Conformational analysis. Part 25.[1] The evaluation of molecular geometries by the lanthanide induced shift (LIS) technique

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A refined lanthanide induced shift (LIS) technique, using $Yb(fod)_3$ to obtain the paramagnetic induced shifts of all the spin 1/2 nuclei in the molecule, together with complexation shifts obtained by the use of $Lu(fod)_3$ has been used to test the accuracy of molecular geometries obtained by various theoretical methods, including molecular mechanics and *ab initio* calculations with the RHF/6-31G* basis set.

The technique has been applied to a series of aromatic aldehydes, ketones and esters. The relative strengths and weaknesses of the calculated geometries are clearly illustrated by this technique. Although the *ab initio* geometries generally gave better agreement with the observed LIS than geometries generated by molecular modelling programs, as expected, this was not always the case, particularly for the 2,6-difluoro compounds.

The LIS were also used to differentiate between two experimental geometries for 2,6-dimethylacetophenone. Thus the method outlined here is general and can in principle be applied to any derived molecular geometry.

Introduction

The discovery of lanthanide shift reagents by Hinckley in 1969[2] and subsequent advances prompted many investigators to believe this technique could be used in a similar manner to X-ray crystallography to determine molecular structures in solution. This belief was somewhat optimistic, in that the LIS experiment gives only one measured quantity for each NMR active nucleus in the molecule, whereas three measurements for each atom are necessary to define fully the molecular geometry. Nevertheless since these early days the application of the LIS technique has provided a wealth of information on molecular geometries and energies in solution.[3]

In previous parts of this series,[1,4–8] the essential conditions necessary for successful LIS studies have been considered in some detail. 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. Indeed the importance of obtaining as many pseudo-contact shifts as can be measured has been repeatedly emphasised, and with the present advanced techniques in NMR instrumentation it would not be unreasonable to require all quantitative LIS studies now to include all ^1H and ^{13}C nuclei in the molecule.

It was further noted that the diamagnetic complexation shift (ΔD) must be subtracted from the experimental paramagnetic shifts (ΔM) to obtain the required pseudo-contact shift ($\Delta M - \Delta D$). 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.[1] 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. It was therefore of some interest to determine whether such a data set could be used to test directly molecular geometries, either calculated or experimental. For this to be achieved the molecules to be examined must satisfy certain criteria.

(1) They must exist in only one conformation in solution. The additional complexities involved in averaging between two or more rapidly interconverting conformers of unknown populations would undermine the direct testing of the molecular geometries.

(2) There must be only one complexing atom for the lanthanide ion. Again averaging between different complexing sites would introduce too many uncertainties in the analysis.

(3) The LIS complexation model used must be reliable and well characterised.

Molecules which satisfy all these criteria are aromatic carbonyl compounds, which have been studied extensively in previous parts of this series using the LIRAS3 and LIRAS4 programs[6–8] and we present here the application of this method to a series of substituted aromatic aldehydes, ketones and esters.

The 4-methyl derivatives of benzaldehyde, acetophenone and methyl benzoate, in which steric effects are minimal are first examined and then the effects of 2,6-dimethyl and 2,6-difluoro substitution are considered. Thus the competing effects of steric repulsion *vs.* conjugation and the theoretically important F···O interaction may be examined by this technique. The 4-methyl derivatives have the advantage over the parent compounds of an additional LIS centre plus a much simpler aromatic proton spectrum, making the experimental data more definitive without introducing any extra perturbations in the molecules.

Both experiment[9] and theory[10] agree that benzaldehyde is planar with a *ca.* 8 kcal mol^{-1} barrier to rotation of the aldehyde group. Acetophenone and methyl benzoate are also planar in the solid state with reduced barriers to rotation of the acetyl and ester groups. Values of *ca.* 5 kcal mol^{-1} for the acetyl group have been recorded,[9] and we obtained a theoretical value of 6.5 kcal mol^{-1} for the barrier in methyl benzoate (see later).

A previous LIS study[6] concluded that mesitaldehyde (2,4,6-trimethylacetaldehyde) retained the planar skeleton in solution whereas in 2,4,6-trimethylacetophenone the acetyl group was rotated *ca.* 60–90° with respect to the phenyl ring. Recent X-ray studies of 4-*tert*-butyl-2,6-dimethylacetophenone[11] and methyl 4-methoxy-2,6-dimethylbenzoate[12] gave angles to rotation of the acetyl and ester groups of *ca.* 80° and 64° respectively and X-ray[13] and neutron diffraction[14] studies of pentafluorophenyl benzoic acid and tetrafluorophenylterephthalic acid gave the acid–phenyl torsional angles of 30° and 21°, respectively.

Of the numerous modelling and theoretical programs in existence, the ones available to us were the commercial programs PCMODEL,[15] NEMESIS[16] and GAUSSIAN92.[17] The PCMODEL program is 'loosely derived' from the MM2 and MM2P force fields of Allinger[18] and the NEMESIS program uses the simpler COSMIC force field.[19] The *ab initio* GAUSSIAN92 program provides a choice of various basis sets but there is general agreement[20] that the RHF/6-31G* basis set should be used to obtain reasonable molecular geometries and this basis set was used here. In addition, we include 'experimental' geometries when these are available with the important caveat that crystal packing forces can affect the molecular geometry, particularly the torsional angles.

The geometries obtained by the above methods were tested directly against the experimental LIS data. This does show interesting defects in all the geometries in certain cases and intriguingly the sophisticated *ab initio* geometry does not always give the best agreement with the experimental shifts.

Experimental

All samples were obtained commercially (Aldrich and Fluorochem), except the methyl 2,6-difluorobenzoate which was prepared from the corresponding acid by standard procedures. The aldehyde compounds needed to be distilled prior to use, the others were used directly for the LIS experiments. The solutions were made up as 0.5 mol dm^{-3} 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.*[21] The shift reagents were dried *in vacuo* over P_2O_5 at *ca.* 35 °C for 24 h, and maintained *in vacuo* over P_2O_5 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 shift *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)$_3$.

4-Methylbenzaldehyde and 2,6-difluoroacetophenone were recorded on a Bruker AMX-400 spectrometer to give directly the proton, carbon and fluorine LIS. Typical proton spectral widths were 6000 Hz with TD = 128 K Fourier transformed to SI = 128 K, carbon spectral widths were typically 23 000 Hz with TD = 128 K and transformed with SI = 128 K using a line broadening of 2.0 Hz, fluorine spectral widths were 37 000 Hz with TD = 256 K and SI = 256 K.

The remaining compounds were recorded on a Varian Gemini 200 MHz spectrometer operating on ^{1}H and ^{13}C at 20 °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 for the methyl 2,6-difluorobenzoate were recorded in a separate experiment on the Bruker AMX-400 spectrometer involving ^{1}H and ^{19}F measurements. The fluorine shifts were then normalised to the ^{1}H and ^{13}C LIS obtained previously.

Spectral assignments

The spectral assignments were straightforward using either previous literature assignments,[6–8] additive substituent chemical shifts,[22] the size of the ΔM values obtained and for the ^{13}C assignments of the fluoro compounds the C–F couplings which have characteristic values of *ca.* 250 Hz, 20–25 Hz, *ca.* 10 Hz and < 5 Hz for the one, two, three and four bond couplings.[23] Full details of all the spectral assignments are given elsewhere.[24,25] The observed chemical shifts (δ), diamagnetic shifts (ΔD), LIS values (ΔM) and pseudo-contact shifts [ΔM(PC)] are given in Table 1 for the compounds measured here.

Results

The pseudo-contact shifts given in Table 1 can now be used to directly test the accuracy of the calculated molecular geometries obtained from PCMODEL, NEMESIS and the RHF/6-31G* basis set of GAUSSIAN92 using the well documented LIRAS3 and LIRAS4 programs.[6–8] We also include, for comparison, experimental or standard geometries. Full details of all the calculated geometries are given elsewhere,[24,25,26] here we give the most important parameters.

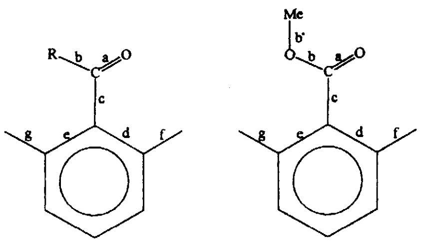

Fig. 1 Explanation of symbols used in Tables 2 and 3

4-Methylbenzaldehyde

The standard geometry used was that derived previously[8] from the microwave geometries of acetaldehyde and benzaldehyde with standard bond lengths and angles for the methyl group (C–C 1.51 Å, C–H 1.09 Å). All the calculated geometries were planar, as expected, and the relevant bond lengths and angles for the formyl group are very similar (Table 2) and all give very good agreement factors AF (Table 2). This agreement is worthy of some comment. The AF of 0.33 gave calculated shifts all within 0.3 ppm of the observed pseudo-contact shifts over a range of 6.6 to 145.9 (Table 1). In a previous LIS investigation of benzaldehyde[8] an AF of 0.013 was considered to indicate good agreement. The AF given here are in percentages, *i.e.* 0.33% is 0.0033 indicating the much greater definition of the present measurements.

4-Methylacetophenone

The experimental geometry was taken from the low temperature crystal structure of acetophenone[27] with the addition of a standard methyl group. The molecular geometries calculated for the acetyl group (Table 2) show quite surprisingly large variations. All the geometries are planar except for the PCMODEL geometry, which gives the angle of twist of the acetyl group as 30.3°. This geometry also gave an unacceptable AF (1.34) and this is clearly due to the dihedral angle as rotating it to zero with the same geometry decreases the AF to 0.67, in good agreement with the other geometries. Thus here the LIS measurements unequivocally confirm the planar geometry.

Another point of interest in these geometries are the bond angles the acetyl group makes with the benzene ring (cd and ce in Table 2). The calculated geometries oscillate between cd > ce and *vice versa.* This is also observed experimentally as the crystal structure of 4-nitroacetophenone[28] gives cd 118.4° and ce 119.8°, almost the reverse of those for acetophenone. It was therefore of interest to optimise this angle using LIRAS3. Both the experimental and GAUSSIAN geometries optimised to a value of 120°, the AF reducing to 0.67 (experimental geometry) and 0.77 (GAUSSIAN). Whilst these changes are too small to be definitive they support the view that the acetyl group is essentially symmetric with respect to the benzene ring. Finally we note that although the NEMESIS geometry differs somewhat from the other geometries it does produce a very acceptable AF (see later).

Methyl 4-methylbenzoate

The standard geometry used here was that derived by Schweizer and Dunitz[29] from a review of the crystal geometries of esters and is given in Table 2 together with the calculated geometries and the agreement factors. All the geometries are planar and they all have the ester methyl group in the staggered orientation with respect to the carbonyl group, in contrast to the situation in acetophenone. The barrier to rotation of the ester group in

Table 1 Observed carbon, proton and fluorine chemical shifts (δ), LIS values (ΔM), diamagnetic shifts (ΔD), pseudo-contact shifts [ΔM(PC)] for aromatic carbonyl compounds

Compound	NMR experiment	Resonance											
		C=O	C1	C2,6	C3,5	C4	CMe	H2,6	H3,5	CHO	HMe		
4-Methylbenzaldehyde	Shift[a]	191.95	134.26	129.86	129.72	145.54	21.87	7.769	7.321	9.957	2.431		
	ΔM	153.96	53.67	35.98	17.91	17.29	8.12	34.03	11.50	82.32	6.61		
	ΔD	8.02	−1.61	2.28	0.37	3.23	0.28			−0.23			
	ΔM(PC)	145.94	55.28	33.71	17.54	14.06	7.84	34.03	11.50	82.55	6.61		
		CO	C1	C2,6	C3,5	C4	CAc	CMe	H2,6	H3,5	HAc	HMe	
4-Methylacetophenone	Shift[b]	197.8	134.8	128.4	129.2	143.8	26.5	21.6	7.86	7.25	2.57	2.40	
	ΔM	162.7	65.04	41.28	18.87	17.96	68.70	7.74	41.35	11.27	44.30	6.16	
	ΔD	10.46	−1.18	2.38	0.63	3.85	−1.06	0.31					
	ΔM(PC)	152.19	66.22	38.90	18.24	14.11	69.76	7.43	41.35	11.27	44.30	6.16	
		CO	C1	C2,6	C3,5	C4	OMe	4-Me	H2,6	H3,5	OMe	4-Me	
Methyl 4-methylbenzoate	Shift[c]	167.2	127.5	129.6	129.1	143.5	51.9	21.6	7.93	7.22	3.89	2.39	
	ΔM	165.8	68.36	39.12	15.29	13.95	57.99	4.98	37.44	7.14	41.87	3.69	
	ΔD	5.79	−2.26	1.56	0.49	2.75	2.96						
	ΔM(PC)	160.0	70.92	37.56	14.95	11.20	55.03	4.98	37.44	7.14	41.87	3.69	
		CO	C1	C2,6	C3,5	C4	2,6Me	4-Me	CHO	H3,5	2,6Me	4-Me	
Mesitaldehyde	Shift[d]	192.7	130.0	141.3	130.4	143.7	20.43	21.43	10.54	6.883	2.566	2.305	
	ΔM	143.15	49.53	35.40	16.97	17.20	27.28	7.45	80.88	12.02	25.17	6.99	
	ΔD	6.42	−1.23	4.07	0.78	4.13	0.32	0.37	−0.10				
	ΔM(PC)	136.73	50.76	31.33	16.19	13.07	26.96	7.08	80.98	12.02	25.17	6.99	
		CO	C1	C2,6	C3,5	C4	CAc	CMe	H3,5	H4	HAc	HMe	
2,6-Dimethylacetophenone	Shift[e]	208.4	142.6	132.2	127.8	128.5	32.1	19.11	7.01	7.14	2.47	2.24	
	ΔM	159.3	61.91	39.60	20.47	17.57	64.33	30.46	13.30	10.70	38.00	26.34	
	ΔD	9.90	−1.60	1.40	0.50	1.50					0.20		
	ΔM(PC)	149.4	63.47	38.22	20.00	16.10	64.16	30.46	13.30	10.70	38.00	26.34	
		CO	C1	C2,6	C3,5	C4	OMe	4-Me	2,6Me	H3,5	OMe	4-Me	2,6Me
Methyl mesitoate	Shift[f]	170.6	130.9	135.2	128.4	139.3	51.71	21.11	19.76	6.84	3.88	2.28	2.27
	ΔM	162.7	68.99	41.07	18.47	15.39	55.39	6.42	32.07				
	ΔD	4.88	−2.47	1.64	0.75	1.92	2.76						
	ΔM(PC)	157.8	71.46	39.43	17.72	13.47	52.63	6.42	32.07	10.64	38.79	5.05	26.15
		CO	C1	C2,6	C3,5	C4	CAc	H3,5	H4	HAc	F		
2,6-Difluoroacetophenone	Shift[g]	194.8	118.3	160.2	112.2	132.6	32.46	6.95	7.40	2.60	49.74		
	ΔM	114.0	45.30	28.38	13.52	13.23	47.80	8.25	6.44	30.50	28.37		
	ΔD	3.63	−0.61	0.61	0.20	1.02	−0.08				1.70		
	ΔM(PC)	110.4	45.91	27.77	13.32	11.21	47.88	8.25	6.44	30.50	26.67		
		CO	C1	C2,6	C3,5	C4	CEs	H3,5	H4	HEs	F		
Methyl 2,6-difluorobenzoate	Shift[h]	162.1	111.1	160.8	112.1	132.8	52.81	6.954	7.417	3.955	51.45		
	ΔM	140.0	61.34	35.54	14.46	12.44	47.45	7.34	5.75	34.47	35.94		
	ΔD	2.91	−0.29	0.58	0.58	1.45	1.64				1.56		
	ΔM(PC)	137.1	61.63	34.96	13.88	10.99	45.81	7.34	5.75	34.47	34.38		

[a] $[S]_0$ 0.50 mol dm^{-3} 10^2 ρ, Yb(fod)$_3$ 4.36, 8.31, 12.39; Lu(fod)$_3$ 2.74, 5.88, 8.80. [b] $[S]_0$ 0.48 mol dm^{-3} 10^2 ρ, Yb(fod)$_3$ 4.74, 13.52, 15.52; Lu(fod)$_3$ 3.62, 6.20, 9.71. [c] $[S]_0$ 0.50 mol dm^{-3} 10^2 ρ, Yb(fod)$_3$ 3.68, 6.92, 11.10; Lu(fod)$_3$ 3.26, 7.16, 10.22. [d] ΔM from ref. 6, $[S]_0$ 0.66 mol dm^{-3} 10^2 ρ, Lu(fod)$_3$ 2.43, 4.89, 7.34, 9.29. [e] $[S]_0$ 0.52 mol dm^{-3} 10^2 ρ, Yb(fod)$_3$ 3.04, 8.08, 13.67. $[S]_0$ 0.50 mol dm^{-3} 10^2 ρ, Lu(fod)$_3$ 3.47, 6.38, 10.95. [f] $[S]_0$ 0.50 mol dm^{-3} 10^2 ρ, Yb(fod)$_3$ 3.81, 6.80, 10.15; Lu(fod)$_3$ 3.52, 7.03, 10.44. [g] $[S]_0$ 0.50 mol dm^{-3} 10^2 ρ, Yb(fod)$_3$ 2.63, 5.72, 9.75; Lu(fod)$_3$ 3.55, 6.98, 9.75. [h] $[S]_0$ 0.50 mol dm^{-3} 10^2 ρ, Yb(fod)$_3$ 5.68, 8.85, 13.29; Lu(fod)$_3$ 6.32, 9.94, 13.77.

methyl benzoate was calculated using GAUSSIAN92 at the RHF/6-31G* with full relaxation of both the ground state (0°) and transition (90°) state to be 7.9 kcal mol^{-1}. Single point calculations at the 6-31G*/MP2 level with these geometries reduced the barrier to 6.5 kcal mol^{-1}.† The geometries are all in reasonable agreement (with one exception, see later) and give good solutions, that for the experimentally derived geometry being slightly better than the calculated ones. Again the PCMODEL geometry gives a much poorer AF and inspection of the geometries shows that the C–O–C angle in the PCMODEL geometry (bb′ in Table 2) is much larger than all the others (123.2° *vs. ca.* 117.0°). It was therefore of interest to determine whether this was the reason for the poor AF and indeed optimising this angle gave a good AF of 0.81 for a value of 120°. Also optimising this angle with the other geometries gave values of *ca.* 119°, though the definition was not very sharp. Thus the LIS support the conclusion that the correct value of this angle is *ca.* 120° in solution.

The non-planar geometries

The remaining molecules to be considered here are the di-*ortho* substituted molecules and in consequence the substituent group and the benzene ring are often no longer coplanar. This has two important consequences. The actual value of the torsional angle is a very sensitive function of the steric interactions and

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† A referee noted that this value agrees with the results of a low temperature ^{13}C NMR study of methyl 3-nitro-4-(dimethylamino)-benzoate, in which the ester barrier to rotation is not greater than 6–7 kcal mol^{-1}.[33]

Table 2 Geometries and LIS agreement factors (AF) for 4-methyl-benzaldehyde, -acetophenone, methyl 4-methylbenzoate and mesitaldehyde[a]

		Geometries								
Compound	Method	a	b	c	ab	ac	cd	ce	AF (%)	
4-Methylbenzaldehyde	EXPTL	1.216	1.10	1.480	118.6	123.9	120.0	120.0	0.33	
	GAUSS	1.191	1.095	1.481	120.4	124.7	120.6	120.1	0.33	
	PCMOD	1.210	1.115	1.482	119.8	126.5	120.9	120.4	0.48	
	NEM	1.228	1.089	1.444	117.5	124.0	120.7	120.8	0.59	
4-Methylacetophenone	EXPTL	1.216	1.499	1.494	121.0	120.0	122.1	117.9	0.79	
	GAUSS	1.196	1.514	1.498	120.3	120.6	118.5	122.9	0.79	
	PCMOD[b]	1.212	1.520	1.486	120.0	122.6	121.7	119.7	1.34	
	NEM	1.227	1.502	1.449	115.4	122.6	118.6	123.6	0.64	
		a	b	c	b′	ab	ac	bb′	AF (%)	
Methyl 4-methylbenzoate	EXPTL	1.199	1.343	1.484	1.445	123.4	125.0	117.2	0.76	
	GAUSS	1.192	1.325	1.488	1.416	122.9	124.0	116.8	0.98	
	PCMOD	1.213	1.352	1.490	1.414	121.2	123.6	123.2	1.24	
	NEM	1.237	1.353	1.453	1.417	118.7	122.2	117.4	0.89	
		a	b	c	ab	ac	cd	ce	df/ge	AF (%)
Mesitaldehyde	EXPTL	1.216	1.10	1.480	118.6	123.9	120.0	120.0	124.0	0.75
	GAUSS	1.194	1.090	1.483	118.6	126.1	121.4	118.7	123.0	0.75
	PCMOD[c]	1.209	1.115	1.479	120.4	126.1	120.0	119.8	121.5	1.42
	NEM	1.228	1.088	1.452	115.8	125.5	121.2	120.2	122.2	0.96

[a] Distances in Å and angles in degrees. [b] Torsional angle of 30.3° (see text). [c] Torsional angle of 48.3° (see text).

torsional potentials in these molecules and therefore we expect and find much larger differences between the calculated geometries than for the planar molecules considered previously.

Furthermore, due to the molecular symmetry the conformation at 90° torsional angle will be either a maximum or minimum on the molecular energy profile. Thus for molecules in which the minimum energy conformation is predicted to have a torsional angle of *ca.* 80° or greater, the barrier to rotation about the 90° transition state will be very small indeed, probably less than the zero-point energy of the molecule. In solution the molecules will be interconverting rapidly between the two identical conformations about 90°, thus the LIS measurements will be the average of the molecular vibrations around 90°. However, even with this caveat the LIS measurements do provide a critical test of the calculated geometries investigated.

Mesitaldehyde

The standard geometry used was derived from that given earlier for benzaldehyde with the addition of standard methyl groups. This gave the best agreement for a planar geometry but with only a moderate AF of 1.08. Relaxing the *ortho* methyl C–C–C angles to 124° gave a satisfactory AF of 0.75 (Table 2). The GAUSSIAN and NEMESIS geometries are planar and also have the *ortho* methyl C–C–C angles relaxed to 123° and 122° respectively, thus it is not surprising that these geometries give similar AFs of 0.78 and 0.96 respectively. In contrast, the PCMODEL geometry has a formyl torsional angle of 48° and gave poor agreement with the LIS (AF 1.42, Table 2). Merely altering the torsional angle to 0° gave a much better agreement (AF 0.87), confirming that this was the reason for the poor agreement with the LIS.

These results unequivocally confirm the conclusion from a previous LIS investigation[6] that this compound is planar in solution with the steric strain relieved mainly by a relaxation of the *ortho* methyl C–C–C angles.

2,6-Dimethylacetophenone

The experimental geometry initially used for this molecule was from the X-ray structure of 4-*tert*-butyl-2,6-dimethylacetophenone[11] which gave a torsional angle of 80° between the acetyl and ring planes. This, however, gave a very poor agreement factor (1.31). Rotating the acetyl group made little difference to this AF. This geometry was therefore rejected and the geometry of acetophenone (Table 2) used plus standard methyl groups. This gave a good agreement factor of 0.74 for a torsional angle of 90° (Table 3). The three calculated geometries do not show any significant changes in the C–CO and C–C=O bond lengths (a and b in Table 2) from the values in Table 2, and are not repeated in Table 3. The other parameters do show large changes and in consequence the AF are also very different. In particular the calculated value of the acetyl torsional angle varies from 85° in GAUSSIAN to 75° in PCMODEL to 29° in NEMESIS and the AF varies from a barely acceptable value in GAUSSIAN (0.87) to an excellent value in PCMODEL (0.28) to an unacceptable value in NEMESIS (1.06). Inspection of the geometries in Table 3 shows also that the NEMESIS geometry has an unusually small Me–C–O angle of 113.3° compared to *ca.* 121° for all the other geometries. To test the above variations the Me–C–O angle was changed to 121° in the NEMESIS geometry and the acetyl torsional angle varied for the best fit. This procedure gave a good AF (0.66) for a torsional angle of 55°. In contrast varying the torsional angle with the GAUSSIAN geometry did not affect the value of the AF.

These results show that both experimental and calculated geometries can be directly tested with the LIS data. They also confirm the too small value of the Me–C=O angle in the NEMESIS force field and conclude that the torsional angle of the acetyl group in this molecule in solution is 80° (± 5°). Thus from the discussion given previously, in solution the acetyl group will be effectively orthogonal to the benzene ring.

Methyl mesitoate

The experimental geometry was that used previously for the ester group (Table 2) with the addition of standard methyl groups. Varying the ester torsional angle gave a reasonable AF (0.73) for a torsional angle of 65°. Inspection of the calculated shifts showed that both the ester carbon and protons had large errors (*ca.* 1.0 ppm) compared with the observed values whereas the remaining shifts were very well reproduced. This suggested that, as in the 4-methylbenzoate the C–O–Me angle was too small and increasing this to 120° gave an excellent AF of 0.38 and this with the optimised geometry is given in Table 3.

In contrast, the calculated geometries show considerable

Table 3 Geometries and LIS agreement factors (AF) for 2,6-di-*ortho* substituted compounds[a]

		Geometries									
Compound	Method	c	d/e	f/g	ab	ac	cd	df/ge	Ψ[b]	AF (%)	
2,6-Dimethylacetophenone	EXPTL	1.494	1.397	1.510	121.0	120.0	120.0	120.0	90.0	0.74	
	GAUSS	1.514	1.395	1.515	121.6	121.4	119.8	121.7	84.7	0.87	
	PCMOD	1.480	1.405	1.508	121.5	122.7	119.4	120.8	74.9	0.28	
	NEM	1.454	1.416	1.510	113.3	123.2	119.6	121.8	28.7	1.06	
2,6-Difluoroacetophenone	EXPTL	1.494	1.397	1.354	121.0	120.0	120.0	120.0	20.0	0.82	
	GAUSS	1.513	1.387	1.322	122.4	120.0	120.9	118.6	57.1	1.84	
	PCMOD	1.477	1.399	1.351	121.1	122.4	120.5	120.3	59.5	2.23	
	NEM	1.444	1.413	1.330	114.3	123.0	119.9	120.9	0.2	0.84	
		c	d/e	f/g	ab	ac	bb′	cd/ce	df/eg	Ψ[b]	AF (%)
Methyl mesitotate	EXPTL	1.484	1.397	1.510	123.4	125.0	120.0	120.0	120.0	65.0	0.38
	GAUSS	1.497	1.400	1.515	122.3	124.7	116.9	121.2	123.2	46.6	1.58
	PCMOD	1.480	1.406	1.509	122.9	123.6	123.0	120.1	121.5	60.9	0.71
	NEM	1.463	1.415	1.511	117.5	123.0	118.0	120.5	122.4	9.4	3.10
Methyl 2,6-difluorobenzoate	EXPTL	1.484	1.397	1.354	123.4	125.0	120.0	120.0	120.0	0.0	0.49
	GAUSS	1.498	1.387	1.320	124.1	123.8	116.8	122.8	119.1	46.4	2.00
	PCMOD	1.476	1.400	1.351	122.8	123.6	123.1	120.3	120.6	50.8	1.71
	NEM	1.448	1.408	1.330	118.0	122.7	117.6	121.0	120.7	0.0	1.82

[a] Distances in Å and angles in degrees. [b] CO-Ring torsional angle.

variation and in consequence large changes in the AF obtained. The PCMODEL geometry, which has a torsion angle of 61° gave a very reasonable AF of 0.71 and reducing the C–O–C angle to 120° (see above) gave an improved AF of 0.54. In contrast both the GAUSSIAN and NEMESIS geometries gave much smaller values of the torsional angle (46° and 9° respectively) and also quite unacceptable values of the AF. Varying the torsional angle made this only slightly better. The AF for the GAUSSIAN geometry decreased to 1.48 for a 60° angle, whilst that for the NEMESIS geometry decreased to 1.96 for a 50° torsion angle. These are still unacceptably high values for the AF.

Inspection of the molecular geometries showed that the GAUSSIAN geometry was reasonably consistent with the other geometries except for the C–O–C angle (bb′ in Table 3) which at 116.9° seems rather too small. Indeed merely altering this angle to 120° as above for the experimental geometry, gave an acceptable AF of 0.83 for a torsion angle of 70°. The NEMESIS geometry however shows noticeable differences from the other geometries of Table 3 in many of the molecular parameters and it was not considered feasible to vary all these parameters to search for the minimum AF.

In conclusion the LIS measurements of this molecule taken together with the molecular geometries obtained give a torsional angle for the ester group in solution of 65–70°, and also suggest that the C–O–C angle in this molecule is somewhat larger than the value calculated by the 6-31G* basis set. Interestingly the 6-31G basis set gives a value for this angle of 119.4°, which is very close to the one suggested by the LIS measurements (and in consequence the 6-31G geometry gives a better AF than the 6-31G* geometry). However, the reason for the large effect on the calculated value of this angle of the inclusion of polarisation functions is beyond the scope of this manuscript.

2,6-Difluoroacetophenone

Fluorine poses considerable problems in both quantum mechanics and molecular modelling,[30] thus it was of some interest to see how the programmes coped with the difluoro compounds studied.

The standard geometry used for the difluoroacetophenone was obtained by adding fluorine atoms to the acetophenone geometry and then rotating the acetyl group for the best AF. This gave a reasonable AF of 0.82 for a torsional angle of 20° (Table 3).

In contrast, the calculated geometries (Table 3) all gave poorer AF and also very different values of the torsional angle. The AF for the NEMESIS geometry with a dihedral angle of 0° is reasonable but those for the PCMODEL and GAUSSIAN geometries both with torsional angles *ca.* 60°, are quite unacceptable. It was therefore of interest to see whether it was the value of the torsional angle in these geometries which was producing such poor results and the torsional angle was varied for the best AF in both cases. For both geometries the iteration converged to much better AFs (0.64 and 1.10 for the GAUSSIAN and PCMODEL respectively) for torsional angles of 25° and 30° respectively.

In the case of the NEMESIS geometry the 0° dihedral angle gave the lowest AF. Changing the value of the Me–C–O angle to the experimental value and varying the torsional angle gave a similar AF of 0.93 for a torsional angle of 25°.

Thus the overwhelming conclusion from these results is that the acetyl torsional angle in this molecule in solution is 25–30°. This is quite different from the value predicted by all of the programs used, even the 6-31G* basis set.

Methyl 2,6-difluorobenzoate

The experimental geometry used for this molecule was that used previously for methyl benzoate, with the C–O–C angle of 120° and the addition of standard fluorines (Table 3). Rotating the ester group for the best agreement gave a very good AF of 0.49 for a planar molecule. In contrast, in exactly analogous manner to the 2,6-difluoroacetophenone the GAUSSIAN and PCMODEL geometries gave non-planar geometries and very poor agreement with the LIS data (torsional angles of 46° and 51° and AF of 2.0 and 1.7 for GAUSSIAN and PCMODEL respectively). Varying the torsional angle for the best agreement gave values of 0° and 10° with much better AF of 0.75 and 0.47 respectively.

In contrast, the NEMESIS geometry is planar but still gives poor agreement (AF 1.82). Varying the dihedral angle with the C–O–Me angle of 120° gives a better solution (AF 1.11) for a torsional angle of 10° but this is still a poor value for the AF.

Thus the results for this molecule again demonstrate that all the calculated geometries give very poor agreement with the LIS measurements and this is largely due, in the case of the GAUSSIAN and PCMODEL geometries to the value of the torsional angle. The LIS data clearly support a planar geometry for this molecule in solution.

Discussion

The LIS studies confirm the calculated planar geometries for the 4-methyl compounds and also the essentially orthogonal geometry of the 2,6-dimethylacetophenone, but predict quite different conformations for the 2,6-dimethylbenzoate and particularly the 2,6-difluoro derivatives than those obtained by either *ab initio* or molecular mechanics calculations. It is therefore of some interest to determine whether these results are supported by other physical measurements. X-Ray determinations of the conformations of these molecules in the crystal largely confirm the LIS results, in that the torsional angle in the 2,6-dimethylacetophenone fragment is 80° in the solid[11] and in the 2,6-dimethylbenzoate and mesitoic acid fragments the angle is 64° and 48° respectively.[12,31] Again in the solid the ring to carbonyl torsional angle is much less in the corresponding 2,6-difluoro derivatives, values of 30° and 21° having been reported for fluorinated benzoic acids.[13,14] There is, however, always the question of the effect of crystal packing forces on the molecular conformation, particularly in the hydrogen bonded acid molecules.

The diamagnetic complexation shifts (ΔD,La) have been shown to be a sensitive function of the transmission of π electron density to the carbon atom under consideration, and are affected by both the degree of conjugation of the carbonyl group and the π electron donating or withdrawing effects of the substituents.[32] Thus the contrasting effects on the diamagnetic complexation shifts of *ortho* methylation of benzaldehyde in which the shifts are increased and of acetophenone in which the complex shifts are much reduced was given previously[32] as strong supporting evidence for the retention of the planar conformation in mesitaldehyde and of the orthogonal conformation in the corresponding ketone. A very similar pattern is observed in the (ΔD,Lu) shifts for the aldehydes and ketones studied here. In the case of methyl benzoate, di-*ortho* methylation has a small effect on the ΔD values and this is again consistent with the proposed conformation, the increase in the ΔD values due to methyl substitution being compensated by the non planarity of the ester group in the methyl mesitoate. For the fluoro substituted compounds the effects are less obvious, as fluorine substitution produces an intrinsic decrease in the ΔD values (*e.g.* in 4-fluorobenzaldehyde the ΔD,Lu value at C-4 is 1.77,[24] *ca.* half that in 4-methylbenzaldehyde 3.23, Table 1). The diamagnetic complexation shifts at C-4 are somewhat larger for the 2,6-difluoromethylbenzoate than those for 2,6-difluoroacetophenone, even though the comparable values for the 4-methyl compounds are reversed, the ester value being less than the ketone (Table 1), and this again supports the planar conformation in the 2,6-difluorobenzoate.

Another NMR parameter which is sensitive to the torsional angle between the carbonyl group and the benzene ring is the C-13 chemical shift[23] and the contrasting effects of 2,6-dimethyl substitution in the molecules studied here is clearly seen in the C-4 chemical shift. In 4-methylbenzaldehyde, acetophenone and methyl 4-methylbenzoate the effect of 2,6-dimethyl substitution on the C-4 chemical shift is -1.8, -4.6 and -4.2 ppm, respectively. These shifts are clearly due to the change in the carbonyl–benzene torsional angle as the intrinsic SCS of a *meta* methyl group is only -0.1 ppm[22] and they are exactly what would be expected from the predicted conformations, the ketone giving the largest upfield shift due to the greatest loss of conjugation on *ortho* methylation. Again the effect of fluorine substitution is less obvious. The SCS of a *meta* fluorine substituent is $+1.4$ ppm[22] and this is consistent with the effect on the C-4 chemical shift on the introduction of a 2-fluoro substituent in benzaldehyde ($+1.9$ ppm).[24] In contrast the effect on C-4 of 2,6-difluoro substitution in acetophenone and methyl benzoate is -0.5 and -10.7 ppm, respectively. The small upfield shift in the ketone is consistent with some loss of conjugation on 2,6-difluoro substitution, but the remarkable upfield shift in the 2,6-difluorobenzoate is far too large for such an effect and suggests instead some direct interaction of the fluorine and ester oxygen atoms.

Conclusions

The results given above show clearly that LIS can be used to directly test molecular geometries. For the molecules considered here and in particular the non-planar molecules it is shown very clearly that the calculated geometries often fail to reproduce the observed LIS. This is particularly the case for the 2,6-difluoro compounds where the calculated torsional angles between the substituents and the benzene ring are very different from those obtained from the LIS. This demonstrates very clearly the need for caution in obtaining molecular torsional angles in such molecules even with sophisticated *ab initio* calculations. The LIS can also be used to refine other parameters in a given geometry and to differentiate between different experimental geometries. For the molecules considered here any geometry giving an AF > 1.0 would be considered as unacceptable.

It is important, however, to stress that the converse of this statement does not hold. Due to the reasons mentioned at the beginning of this manuscript good agreement does not *necessarily* mean a correct geomtery. The LIS would need to be augmented by additional data (*e.g.* broadening data) to become more definitive. Similarly, the problems of an underdetermined data set mean that caution must be exercised in obtaining bond and torsional angles from LIS data. Only one, or at most, two molecular parameters can be optimised in this way.

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