were obtained from identical experiments using Lu(fod)₃. In 4-fluorobenzaldehyde, where the correlation coefficient was <0.999 due to impurities scavenging the shift reagent preferentially to the sample, the first data point was excluded giving three data points (the three additions of shift reagent) to achieve the required linearity. In this case the extrapolated intercept is not at δ_0 and is not given in Table 2.

For compounds **1**, **2**, **4** and **5** the LIS measurements were recorded on a Varian Gemini 200 MHz spectrometer operating on ¹H and ¹³C at 22 °C. Digital resolution was better than 0.09 Hz for the proton spectra and 0.36 Hz for the carbon spectra; a 4 s pulse delay was used for the accumulation of the carbon spectra. The fluorine LIS values were recorded in a separate experiment on a Bruker AMX-400 spectrometer involving ¹H and ¹⁹F measurements. The fluorine shifts were then normalised to the ¹H and ¹³C LIS obtained previously. The ¹H, ¹³C and ¹⁹F LIS values for the other compounds were obtained directly on the Bruker AMX-400. Typical proton spectral widths were 600 Hz with 128 K transform, carbon spectral widths were typically 23 000 Hz with 128 K transform using a line broadening of 2.0 Hz, fluorine spectral widths were 37 000 Hz with 256 K transform.

Spectral assignments

The spectral assignments, were straightforward utilising previous literature assignments,^{9,19,20} additive substituent chemical shifts,²¹ the size of the ΔM values obtained and for the ¹³C assignments the C–F couplings which have characteristic values of *ca.* 250, 20–25, *ca.* 10 and <5 Hz for the one, two, three and four bond couplings.²² The observed couplings are given in Table 1 and it can be seen that the ring fluorines couple with all the ring carbon atoms and the CF₃ fluorines mainly to the α - and β -carbons as expected and occasionally to the carbonyl carbon.

Table 3 Carbon, proton and fluorine chemical shifts (δ), LIS values (ΔM), diamagnetic shifts (ΔD), and pseudo-contact shifts $\Delta M(\text{PC})$ for the 2-fluoro substituted compounds

2-Fluorobenzaldehyde 1								
	C-1	C-2	C-3	C-4	C-5	C-6	C=O	
Shift	124.21	164.73	116.53	136.36	124.66	128.71	187.17	
ΔM^a	62.79	34.26	18.86	19.48	22.49	47.55	179.13	
ΔD^b	-0.76	1.86	0.60	2.82	0.62	1.43	9.05	
$\Delta M(\text{PC})$	63.55	32.40	18.26	16.66	21.87	46.12	170.08	
Intercept	124.00	164.62	116.47	136.29	124.59	128.56	186.56	
	H-3	H-4	H-5	H-6	Ald.	F		
Shift	7.184	7.621	7.280	7.887	10.386	52.37		
ΔM	12.54	10.91	14.88	53.27	98.05	29.99		
ΔD	0.07	0.14	0.06	0.18	0.42	3.29		
$\Delta M(\text{PC})$	12.47	10.77	14.82	53.09	97.63	26.70		
Intercept	7.139	7.582	7.229	7.707	10.03			
2-Fluoroacetophenone 2								
	C-1	C-2	C-3	C-4	C-5	C-6	C=O	CH ₃
Shift	125.73	162.27	116.66	134.68	124.38	130.61	195.88	31.45
ΔM^c	65.72	33.44	18.10	17.21	19.43	49.28	161.78	68.63
ΔD^d	-1.16	1.69	0.46	2.96	0.57	1.79	9.99	-0.11
$\Delta M(\text{PC})$	66.88	31.75	17.64	14.25	18.86	47.49	151.79	68.74
Intercept	125.68	162.24	116.65	134.67	124.36	130.57	195.77	31.41
	H-3	H-4	H-5	H-6	CH ₃	F		
Shift	7.104	7.521	7.199	7.879	2.647	52.37		
ΔM	12.42	8.67	10.10	57.45	44.60	23.19		
ΔD	0.05	0.12	0.03	0.32	0.30	3.31		
$\Delta M(\text{PC})$	12.37	8.55	10.07	57.13	44.30	19.88		
Intercept	7.117	7.520	7.184	7.838	2.617	—		
Methyl 2-fluorobenzoate 3								
	C-1	C-2	C-3	C-4	C-5	C-6	C=O	CH ₃
Shift	118.68	161.98	117.01	134.53	124.00	132.18	164.96	52.35
ΔM^e	43.14	23.61	10.47	8.69	9.23	26.56	100.76	34.82
ΔD^f	-1.55	0.78	0.18	1.78	0.44	1.34	5.04	2.47
$\Delta M(\text{PC})$	44.70	22.82	10.29	6.82	8.79	25.26	95.72	32.35
Intercept	118.68	161.98	117.01	134.53	124.00	132.18	164.95	52.35
	H-3	H-4	H-5	H-6	CH ₃	F		
Shift	7.131	7.513	7.198	7.936	3.931	52.29		
ΔM	6.29	3.85	3.07	27.43	24.93	23.82		
ΔD	-0.05	0.03	-0.05	0.15	0.13	2.89		
$\Delta M(\text{PC})$	6.34	3.83	3.12	27.28	24.80	20.93		
Intercept	7.099	7.481	7.168	7.891	3.903	52.28		

^a Yb(fod)₃. S_0 0.32 mm. $\rho \times 10^{-2}$ 4.09, 8.93, 15.20, corr. coef. >0.9986. F corr. coef. 0.994. ^b Lu(fod)₃. S_0 0.40 mm. $\rho \times 10^{-2}$ 1.88, 3.70, 5.17, corr. coef. >0.975. F corr. coef. 0.970. ^c Yb(fod)₃. S_0 0.35 mm. $\rho \times 10^{-2}$ 1.30, 2.99, 4.41, corr. coef. >0.9995. F corr. coef. 0.9996. ^d Lu(fod)₃. S_0 0.35 mm. $\rho \times 10^{-2}$ 1.69, 2.96, 4.37, corr. coef. >0.997; F corr. coef. 0.9999. ^e Yb(fod)₃. S_0 0.46 mm. $\rho \times 10^{-2}$ 5.58, 9.48, 13.75; corr. coef. >0.999. ^f Lu(fod)₃. S_0 0.41 mm. $\rho \times 10^{-2}$ 5.79, 13.76, 17.04, corr. coef. >0.993.

Full details of all the spectral assignments are given elsewhere.^{18,23} The observed chemical shifts (δ), diamagnetic shifts (ΔD), LIS values (ΔM) and pseudo-contact shifts [$\Delta M(\text{PC}) = \Delta M - \Delta D$] are given in Tables 2–4 for the compounds measured here.

Results

The LIS data in Tables 2–4 may now be used to investigate the conformational equilibria in these compounds. It is important to restate the caveat mentioned earlier, that due to the small number of LIS values, only one or two unknowns can be investigated in any given system. Here, we will attempt to determine the conformational equilibrium, *i.e.* the populations of the *cis* and *trans* forms (Scheme 1) and also one key geometric parameter, the CO–ring torsional angle which of course may differ in the *cis* and *trans* conformers. This torsional angle in the comparable 2,6-difluoro compounds was shown to be

very different from that calculated by either molecular mechanics or *ab initio* calculations² and the solution of the LIS analysis is very dependent on this angle. The remainder of the molecular geometries will be taken from the standard experimental data given in ref. 2 and the *ab initio* geometries are from GAUSSIAN92 (94)²⁴ with the recommended 6-31G (6-31G*)²⁵ basis set. Full details of all these geometries are given in refs. 18 and 23. The analysis of the observed LIS was carried out using the LIRAS3 program incorporating the two-site or four-site complexation model. Note that these are identical for a planar substrate geometry. These have been fully described in previous parts of this series.^{2–7} Following ref. 2 we may regard any solution (observed minus calculated shifts) with an agreement factor (AF) <1.0% (*i.e.* 0.01) and with all calculated LIS within 1.0 ppm of the observed shifts as a fully acceptable solution.

Fluorine pseudo-contact shifts

It is necessary first to determine whether the ¹⁹F LIS may be

Table 4 Carbon, proton and fluorine chemical shifts (δ), LIS values (ΔM), diamagnetic shifts (ΔD), and pseudo-contact shifts $\Delta M(\text{PC})$ for the 2-trifluoromethyl substituted compounds

2-Trifluoromethylbenzaldehyde 4									
	C-1	C-2	C-3	C-4	C-5	C-6	C=O	CF ₃	
Shift	133.78	131.09	126.14	133.65	132.37	129.12	188.98	123.78	
ΔM^a	35.21	19.31	10.82	10.79	12.77	28.68	98.46	12.73	
ΔD^b	-1.23	1.37	0.28	1.75	0.13	1.53	5.64	-0.22	
$\Delta M(\text{PC})$	36.44	17.94	10.54	9.04	12.64	27.15	92.82	12.95	
Intercept	133.71	131.05	126.12	133.63	132.35	129.07	188.80	123.76	
	H-3	H-4	H-5	H-6	Ald.	F			
Shift	7.797	7.719	7.720	8.137	10.41	106.17			
ΔM	6.97	5.93	8.00	33.10	54.39	9.89			
ΔD	-0.01	—	—	0.06	-0.13	0.07			
$\Delta M(\text{PC})$	6.97	5.93	8.00	33.10	54.52	9.82			
Intercept	7.79	7.71	7.71	8.08	10.31	—			
2-Trifluoromethylacetophenone 5									
	C-1	C-2	C-3	C-4	C-5	C-6	C=O	CH ₃	CF ₃
Shift	140.50	126.80	126.71	130.18	131.94	127.09	201.90	30.60	123.69
ΔM^c	45.44	28.40	14.56	12.09	13.33	29.42	114.45	47.18	23.57
ΔD^d	-1.54	1.07	0.34	1.87	0.44	1.72	10.52	0.19	0.08
$\Delta M(\text{PC})$	46.97	27.33	14.23	10.22	12.89	27.70	103.93	46.99	23.49
Intercept	140.47	126.79	126.70	130.18	131.94	127.08	201.85	30.58	123.68
	H-3	H-4	H-5	H-6	CH ₃	F			
Shift	7.711	7.577	7.588	7.466	2.578	103.65			
ΔM	9.73	6.54	7.18	27.45	29.88	20.39			
ΔD	0.01	0.05	0.00	0.14	0.26	1.24			
$\Delta M(\text{PC})$	9.73	6.50	7.18	27.31	29.61	19.15			
Intercept	7.709	7.565	7.596	7.454	2.567	103.59			
Methyl 2-trifluoromethylbenzoate 6									
	C-1	C-2	C-3	C-4	C-5	C-6	C=O	CH ₃	CF ₃
Shift	131.19	128.89	126.75	131.24	131.79	130.24	167.36	52.85	123.45
ΔM^e	48.25	24.92	11.08	8.98	9.42	30.16	112.05	37.90	19.88
ΔD^f	-1.58	0.81	0.29	1.25	0.30	1.37	4.15	2.11	0.10
$\Delta M(\text{PC})$	49.83	24.11	10.79	7.73	9.12	28.79	107.90	35.79	19.78
Intercept	131.15	128.88	126.76	131.23	131.78	130.21	167.17	52.78	123.44
	H-3	H-4	H-5	H-6	CH ₃	F			
Shift	7.741	7.609	7.586	7.779	3.933	102.16			
ΔM	7.74	3.96	2.10	28.93	26.94	17.07			
ΔD	0.0	0.0	0.0	0.17	0.10	0.46			
$\Delta M(\text{PC})$	7.74	7.73	2.11	28.76	26.84	16.61			
Intercept	7.727	7.593	7.587	7.733	3.889	102.17			

^a Yb(fod)₃, S₀ 0.50 mm. $\rho \times 10^{-2}$ 2.02, 4.56, 6.90, corr. coef. >0.9994. *F* corr. coef. 0.995. ^b Lu(fod)₃, S₀ 0.50 mm. $\rho \times 10^{-2}$ 1.87, 5.63, 8.89 corr. coef. >0.9956. *F* corr. coef. 0.915. ^c Yb(fod)₃, S₀ 0.41 mm. $\rho \times 10^{-2}$ 1.65, 5.48, 7.38, corr. coef. >0.9994. *F* corr. coef. 0.9993. ^d Lu(fod)₃, S₀ 0.43 mm. $\rho \times 10^{-2}$ 1.76, 4.14, 6.22, corr. coef. >0.999, *F* corr. coef. 0.9991. ^e Yb(fod)₃, S₀ mm. $\rho \times 10^{-2}$ 3.76, 8.60, 16.58, corr. coef. >0.999. ^f Lu(fod)₃, S₀ 0.50 mm. $\rho \times 10^{-2}$ 8.47, 12.38, 16.30, corr. coef. >0.989.

used in this analysis. For this to be achieved the observed LIS must be solely due to the pseudo-contact term with no appreciable contact term (the ¹⁹F diamagnetic shifts are appreciable but these are already removed by the lutetium experiment). This can be investigated from the results for the 4-fluoro- and 4-trifluoromethyl-benzaldehyde (Table 2), in which there is no conformational equilibrium and the molecules are completely planar.

4-Fluorobenzaldehyde

The LIRAS3 analysis of the LIS for this molecule using either the experimental geometry with a standard benzene ring or the 6-31G* geometry gave excellent AF values of 0.45 and 0.39 respectively including the fluorine shift. The good agreement for both cases is of interest, as the geometry of the benzene ring is somewhat different in the two geometries. The GAUSSIAN geometry has a ring angle at C-4 of 122.7°, in agreement with that derived from the crystal structures of *para*-disubstituted

benzenes,²⁶ whereas the experimental geometry has a standard benzene ring (C–C 1.397 Å, C–H 1.085 Å, all angles 120°). The AF is unchanged if the fluorine atom is removed confirming that there is no appreciable contact shift at the *para* fluorine atom.

4-Trifluoromethylbenzaldehyde

Precisely the same pattern was observed in the analysis of the LIS in this molecule. The experimental geometry incorporating for the CF₃ group CC and CF bond lengths of 1.504 and 1.345 Å, respectively, and CCF angles of 111.9°²⁷ and the GAUSSIAN geometry again both gave excellent agreement factors of 0.61 and 0.56, respectively, indicating the absence of a contact contribution on the fluorine atoms. Further supporting evidence comes from the similarity of the $\Delta M(\text{PC})$ for the fluorine atoms (6.40 ppm) and those of the methyl hydrogen atoms in 4-methylbenzaldehyde (6.61).² Thus, we may safely conclude that the fluorine atoms in the *para* fluorine and trifluoromethyl groups experience no significant contact contribution. The cor-

responding fluorine atoms in the *ortho* position are of course much closer to the site of complexation, but we will show that these fluorine LIS may also be treated in a similar fashion and that their contact contributions are minimal.

2-Fluorobenzaldehyde 1

In the case of the 2-fluoro compounds there is no evidence to suggest that the heavy atom skeleton is not planar in either conformer, thus the only unknown quantity in the LIS analysis is the population of the *cis* and *trans* forms. We note immediately that for **1** the C-6 pseudo-contact shift is much greater than that of C-2 indicating a preference for the planar *trans* conformation. This was confirmed by the LIRAS analysis. Using the standard geometry² the analysis converges at 85% *trans* form with an AF of 1.02. Excluding the fluorine LIS gives 88% *trans* form with a somewhat better AF of 0.81. Using the 6-31G optimised geometry gives virtually identical results of 83% *trans* with AF 1.17 (incl. F) and 85% *trans* and AF 0.88 (excl. F). Thus the LIS analysis gives 85(±2)% *trans* form in CDCl₃ solution which corresponds to an energy difference of 1.0 kcal mol⁻¹ in favour of the *trans* form.

2-Fluoroacetophenone 2

We note that again the size of the C-2 and C-6 pseudo-contact shifts are very similar to that in **1** again indicating a preference for the O-*trans* conformer and this is again confirmed by the LIRAS analysis. The analysis using the standard geometry² gives 100% *trans* and an AF of 0.95 (incl. F) and 97% *trans* with an AF 0.71% (excl. F). The 6-31G geometry gives rather poorer AFs of 1.34 for 95% *trans* (incl. F) and 1.14 for 95% *trans* (excl. F). The AF values are significantly better with the experimental geometry and we conclude that the LIS analysis gives essentially all *trans* form with only 1–2% of the *cis* form present in chloroform solution.

Methyl 2-fluorobenzoate 3

The LIS data for this molecule in which the $\Delta M(PC)$ values for C-2 and C-6 are quite similar suggests that the populations of the two forms will be much more equal in this molecule and this is confirmed by the LIRAS analysis. Using the standard geometry with the C–O–C angle of 120° gives the best AF of 1.54 for 70% of the *trans* conformer (incl. F) and exactly the same populations and AF (excl. F). Again the 6-31G geometry gives a significantly poorer AF of 2.83 for 50% *trans* (incl. F) and 1.92 for 63% *trans* (excl. F). An optimised 6-31G* geometry was also used, but this gave even worse AF (*ca.* 2.9) than either of the above geometries. The LIRAS analysis indicates that this molecule exists as 65–70% of the *trans* conformer, corresponding to an energy difference of 0.45 (±0.05) kcal mol⁻¹ in favour of the *trans* form. The alternative possibility of one nearly orthogonal conformation gives an unacceptable AF (>4.0) and also is not consistent with the calculated geometries which all minimise to planar conformations.

2-Trifluoromethylbenzaldehyde 4

The bulky 2-trifluoromethyl substituent may induce the carbonyl group to adopt a non-planar conformation. However, in this compound there is no evidence to support a non-planar conformation and this is confirmed by the analysis of the LIS data. The pseudo-contact shift of C-6 is much greater than that of C-2 suggesting a preference for the *trans* conformer and this was the starting point for the LIS analysis. Using the standard geometry a good AF of 1.14 was given for 100% *trans* conformer, including F. Including the *cis* conformer gave a slightly lower AF of 1.00 for 96% *trans* form, again including F. The *ab initio* geometry gave similar results with an AF of 1.33 for 100% *trans* form and a significantly better AF of 0.74 for 88% *trans* form. In conclusion the LIS data for this compound is fully interpreted on the basis of two planar conformers, with the *trans* form *ca.* 90% populated giving an energy difference of *ca.* 1.3 kcal mol⁻¹.

2-Trifluoromethylacetophenone 5

The pseudo-contact shifts of the 2,6 and 3,5 carbons and protons are similar and this could be due to either an almost orthogonal conformation of the acetyl group or two almost equally populated conformers. Thus, the LIS analysis considered both models. When the planar *cis* or planar *trans* geometries were input to the LIRAS3 program no acceptable solution was obtained and this was also the case for any proportion of these two geometries. This suggests that both the conformers for this molecule have a non-planar skeleton. Thus in this compound both the two acetyl-ring dihedral angles and the populations of the two conformers need to be obtained from the LIS data.

As previously, the standard geometry model was first used. The first model attempted was that of one conformer, which gave an AF of 2.66 for the *trans* conformer with an acetyl-ring torsional angle of 80° and this was reduced to an almost acceptable AF of 1.69 by small changes in the bond angles, particularly the Me–C=O and H–C–C=O angles to 126 and 112°, respectively. These are not unreasonable changes considering the steric interactions in this molecule, but the question remains as to whether this solution is definitive or merely due to the averaging of the LIS of two less orthogonal conformations. Thus the two conformer model was attempted again using the standard geometry and varying both dihedral angles and the conformer populations. A global minimum was obtained with 50:50 populations of the *trans* and *cis* conformers, the *trans* conformer with an acetyl-ring dihedral angle of 25° and the *cis* with one of 45°. Again small changes to the H–C–C=O angles in both conformers to 112° and to the C–1C=O angle in the *trans* form (118°) reduced the AF to 1.50. Similar, but poorer, results were obtained using the *ab initio* geometry. The one conformer model, varying the acetyl-ring dihedral angle for the best solution gave a poor AF of 2.08 for an 85° dihedral angle. The two conformer model optimising the acetyl to ring dihedral angles and conformer populations also gave an identical AF for a 75:25 *cis:trans* ratio with acetyl-ring dihedral angles of 15° (*trans*) and 50° (*cis*).

In conclusion the LIS analysis gives barely acceptable solutions for either the one-conformer model in which the optimum solution is for an essentially orthogonal conformer, or for the two-conformer model in which the optimum AF occurs for approximately equal populations of the two conformers. The standard and *ab initio* geometries give similar solutions but the *ab initio* geometry gives poorer AF values for both models. In view of the small difference between the AF values for both models neither of which gives a fully acceptable AF, the LIS data cannot unambiguously differentiate between these two models and other factors need to be considered to decide between them (see below).

Methyl 2-trifluoromethylbenzoate 6

The pseudo-contact shifts of the 2,6 and 3,5 carbons and protons in this molecule are much less similar than those for the corresponding trifluoromethylacetophenone (Table 4) and this suggests that the compound exists either as one twisted but not orthogonal conformer or two interconverting conformers and again both models were considered. Using the standard geometry neither of the planar conformers gave an acceptable solution, but varying the ring to carbonyl dihedral angle gave a good AF of 0.91 for the *trans* conformer with a dihedral angle of 45°. The two-conformer model was then attempted initially varying only the populations of the two planar conformers and this did not give an acceptable AF. Varying both the proportions of the conformers and their dihedral angles gave a global minimum with an even better AF of 0.84 for 96% of the *trans* form with ester-ring torsional angles of 45° (*trans*) and 20° (*cis*). Fully acceptable AF values were also obtained for up to 10% of the *cis* form with torsional angles of 35–40° (*trans*) and 20–40° (*cis*).

Table 5 Observed and calculated pseudo-contact shifts for the 2-substituted compounds **1–6**

	1		2		3		4		5		6	
	Obs.	Calc. ^a	Obs.	Calc. ^b	Obs.	Calc. ^c	Obs.	Calc. ^d	Obs.	Calc. ^e	Obs.	Calc. ^f
CO	170.1	169.8	151.8	152.1	95.7	95.8	92.8	92.6	103.9	104.2	107.9	107.8
C-1	63.8	65.3	66.9	65.6	44.7	43.5	36.4	37.3	47.0	46.9	49.8	49.3
C-2	32.4	33.1	31.8	31.4	22.8	23.1	17.9	18.0	27.3	26.8	24.1	24.4
C-3	18.3	18.3	17.6	17.6	10.3	10.1	10.5	10.2	14.2	13.4	10.8	11.4
C-4	16.7	16.3	14.3	14.6	6.8	7.4	9.0	9.1	10.2	10.5	7.7	7.5
C-5	21.9	22.2	18.9	18.5	8.8	9.0	12.6	12.6	12.9	13.4	9.1	9.0
C-6	46.1	45.7	47.5	45.6	25.3	26.1	27.1	27.4	27.7	27.6	28.8	28.9
CH ₃	—	—	68.7	69.0	32.3	32.9	—	—	47.0	46.9	35.8	36.3
CF ₃	—	—	—	—	—	—	12.9	12.8	23.5	22.8	19.9	19.8
H-3	12.5	12.0	12.4	11.9	6.3	5.5	7.0	6.7	9.7	8.8	7.7	7.3
H-4	10.8	10.7	10.8	8.6	3.8	3.9	5.9	5.8	6.5	6.6	4.0	3.7
H-5	14.9	15.6	10.1	9.6	3.1	2.9	8.0	8.5	7.2	8.7	2.1	2.2
H-6	53.1	52.2	57.1	57.2	27.3	27.4	33.1	32.7	27.3	26.5	28.9	28.9
CHO	97.6	97.5	—	—	—	—	54.5	54.5	—	—	—	—
CH ₃	—	—	44.3	44.4	24.8	24.7	—	—	29.6	30.5	26.9	27.0
F	26.7	26.1	23.0	24.0	20.9	20.7	9.8	9.6	19.1	19.4	16.6	16.7

^a Standard geom. 85% *trans*, AF 1.00%, r 2.63 Å, ϕ 60°, ψ 132°, Pop 100%. ^b Standard geom. 100% *trans*, AF 0.95%, r 2.88 Å, ϕ 64°, ψ 140°, Pop 86%. ^c Standard geom. 70% *trans*, AF 1.54%, r 2.88 Å, ϕ 64°, ψ 158°, Pop 38%. ^d Standard geom. 96% *trans*, AF 1.00%, r 2.70 Å, ϕ 55°, ψ 142°, Pop 100%. ^e Standard geom. 85° dihedral, AF 1.81%, r 2.92 Å, ϕ 90°, ψ 140°, Pop 82%. ^f Standard geom. 96% *trans*, AF 0.84%, r 2.84 Å, ϕ 84°, ψ 152°, Pop 34%.

Table 6 Conformer energies, dipole moments and solvation energies for the 2-substituted compounds

	Conformer	$E_{\text{rel}}/\text{kcal mol}^{-1}$		Dip. mom./D ^a	Solv. En./kcal mol ⁻¹		
					$\epsilon = 2.2 \quad 4.8 \quad 21.2$		
		HF ^b	PCMODEL				
1	<i>trans</i>	0.0	0.0	3.26	1.23	2.16	3.26
	<i>cis</i>	2.6 ^c	2.4	4.42	2.27	4.00	6.02
2	<i>trans</i>	0.0		3.08	1.16	2.02	3.01
	<i>cis</i>	3.9		4.60	2.20	3.85	5.75
3	<i>trans</i>	0.0	0.0	2.16	1.08	1.83	2.68
	<i>cis</i>	0.9	0.1	3.38	1.61	2.78	4.11
4	<i>trans</i>	0.0	0.0	3.19	1.31	2.25	3.33
	<i>cis</i>	3.2	0.3	4.81	1.88	3.30	4.94
6	<i>trans</i>	0.0	0.0	2.23	0.97	1.64	2.38
	<i>cis</i>	1.4	0.0	3.53	1.14	1.96	2.89

^a From CHARGE4. ^b 6-31G basis set. ^c MP2/6-31G*.

The *ab initio* geometries for this molecule had ring to ester dihedral angles of 36 (42°) and 25 (32°) for the *trans* and *cis* conformers respectively at the 6-31G (6-31G*) levels, but neither of these geometries gave an acceptable solution on varying the conformer populations or even varying both the populations and ring to ester dihedral angles. We note that the *ab initio* geometries for the methyl 2-fluorobenzoate (above) and for the esters in ref. 2 did not give good solutions and this suggests that the ester group geometry is not given very precisely by *ab initio* calculations at this level of MO theory. In contrast a PCMODEL²⁸ geometry with ring to ester dihedral angles of 48° (*trans*) and 47° (*cis*) gave a reasonable solution with an AF of 1.25 for 90% of the *trans* form.

In conclusion the LIS data for this molecule is fully explained on the basis of the two interconverting non-planar forms both with torsional angles of *ca.* 40° with *ca.* 5% of the *cis* form giving an energy difference of *ca.* 1.7 kcal mol⁻¹ in favour of the *trans* form.

Table 5 gives the observed *vs.* calculated shifts for the 2-substituted compounds together with the lanthanide complexation parameters for the best solutions and it can be seen that in nearly all the cases an acceptable solution of the experimental shifts, including the fluorine LIS has been obtained. This demonstrates unequivocally that the fluorine LIS may be used with the same confidence as those of protons and carbon in any LIS study.

Discussion

It is instructive to compare the results obtained here for the conformer energies with both those of other investigations and

with *ab initio* and modelling calculations. These are often in different solvents and the theoretical calculations are of course for the vapour phase; thus there is the solvent dependence of the conformational equilibrium to consider. All the compounds investigated are highly polar and the distinct conformers have very different dipole moments and therefore their relative populations and energies will be very solvent dependent. The solvent dependence of the conformer energies is given quantitatively in Table 6 for those compounds interconverting between planar *cis* and *trans* forms using the MODELS theory with the standard geometries and partial atomic charges calculated by the CHARGE routine. These programs have been given in detail elsewhere^{29,30} but we note that the CHARGE4 calculated dipole moments for benzaldehyde, acetophenone, methyl benzoate, fluorobenzene and trifluoromethylbenzene are 3.07, 3.19, 2.06, 1.35 and 1.86 D, respectively, in good agreement with the observed values (3.2, 2.9, 1.9, 1.5 and 2.6 D), supporting the use of these solvation calculations which utilise the molecular dipole and quadrupole reaction fields for these compounds. We give in Table 6 the calculated solvation energy ($E_{\text{solv}} - E_{\text{vap}}$) for the *cis* and *trans* conformers for three values of the solvent dielectric constant, ϵ 2.2, 4.8 and 21.2 corresponding to non-polar solvents (cyclohexane, CCl₄), chloroform and acetone, respectively.

The LIS results can now be considered together with those of other investigations using the data of Table 6. For example the LIS value of the energy difference ($E_{\text{cis}} - E_{\text{trans}}$) for 2-fluorobenzaldehyde of 1.0 kcal mol⁻¹ in CDCl₃ solution together with the data of Table 6 predicts values of the energy

† IUPAC name: relative permittivity.

difference for the vapour, cyclohexane and acetone solutions of 2.8, 1.7 and 0.1 kcal mol⁻¹, respectively. Schaefer and Wasylishen,^{9,12} determined the proportion of the *cis* and *trans* forms in CS₂-C₆D₁₂ and acetone solvents as 96 and 86% *trans* corresponding to free energy differences of 1.8 and 1.1 kcal mol⁻¹, respectively, in generally good agreement with these predictions. Their calculated value of the vapour phase energy difference of 2.2 kcal mol⁻¹ at the 6-31G level is also in good agreement with the value given in Table 6 (2.6 kcal mol⁻¹) which was at a somewhat higher basis set level (MP2/6-31G*). This latter value is in excellent agreement with the value estimated from the solvent theory, thus in this molecule a complete description of the conformer energies in different media is obtained.

In the case of 2-fluoroacetophenone the equilibrium is so biased towards the *trans* form that a similar analysis is not possible without a definitive measure of the energy difference in one solvent. Thus a low-temperature NMR experiment was attempted using a 1:1 mixture of CFC₃-CDCl₃ as solvent. The ¹⁹F signal coalesced at 163 K and at 135 K two signals separated by 3214 Hz corresponding to the distinct *cis* and *trans* forms were observed with the intensity 2.1:97.9. This gives the free energy difference ($E_{cis} - E_{trans}$) as 1.0 kcal mol⁻¹ and the barrier to interconversion of 6.4 kcal mol⁻¹, the latter slightly greater than that recorded for acetophenone³¹ of 5.35 kcal mol⁻¹. The dielectric constant of the solvent mixture at 135 K was estimated as *ca.* 12 and this with the data of Table 6 would predict values of the energy difference in the vapour, non-polar solvents, CDCl₃ and acetone of 3.8, 2.8, 2.0 and 0.9 kcal mol⁻¹, respectively. The value for chloroform agrees with the LIS data (2% *cis* corresponds to 2.2 kcal mol⁻¹) and the vapour state energy difference is in excellent agreement with the *ab initio* value (Table 6). Bock *et al.*¹⁴ interpreted their dipole moment measurements in CCl₄ and benzene from INDO calculations as due to *ca.* 10% *cis* form, but closer examination of their results does not support these conclusions. The observed dipole moments in CCl₄ and benzene solution are 2.76 and 2.78 D, respectively, but these values are *less* than the estimated dipole moment for the *trans* conformer (*cf.* Table 6, 3.08 D and *ref.* 14 quotes 2.81 D from group dipole moments and 2.90 D INDO calculations). Thus the dipole moment measurements are only consistent with essentially 100% *trans* form. This would be expected from the above results.

The LIS results for methyl 2-fluorobenzoate when combined with the data of Table 6 predict the conformer energy difference ($E_{cis} - E_{trans}$) as 1.4 kcal mol⁻¹ in the vapour decreasing to 0.87 kcal mol⁻¹ in CCl₄, 0.45 kcal mol⁻¹ in chloroform and *ca.* 0.0 kcal mol⁻¹ in acetone solution. There is little experimental data to test these predictions, but the observed dipole moment in benzene solution (2.30 D³²) is consistent with *ca.* 15% *cis* form in general agreement with these predictions and the calculated (6-31G) energy difference of 0.9 kcal mol⁻¹ (Table 6) is in excellent agreement with the above value. In contrast the energy difference given by PCMODEL is somewhat low, and this may be due to the large electrostatic interactions in this molecule.

Similar comments can be made with respect to the conformer equilibrium in 2-trifluoromethylbenzaldehyde **4**. The LIS results together with the data of Table 6 give the value of $E_{cis} - E_{trans}$ as 2.4 kcal mol⁻¹ in the vapour decreasing to 1.8 kcal mol⁻¹ in CCl₄, 1.3 in chloroform and 0.7 in acetone solution. The extrapolated vapour state energy difference is in fair agreement with the *ab initio* calculated value of 3.2 kcal mol⁻¹ (Table 6) and again the PCMODEL calculated energy difference (0.3 kcal mol⁻¹) is much too low.

The LIS results for the conformational equilibrium of methyl 2-trifluoromethylbenzoate **6** when taken with the data of Table 6 predict the conformer energy difference ($E_{cis} - E_{trans}$) as *ca.* 2.0 kcal mol⁻¹ in the vapour decreasing to 1.8 kcal mol⁻¹ in CCl₄, 1.7 kcal mol⁻¹ in chloroform and 1.5 kcal mol⁻¹ in acetone

solution with both of the conformers non-planar with ester-ring torsional angles *ca.* 40°. Both the geometries and energies are in good agreement with the values obtained from the *ab initio* calculations (1.4 kcal mol⁻¹, Table 6) with ester-ring dihedral angles of *ca.* 30 and 40°. The PCMODEL geometries are also in good agreement with the LIS results but the calculated value of the conformer energy is again too small.

The conformational equilibrium in 2-trifluoromethylacetophenone **5** presents a different problem, as the analysis of the LIS data by itself could not differentiate between one essentially orthogonal conformer and an equilibrium between two less twisted conformers. Supporting evidence for an essentially orthogonal conformation comes from a variety of sources. The calculated carbon chemical shifts for **5** obtained from the substituent chemical shifts (SCS) of trifluoromethylbenzene³³ and acetophenone are in poor agreement with the experimental data, but the agreement is much improved when the SCS of the orthogonal 2,6-dimethylacetophenone² was used. The values of the complexation shifts (ΔD) for the carbon atoms in the planar 2-fluoroacetophenone **2** are significantly greater than those of 2-trifluoroacetophenone **5** especially for the 2 and 4 positions. It has been shown previously³⁴ that the ¹³C ΔD values are due to the aromatic π system redistributing the electron density on complexation and this again supports the non-planarity of **5**. Finally, Bock *et al.*¹⁴ measured the dipole moment of **5** as 4.07 and 4.18 D in CCl₄ and benzene solution, respectively, and noted that this was in very good agreement with that calculated by INDO for an orthogonal conformation.

The *ab initio* calculations for **5** provide further support for the essentially orthogonal conformation of this molecule. GAUSSIAN92 at the 6-31G* level optimised on two low energy conformations, a *trans* conformer with an acetyl-ring dihedral angle of 53.9° and a *cis* conformer with an acetyl-ring dihedral of 67.3°. These geometries were almost identical in energy (to 0.02 kcal mol⁻¹) and this suggests that these solutions may be local minima on an almost flat potential surface with essentially no barrier between them. This was confirmed by optimising at the MP2/6-31G* level which gave only one optimised geometry starting from either the *cis* or the *trans* geometries which was for the *cis* form with a dihedral angle 58.5°. Bock *et al.* from INDO calculations suggested that the acetyl group executes a rocking motion of *ca.* 20° about the 90° out of plane conformation and this is in agreement with the above calculations. In conclusion the available evidence strongly suggests that **5** adopts an essentially orthogonal conformation both in the vapour and in solution.

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