Conformational analysis. Part 24.[1] A lanthanide-induced-shift (LIS) NMR investigation of aromatic ketones. Lutetium *versus* lanthanum reagents in probing diamagnetic complexation shifts

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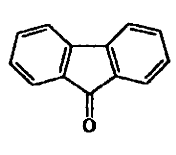
The possible use of Lu(fod)$_3$ *vs.* La(fod)$_3$ in probing diamagnetic complexation contributions to the shifts induced by Yb(fod)$_3$ on the ^{1}H and ^{13}C NMR signals of aromatic ketones has been investigated. For all the compounds examined the patterns of the shifts caused by the two diamagnetic reagents are qualitatively similar, reflecting predominantly π-electron-density transmission. For the less activated substrates fluoren-9-one **1** and 2,6-dimethyl-4-nitroacetophenone **3** the use of either La(fod)$_3$ or Lu(fod)$_3$ yielded very similar sets of data, indicating in **3** a *ca.* 90° torsion angle between the acetyl and the ring. More interestingly, in the case of acetophenone **2**, 2-acetylnaphthalene **4**, 3-methoxyacetophenone **5** and 2-methylacetophenone **6** the use of Lu(fod)$_3$ gave a markedly improved definition of essentially the same solutions. These are a planar conformation for **2**, a prevalence (*ca.* 68%) of the *E* conformer for **4** and of the *Z* conformer for **5** and **6** (*ca.* 63% and 92%, respectively). In the case of **6** the geometries of the two conformers to be submitted to LIS analysis have been obtained through an *ab initio* RHF 6-31G* full-optimization process, indicating a planar structure for the *Z* and a 35°-rotated structure for the *E* conformer. In conclusion the analysis using Lu(fod)$_3$, while supporting the results obtained with its lanthanum analogue, appears to reproduce better the diamagnetic contribution to induced shifts in strongly coordinating substrates. With the unhindered substrates **2**, **4** and **5**, where very reliable starting geometries could be adopted, solutions obtained through the use of Lu(fod)$_3$ have been particularly good (R_{cryst} 0.2–0.4%), as pseudocontact shifts ranging up to 130–150 ppm could be reproduced with an average absolute error of ±0.1 ppm. This shows how accurate the LIS method can be in the absence of additional problems and leaves little doubt about the accuracy of its theoretical background.

In recent years we have shown [1,2] that the Lanthanide-Induced-Shift (LIS) technique can be successfully applied to the study of the conformation and structure of aromatic carbonyl compounds, provided that (*i*) Yb(fod)$_3$ induced shifts (ΔM values) on both ^{1}H and ^{13}C signals are used, in order to obtain over-determined data-sets, not contaminated by Fermi-contact effects; (*ii*) the diamagnetic complexation contributions (ΔD values) are evaluated by the use of La(fod)$_3$, according to the hypothesis that the electronic rearrangement caused in a substrate is analogous for the same lanthanum or ytterbium derivative; (*iii*) the experimental ($\Delta M - \Delta D$) values are reproduced according to the McConnell–Robertson equation [3] and by a computer program (*e.g.* LIRAS-3) [2a] simulating a chemically reasonable lanthanide-ion-binding model. This procedure has given well defined minima in the plots of the error-function [4] R_{cryst} *versus* the conformational variable (a torsion angle or a conformer percentage) for a variety of conformational processes in these molecules. As a bonus, La(fod)$_3$ data have been found [2c] to be related to π-electron delocalization patterns and to provide readily accessible help in ^{13}C NMR assignments, complementary to that of paramagnetic lanthanide reagents.

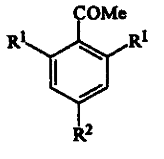
However, our previous conformational analysis of acetophenone [2b] showed the possibility that some features of the method could be further improved. This analysis gave unexpectedly a less definitive result when the shift of the carbonyl carbon was included in the calculations, while this shift centre, being very close to the coordination site, should in principle significantly contribute to the definition of the problem. One possible rationale is that the evaluation of the diamagnetic complexation contributions by the use of La(fod)$_3$ was not accurate enough for this conformational problem (the correction for the diamagnetic contribution is much more important for the carbonyl carbon than for the other nuclei). Diamagnetic contributions could be alternatively evaluated through the use of Lu(fod)$_3$.[5] Lutetium is diamagnetic, as lanthanum is, being much more similar to ytterbium in electronic configuration and ionic radius (trivalent ionic radii for La, Yb and Lu are reported to be 1.061, 0.858 and 0.848 Å respectively).[6] The known diamagnetic complexation contributions, calculated by La(fod)$_3$, are a significant part of the total Yb(fod)$_3$ shifts (0–10%) and any systematic errors will affect the derived results.

Therefore in the present work we have tested the two alternative procedures on a compound of known structure, fluoren-9-one **1** and in the conformational studies of acetophenone **2**, 2,6-dimethyl-4-nitroacetophenone **3**, 2-acetylnaphthalene **4**, 3-methoxyacetophenone **5** and 2-methylacetophenone **6**.

For the planar and rigid molecule of fluoren-9-one an X-ray crystal structure is available.[7a] LIS investigations on this substrate have already been performed by other groups; Giraud and Marzin,[7b] after assigning proton and carbon signals by studying deuteriated derivatives, have reported the relative shifts induced by Eu(fod)$_3$ on both proton and carbon signals (the latter, however, are affected by contact contributions). An opposite assignment of the two quaternary carbons, on the basis of selective-decoupling experiments, has been given by Drake and Jones,[7c] who also reported Eu(fod)$_3$ data. Successive NMR work by Stothers and co-workers [7d] supported this assignment

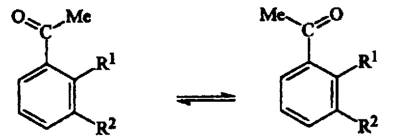


1



2: $R^1 = R^2 = H$
3: $R^1 = Me$; $R^2 = NO_2$

(*E*)-4 (*Z*)-4



5: $R^1 = H$; $R^2 = OMe$
6: $R^1 = Me$; $R^2 = H$

(*E*)-5,6 (*Z*)-5,6

on the basis of the dominant relaxation processes operative at the quaternary carbons. Ammon and co-workers[7e] investigated $Yb(fod)_3$ induced shifts on proton and carbon signals obtained from different samples, so that they could not be used together in the LIS analysis; in addition no correction for the diamagnetic contributions was made and the lanthanide ion was assumed to be in the sterically crowded plane of the carbonyl; their assignments were in agreement with those of Giraud and Marzin. Our previous $La(fod)_3$ work further supported[2c] the assignment of Giraud and Marzin. The reason for checking $Lu(fod)_3$ *vs.* $La(fod)_3$ data in this molecule comes from the steric hindrance on either side of the carbonyl group provided by protons bonded to C-1 and C-8. Thus fluoren-9-one can be a convenient test of a possible different steric requirement of the two diamagnetic lanthanide reagents.

In acetophenone 2 the acetyl group would be expected to be coplanar to the ring. This is supported by X-ray crystal studies of acetophenone itself[8a] and of its 4-amino-[8b] and 4-nitro-derivatives.[8c] Torsional barriers in 4-X-acetophenones were determined[9] as 34.7, 22.4 and 18.4 kJ mol^{-1} respectively for X = NMe_2, H, NO_2 by dynamic NMR spectroscopy, supporting a significant conjugative interaction between the aryl moiety and the acetyl group and the expectation of a planar structure at least for the first two compounds. However, the steric interaction between the acetyl group and the benzene ring in planar ground states has been found[9] to be meaningful [6 (± 1) kJ mol^{-1}]. On the other hand, 2,6-dimethylacetophenones, like 3, should exhibit a marked torsion angle (ω) between the acetyl and the aryl moieties, as a consequence of steric hindrance between the acetyl methyl and methyls bonded to *ortho* carbons.[10a] A recent crystal study of 2,6-dimethyl-4-*tert*-butylacetophenone[10b] indicated an 80° value for this torsion angle. For 2,4,6-trimethylacetophenone a *ca.* 60° ω value has been obtained on the basis of dipole moments and UV measurements (also inferring a possible dependence on *para*- and *meta*-substituents)[10a] in agreement with the results of MM-2 calculations;[10c] in addition, a LIS analysis[2d] of Abraham and co-workers showed that the steric hindrance is relieved by a substantial (60–90°) ω value rather than by a steric relaxation of the two *ortho* methyl groups as found for the corresponding aldehyde.

2-Acetylnaphthalene 4, 3-methoxyacetophenone 5 and 2-methylacetophenone 6 provide a different conformational problem to test the usefulness of $Lu(fod)_3$, in that the variable to be determined is the relative population of two conformers. In particular, in the case of 6 steric hindrance could prevent the planarity of the two conformers and also affect their bond angles and lengths. Taddei and co-workers,[11a] in their analysis of $Eu(fod)_3$-induced shifts on the proton signals of 4 and 6, with the assumption of a single lanthanide position and of a 3.0 Å lanthanide–oxygen distance, found a 69% population of the *E* conformer for 4 and 70% of *Z* for 6 (assuming only planar structures); a semiempirical MO method, PCILO, yielded an 80% population of the *E* conformer for 4. In a previous study[11b] of 6 the assumption of distorted *E* (45° or 60°) and *Z* (30°) conformers and a simple analysis of $Eu(fod)_3$-induced shifts on 6-H and 2-Me protons supported a prevalence (80%–84%) of the *Z* conformer. Nuclear Overhauser effect NMR studies[11c] gave 68% of the *E* conformer for 4 and 64% of the *Z* conformer for 5.

Experimental

Commercial 1 and 4 have been used after crystallization, 2, 5 and 6 after distillation. Synthesis of 3 has been reported in ref. 12, that of $Lu(fod)_3$ in ref. 5. The synthesized $Lu(fod)_3$ as well as commercial $La(fod)_3$ and $Yb(fod)_3$ have been dried at 0.5 mmHg and 40 °C for 24 h immediately before use. Solutions have been prepared with $CDCl_3$ which had been stored over molecular sieves. Substrates and shift reagents have been weighted with an accuracy of 1×10^{-4} g.

The ^1H and ^{13}C spectra for the LIS analyses have been recorded at 200 and 50 MHz respectively on the same samples at a probe temperature of *ca.* 20 °C. Spectral parameters have been adjusted in order to obtain, after zero-filling to 64 K, a digital resolution of 0.0005 ppm for ^1H and 0.0086 ppm for ^{13}C.

LIS experiments have been performed with the incremental weighting method.[1,2] In the case of fluoren-9-one, as previously observed with another tricyclic compound, 9-anthraldehyde,[2f] both the unperturbed chemical shifts and the LIS results have been found to be sensitive to the substrate concentration, presumably because of substrate–substrate interactions;[13] therefore 0.2 mol dm^{-3} solutions of fluorenone have been used, and two amounts of lanthanide reagent added. For all the other compounds the substrate concentration has been 0.5 mol dm^{-3} and three amounts of lanthanide reagent have been added. In all cases the experimental points have all been obtained with a molar ratio $\rho = [L]/[S]$ (L = lanthanide reagent, S = substrate) in the range 0.00–0.16. This corresponds to incremental additions of 15–20 mg of shift reagent. For $Yb(fod)_3$ experiments very good correlation coefficients ($\geqslant 0.999$) demonstrate the accurate linearity of observed chemical shifts *vs.* ρ values. In the $Lu(fod)_3$ and $La(fod)_3$ experiments correlation coefficients 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. Taking into account that the ΔM and ΔD values are obtained by extrapolation to a molar ratio of 1, the digitization error of the single experimental measurement (see above) is estimated to be equivalent to errors in the ΔM and ΔD values of *ca.* 0.02 ppm for ^1H and 0.30 ppm for ^{13}C.

Theory

The experimental pseudo-contact contributions (either $\Delta M - \Delta D_{Lu}$ or $\Delta M - \Delta D_{La}$ values) have been simulated by the program LIRAS-3 (described previously).[2a]

The geometry used for fluorenone follows from an X-ray

Table 1 Observed chemical shifts (δ), Yb(fod)$_3$ induced shifts (ΔM/ppm), Lu(fod)$_3$ induced shifts (ΔD_{Lu}/ppm), La(fod)$_3$ induced shifts (ΔD_{La}/ppm) and pseudo-contact shifts calculated by the two methods ($\Delta M - \Delta D_{Lu}$/ppm and $\Delta M - \Delta D_{La}$/ppm) for fluoren-9-one **1**

Nucleus	δ[a]	ΔM[b]	ΔD_{Lu}[c]	ΔD_{La}[d]	$\Delta M - \Delta D_{Lu}$	$\Delta M - \Delta D_{La}$
C=O	193.87	130.74	5.58	4.78	125.16	125.96
C-1,8	124.29	31.58	2.71	2.35	28.87	29.23
C-2,7	129.06	12.03	0.32	0.31	11.71	11.72
C-3,6	134.66	12.43	2.07	1.64	10.36	10.79
C-4,5	120.29	14.74	0.40	0.16	14.34	14.58
C-4a,4b	144.41	28.13	0.80	0.63	27.33	27.50
C-8a,9a	134.14	53.40	−0.72	−0.40	54.12	53.80
1,8-H	7.65	23.20	—	—	23.20	23.20
2,7-H	7.28	4.93	—	—	4.93	4.93
3,6-H	7.49	6.27	—	—	6.27	6.27
4,5-H	7.49	10.21	—	—	10.21	10.21

[a] $[S]_0 = 0.2$ mol dm^{-3} in CDCl$_3$. [b] From two additions of Yb(fod)$_3$, $\rho \times 10^2 = 8.74$ and 14.74. All correlation coefficients $\geqslant 0.9987$. [c] From two additions of Lu(fod)$_3$, $\rho \times 10^2 = 6.39$ and 12.54. [d] From two additions of La(fod)$_3$, $\rho \times 10^2 = 7.01$ and 12.84. With respect to ΔD values obtained from 1 mol dm^{-3} solutions of fluorenone [ref. 1(*c*)] the pattern is similar but the figures are markedly different (see Experimental).

Table 2 Observed chemical shifts (δ), Yb(fod)$_3$ induced shifts (ΔM/ppm), Lu(fod)$_3$ induced shifts (ΔD_{Lu}/ppm), La(fod)$_3$ induced shifts (ΔD_{La}/ppm) and pseudo-contact shifts calculated by the two methods ($\Delta M - \Delta D_{Lu}$/ppm and $\Delta M - \Delta D_{La}$/ppm) for acetophenone **2**

Nucleus	δ[a]	ΔM[b]	ΔD_{Lu}[c]	ΔD_{La}[d]	$\Delta M - \Delta D_{Lu}$	$\Delta M - \Delta D_{La}$
C=O	198.09	166.85	9.02	13.88	157.83	152.97
COCH$_3$	26.60	70.58	−0.80	−1.30	71.38	71.88
C-1	137.15	66.66	−1.17	−2.42	67.83	69.08
C-2,6	128.31	42.41	1.80	2.86	40.61	39.55
C-3,5	128.57	19.37	0.45	0.18	18.92	19.19
C-4	133.09	17.71	2.52	3.34	15.19	14.37
COCH_3	2.60	46.07	0.16	—	45.91	46.07
2,6-H	7.96	43.04	—	—	43.04	43.04
3,5-H	7.46	11.52	—	—	11.52	11.52
4-H	7.57	9.60	—	—	9.60	9.60

[a] $[S]_0 = 0.5$ mol dm^{-3} in CDCl$_3$. [b] From ref. 1(*b*); three additions of Yb(fod)$_3$, $\rho \times 10^2 = 2.87$, 9.52 and 13.49. All correlation coefficients $\geqslant 0.9993$. [c] From three additions of Lu(fod)$_3$, $\rho \times 10^2 = 3.56$, 8.06 and 11.05. [d] From three additions of La(fod)$_3$, $\rho \times 10^2 = 3.13$, 6.54 and 10.15.

crystal structure determination.[7a] For compounds **2**–**6**, as for our previous LIS analysis of analogous compounds,[2a,d] the acetyl geometry has been taken from the crystal studies of acetophenone at 154 K,[8a] with a methyl hydrogen eclipsing the carbonyl oxygen. The acetyl group has been assumed to bisect the C(6)–C(1)–C(2) external angle in benzene derivatives, the C(1)–C(2)–C(3) external angle in **4**. Standard values have been attributed to the structural parameters of the benzene ring (C–C 1.397 Å, CCC 120°, C–H 1.085 Å) and of ring methyls (2,6-CH$_3$: C–C 1.505 Å, C–H 1.095 Å, CCH tetrahedral, with a hydrogen atom eclipsed with C-3,5). Naphthalene ring parameters followed from ref. 14. For the hindered acetophenone **3** the X-ray crystal parameters of 4-*tert*-butyl-2,6-dimethylacetophenone[10b] have also been tried, either for the acetyl group or for the whole molecule, but with poorer results. For 2-methylacetophenone **6** the geometries of the two conformers were refined by *ab initio* calculations (see later).

The general model derived from our previous investigations on ketones is of a four-site lanthanide-ion complexation, in which the lanthanide position is reflected both in the plane of the carbonyl π-electrons and in the plane of the carbonyl itself; this is equivalent, of course, to a two-site model for planar molecules. The program scans the coordinates (r, φ, ψ) of the four symmetric positions and the relative population of the two positions on either side of the carbonyl π-electron plane; however, for the symmetric ketone **1**, the relative population can be assumed as 50%. The normalization constant of the McConnell and Robertson equation is given that value which minimizes R_{cryst}.[2a] Therefore we have four unknowns for fluorenone and six for compounds **2**–**6**, as they include also the relative populations of the two sets of lanthanide positions and the conformational variable. Each of the studied molecules provides an over-determined data-set to check the precise reproduction of pseudo-contact shifts for the model compound **1** and to determine the conformational variable for compounds **2**–**6**. Even if absolute values of induced shifts are input as experimental data, calculated R_{cryst} values and then conformational results are actually determined by relative chemical shifts, thus any error affecting chemical shifts as a scale factor (such as those in weightings) can only alter the calculated normalization factor.

Results and discussion

For compounds **1**–**6** the diamagnetic complexation shifts (ΔD_{Lu} or ΔD_{La}), evaluated by use of either Lu(fod)$_3$ or La(fod)$_3$, are reported in Tables 1–6. It can be seen that they are always qualitatively similar. As previously shown for the ΔD_{La} data of several molecules,[2c] the ΔD_{Lu} or ΔD_{La} patterns exhibited in Tables 1–6 are clearly identifiable as reflecting predominantly π-electron-density transmission. Both diamagnetic reagents largely deshield, as expected, the carbonyl carbon and, to a lesser extent, the carbons *ortho* and *para* to the carbonyl, while the *meta* carbons and all the protons are scarcely affected. A significant shielding is experienced by C-1 [as observed in ref. 2(*c*)] and in some cases also by the acetyl methyl carbon; the former could arise from a separate polarization of the benzene ring induced by that of the carbonyl. In this connection it seems worth noting that an electric dipole close to a benzene ring was calculated[15] to cause opposite charges on the closest ring carbon and on the carbons *ortho* and *para* to it. In addition, as previously observed for La(fod)$_3$-induced shifts in 2,4,6-trimethylacetophenone[2c] and 2-naphthaldehyde,[2f] respectively, it can be noted that (*i*) both diamagnetic reagents cause smaller

Table 3 Observed chemical shifts (δ), Yb(fod)$_3$ induced shifts (ΔM/ppm), Lu(fod)$_3$ induced shifts (ΔD_{Lu}/ppm), La(fod)$_3$ induced shifts (ΔD_{La}/ppm) and pseudo-contact shifts calculated by the two methods ($\Delta M - \Delta D_{\mathrm{Lu}}$/ppm and $\Delta M - \Delta D_{\mathrm{La}}$/ppm) for 2,6-dimethyl-4-nitroacetophenone **3**

Nucleus	δ[a]	ΔM[b]	ΔD_{Lu}[c]	ΔD_{La}[d]	$\Delta M - \Delta D_{\mathrm{Lu}}$	$\Delta M - \Delta D_{\mathrm{La}}$
C=O	206.03	163.82	11.03	9.85	152.79	153.97
CO*C*H$_3$	31.60	65.80	0.42	0.32	65.38	65.48
C-1	148.11	63.28	−1.87	−1.45	65.15	64.73
C-2,6	134.45	40.13	1.02	0.72	39.11	39.41
C-3,5	122.77	21.36	0.30	0.19	21.06	21.17
C-4	147.57	19.00	0.90	0.72	18.10	18.28
2,6-*C*H$_3$	19.10	30.66	−0.21	−0.31	30.87	30.97
COC*H*$_3$	2.51	39.89	—	—	39.89	39.89
2,6-C*H*$_3$	2.35	26.58	—	—	26.58	26.58
3,5-H	7.90	14.43	—	—	14.43	14.43

[a] [S]$_0$ = 0.5 mol dm^{-3} in CDCl$_3$. [b] From three additions of Yb(fod)$_3$, $\rho \times 10^2$ = 3.27, 6.54 and 12.34. All correlation coefficients $\geqslant$0.9994. [c] From three additions of Lu(fod)$_3$, $\rho \times 10^2$ = 3.19, 6.75 and 9.91. [d] From three additions of La(fod)$_3$, $\rho \times 10^2$ = 4.08, 6.60 and 9.79.

Table 4 Observed chemical shifts (δ), Yb(fod)$_3$ induced shifts (ΔM/ppm), Lu(fod)$_3$ induced shifts (ΔD_{Lu}/ppm), La(fod)$_3$ induced shifts (ΔD_{La}/ppm) and pseudo-contact shifts calculated by the two methods ($\Delta M - \Delta D_{\mathrm{Lu}}$/ppm and $\Delta M - \Delta D_{\mathrm{La}}$/ppm) for 2-acetylnaphthalene **4**

Nucleus	δ[a]	ΔM[b]	ΔD_{Lu}[c]	ΔD_{La}[d]	$\Delta M - \Delta D_{\mathrm{Lu}}$	$\Delta M - \Delta D_{\mathrm{La}}$
C=O	197.77	142.99	9.66	14.16	133.33	128.83
CO*C*H$_3$	26.58	61.18	−0.77	−1.07	61.95	62.25
C-1	130.04	35.68	3.20	4.26	32.48	31.42
C-2	134.43	56.43	−1.17	−2.00	57.60	58.43
C-3	123.79	37.69	0.76	1.32	36.93	36.37
C-4	128.28	17.70	0.68	0.40	17.02	17.30
C-4a	135.48	14.78	1.51	1.80	13.27	12.98
C-5	127.66	7.90	0.41	0.25	7.49	7.65
C-6	128.33	7.17	1.67	1.86	5.50	5.31
C-7	126.64	6.70	0.76	0.54	5.94	6.16
C-8	129.43	10.08	0.83	0.78	9.25	9.30
C-8a	132.43	16.57	0.18	−0.15	16.39	16.72
COC*H*$_3$	2.68	39.67	0.31	0.23	39.36	39.44
1-H	8.42	32.89	0.22	0.09	32.67	32.89
3-H	8.01	40.88	0.08	0.07	40.80	40.88
4-H	7.84	10.30	—	—	10.30	10.30
5-H	7.84	5.72	—	—	5.72	5.72
6-H	7.54	4.10	—	—	4.10	4.10
7-H	7.54	4.10	—	—	4.10	4.10
8-H	7.92	7.70	—	—	7.70	7.70

[a] [S]$_0$ = 0.5 mol dm^{-3} in CDCl$_3$. [b] From three additions of Yb(fod)$_3$, $\rho \times 10^2$ = 3.11, 6.37 and 12.37. All correlation coefficients $\geqslant$0.9994. [c] From three additions of Lu(fod)$_3$, $\rho \times 10^2$ = 3.26, 5.80 and 11.92. [d] From three additions of La(fod)$_3$, $\rho \times 10^2$ = 3.31, 6.83 and 12.95.

Table 5 Observed chemical shifts (δ), Yb(fod)$_3$ induced shifts (ΔM/ppm), Lu(fod)$_3$ induced shifts (ΔD_{Lu}/ppm), La(fod)$_3$ induced shifts (ΔD_{La}/ppm) and pseudo-contact shifts calculated by the two methods ($\Delta M - \Delta D_{\mathrm{Lu}}$/ppm and $\Delta M - \Delta D_{\mathrm{La}}$/ppm) for 3-methoxyacetophenone **5**

Nucleus	δ[a]	ΔM[b]	ΔD_{Lu}[c]	ΔD_{La}[d]	$\Delta M - \Delta D_{\mathrm{Lu}}$	$\Delta M - \Delta D_{\mathrm{La}}$
C=O	197.89	166.26	9.59	13.64	156.67	152.62
CO*C*H$_3$	26.72	45.04	−0.81	−1.22	70.68	71.09
C-1	138.50	65.52	−1.36	−2.18	66.88	67.70
C-2	112.35	44.19	1.52	3.14	42.67	41.05
C-3	159.82	20.47	0.49	0.27	19.98	20.20
C-4	119.59	18.31	2.74	2.90	15.57	15.41
C-5	129.56	19.35	0.49	0.37	18.86	18.98
C-6	121.12	40.13	1.96	2.39	38.17	37.74
ArO*C*H$_3$	55.41	6.54	0.00	−0.18	6.54	5.41
COC*H*$_3$	2.59	45.04	—	—	44.86	44.92
2-H	7.54	47.72	—	—	47.61	47.61
4-H	7.11	10.03	—	—	9.94	10.00
5-H	7.36	12.00	—	—	11.99	12.11
6-H	7.49	38.41	—	—	38.38	38.50
ArOC*H*$_3$	3.85	5.20	—	—	5.24	5.41

[a] [S]$_0$ = 0.5 mol dm^{-3} in CDCl$_3$. [b] From three additions of Yb(fod)$_3$, $\rho \times 10^2$ = 4.64, 11.62 and 15.72. All correlation coefficients $\geqslant$0.9993. [c] From three additions of Lu(fod)$_3$, $\rho \times 10^2$ = 5.95, 9.26 and 13.81. [d] From three additions of La(fod)$_3$, $\rho \times 10^2$ = 3.71, 7.21 and 11.36.

Table 6 Observed chemical shifts (δ), Yb(fod)$_3$ induced shifts (ΔM/ppm), Lu(fod)$_3$ induced shifts (ΔD_{Lu}/ppm), La(fod)$_3$ induced shifts (ΔD_{La}/ppm) and pseudo-contact shifts calculated by the two methods ($\Delta M - \Delta D_{Lu}$/ppm and $\Delta M - \Delta D_{La}$/ppm) for 2-methylacetophenone **6**

Nucleus	δ[a]	ΔM[b]	ΔD_{Lu}[c]	ΔD_{La}[d]	$\Delta M - \Delta D_{Lu}$	$\Delta M - \Delta D_{La}$
C=O	201.64	173.75	9.25	13.47	164.50	160.26
COCH$_3$	29.52	70.22	−1.17	−1.33	71.39	71.55
C-1	137.64	66.72	−2.13	−2.98	68.85	69.70
C-2	138.42	51.91	3.24	3.95	48.67	47.96
C-3	132.04	23.80	0.83	0.63	22.97	23.17
C-4	131.50	20.14	2.85	3.35	17.29	16.79
C-5	125.69	20.15	0.55	0.47	19.60	19.68
C-6	129.35	37.59	2.49	2.95	35.10	34.64
Ar*C*H$_3$	21.60	46.04	0.55	0.47	45.49	45.57
COC*H*$_3$	2.57	42.48	—	—	42.48	42.48
3-H	7.24	15.19	—	—	15.19	15.19
4-H	7.26	11.19	—	—	11.19	11.19
5-H	7.38	13.06	—	—	13.06	13.06
6-H	7.69	31.22	—	—	31.22	31.22
ArC*H*$_3$	2.53	39.87	—	—	39.87	39.87

[a] $[S]_0 = 0.5$ mol dm^{-3} in CDCl$_3$. [b] From three additions of Yb(fod)$_3$, $\rho \times 10^2 = 3.04$, 8.08 and 13.67. All correlation coefficients $\geqslant 0.9998$. [c] From three additions of Lu(fod)$_3$, $\rho \times 10^2 = 4.82$, 9.55 and 14.90. [d] From three additions of La(fod)$_3$, $\rho \times 10^2 = 4.32$, 8.87 and 12.81.

Table 7 Results of the LIS analysis for substrates **1**–**6**, with the diamagnetic complexation shift removed by Lu(fod)$_3$ or La(fod)$_3$

		Result	R_{cryst}(%)	r/Å	φ(°)	ψ(°)	pop(%)[a]
1	Lu	—	0.9	2.75	65	155	50
	La	—	0.8	2.75	65	155	50
2	Lu	$\omega = 0°$	0.2	2.92	55	141	90
	La	$\omega = 0°$	1.2	2.96	62	140	86
3	Lu	$\omega = 85°$	0.7	2.65	70	145	100
	La	$\omega = 85°$	0.8	2.65	70	145	100
4	Lu	$E = 68\%$	0.4	2.98	60	136	91
	La	$E = 68\%$	1.6	3.01	65	136	90
5	Lu	$Z = 63\%$	0.3	2.94	52	141	95
	La	$Z = 63\%$	1.2	2.97	57	140	92
6[b]	Lu	$Z = 92\%$	0.8	2.68	66	144	98
	La	$Z = 92\%$	1.5	2.69	70	145	98

[a] For the symmetric ketone **1**, lanthanide population has been assumed to be 50% on either side of the carbonyl π-electron plane, while for methyl ketones **2**–**6** the calculated population on the side closer to the acetyl methyl is shown. [b] For the *E* conformer a ω value of 35° was assumed, according to *ab initio* calculations.

effects on the *ortho* and *para* carbons of 2,6-dimethyl-4-nitroacetophenone (**3**), which can easily be related to steric inhibition to through-conjugation, and (*ii*) in 2-acetylnaphthalene **4** both reagents clearly discriminate between the real and pseudo *ortho* position with respect to the acetyl group.

From a quantitative point of view, inspection of Tables 1 and 3 reveals that in the case of fluorenone and 2,6-dimethyl-4-nitroacetophenone diamagnetic complexation shifts evaluated by either Lu(fod)$_3$ or La(fod)$_3$ are not significantly different. In fluorenone, the presence of some steric hindrance on both sides of the carbonyl caused by 1-H and 8-H, which may affect the position of the lanthanide ion, does not appear to cause any difference between the shifts induced by the two diamagnetic reagents.

By contrast, for acetophenone **2**, 2-acetylnaphthalene **4**, 3-methoxy- **5**, and 2-methyl-acetophenone **6** (see Tables 2, 4–6), the differences are significant. This behaviour seems to be exhibited by those aromatic ketones which are not deactivated in coordinating the lanthanide. As only the relative ($\Delta M - \Delta D$) values of the various nuclei are really important in determining LIS results, it is interesting to note that with respect to ΔD_{La}, ΔD_{Lu} values are smaller particularly for the carbonyl carbon and the other nuclei close to the coordinating site (note also the opposite effect caused by the lanthanide change when the ΔD value is negative, as for C-1 and the acetyl methyl carbon). In conclusion, we can expect that for compounds **2** and **4**–**6** the use of lutetium in evaluating diamagnetic contributions can lead to different results in LIS analysis.

As expected on the basis of the previous discussion, the use of either Lu(fod)$_3$ or La(fod)$_3$ produced identical solutions for compounds **1** and **3**. In the case of fluorenone the problem of the assignment of the quaternary carbons (see Introduction) could be easily solved by assigning the higher-field signal, exhibiting negative ΔD values, to the carbon directly bonded to the carbonyl group, in agreement only with refs. 8(*a*) and (*d*). Results in Table 7 show that the fit between experimental and calculated shifts is good (R_{cryst} 0.8–0.9%) and that the lanthanide position exhibits a somewhat large ψ coordinate, mirroring steric hindrance on either side of the carbonyl. For 2,6-dimethyl-4-nitroacetophenone **3** a nicely defined solution (R_{cryst} 0.7%–0.8%) for a conformation with the plane of the acetyl group essentially perpendicular to the ring (see Fig. 1) could be obtained. The corresponding lanthanide position was essentially on the side of the acetyl methyl and somewhat out of the carbonyl plane (Table 7). It must be mentioned in this respect that in any LIS study the resulting conformational solution actually refers to the coordinated substrate and the question arises whether the same solution holds for the free substrate too. While in unconjugated carbonyl derivatives this could be successfully checked, no test could yet be run for aromatic compounds. As a matter of fact, the measured ΔD values show that complexation perturbs the π-electron-density distribution in the whole molecule of substrate. This could correspond to an increased conjugation between the acetyl and the ring and could be associated with a slight decrease in the ω value. Nevertheless, the results herein obtained for compound **3** do not appear to be affected by a flattening effect of complexation. However, different substrates could have different conformational flexibilities and/or π-electron-density polarizabilities, so that no general conclusion can be drawn.

With regard to acetophenone **2**, either kind of ($\Delta M - \Delta D$) shifts yield curves of R_{cryst} *vs.* ω values exhibiting a minimum at $\omega = 0$ [see Fig. 1(*a*)], as expected, but the minimum obtained by the use of Lu(fod)$_3$ is much lower ($R_{cryst} = 0.2\%$ *vs.* 1.2%) and better defined. If the experimental errors correspond to an uncertainty in R_{cryst} of 100% (which is considerably large), then this corresponds to an error in the ω value of ±17° for the Lu(fod)$_3$ and ±54° for the La(fod)$_3$ experiment, dramatically illustrating the much greater definition produced by the Lu(fod)$_3$ technique. This corresponds to a simulation of

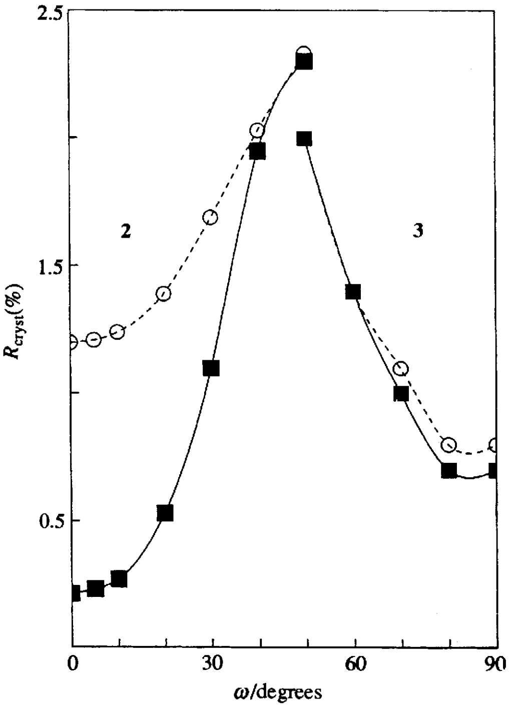


Fig. 1 Plots of R_{cryst} *vs.* the torsion angle ω between the acetyl and the ring planes for acetophenone **2** and 2,6-dimethyl-4-nitroacetophenone **3** with the diamagnetic complexation shift removed by lutetium (solid curves) or lanthanum (dashed curves) reagents

pseudocontact values, ranging from 157.8 to 9.6 ppm, all within ±0.2 ppm. These findings show that for this substrate the electronic interaction of Yb(fod)$_3$ with the carbonyl and hence its diamagnetic complexation shifts are better reproduced by Lu(fod)$_3$ than by its lanthanum analogue, so that a more definite conformational solution can be obtained. With either diamagnetic reagent the calculated lanthanide positions are similar and largely (85%–90%) on the methyl side of the carbonyl (see Table 7).

The result of the present analysis of acetophenone confirms the expectation of a planar structure for this molecule and also that planar structures can be used in studying the conformation equilibria of 2-acetylnaphthalene **4** and 3-methoxyacetophenone **5**. The latter will be discussed first.

3-Methoxyacetophenone **5** provides a more extended data set because of the asymmetrically substituted ring. However, the two very low pseudocontact shifts exhibited by the methoxy group cannot help in determining its orientation with respect to the aromatic moiety, thus we have had to exclude them from the analysis as we cannot know the actual position of these shift centres. Even with this inconvenience, we have still 13 shifts to determine the acetyl orientation and the other five unknowns discussed in the theory section. Fig. 2 shows that the two methods of isolating pseudocontact shifts have given the same solution (63% of *Z* conformation), but the use of Lu(fod)$_3$ has produced a much better definition of the minimum, corresponding to an R_{cryst} value of 0.3% *vs.* 1.2%. If the experimental errors correspond to an uncertainty in R_{cryst} of 100%, this gives an error in the *Z* value of ±2% for the Lu(fod)$_3$ and ±8% for the La(fod)$_3$ experiment. In the former case, the average absolute error in reproducing the 13 pseudocontact shifts ranging from 157 to 10 ppm was only 0.1 ppm. It is worth noting that the position of the minimum is determined by the two large shifts of the acetyl methyl. The previously observed difficulty[11a] of LIS analysis in discriminating between two planar and a single rotated conformer could be a good test of our analysis. The hypothesis of a single rotated conformer is clearly discarded by the Lu(fod)$_3$ experiment, as the R_{cryst} value was never better than 3.6% (for a torsion angle of 70° between the acetyl and the ring planes). The present result is in agreement with that produced by NOE studies[11c] and compares with that ($Z = 68\%$) obtained through the analysis of ($\Delta M - \Delta D_{La}$) values for the corresponding aldehyde in the same solvent.[2e]

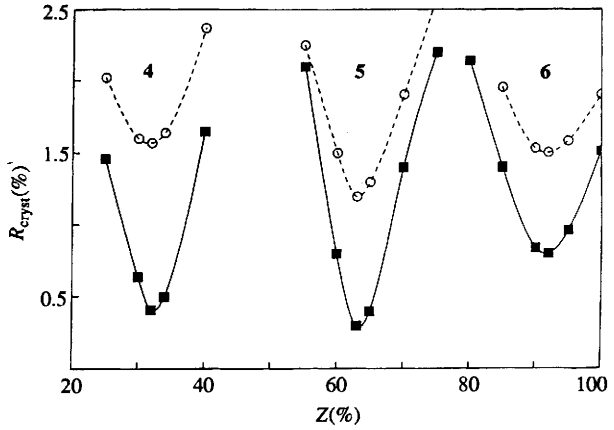
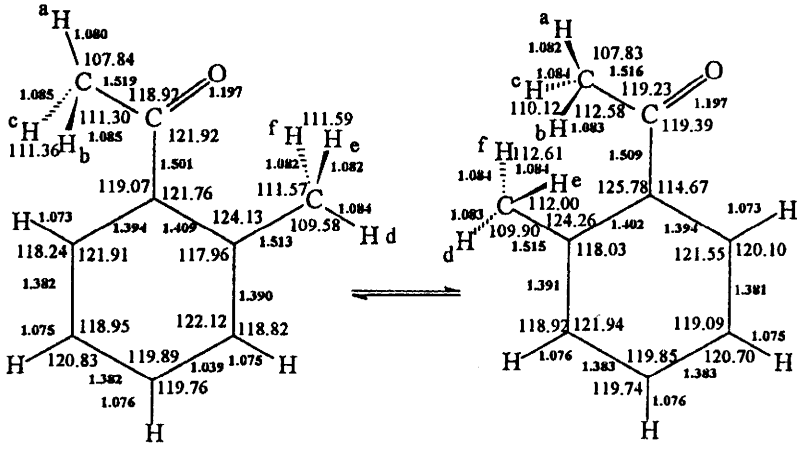


Fig. 2 Plots of R_{cryst} *vs.* the conformer population for 2-acetylnaphthalene **4**, 3-methoxyacetophenone **5** and 2-methylacetophenone **6** with the diamagnetic complexation shift removed by lutetium (solid curves) or lanthanum (dashed curves) reagents

The 12 carbon and the 8 proton shifts of 2-acetylnaphthalene **4** appear to provide a well over-determined data set and thus a good test for our methods of isolating pseudocontact shifts, however the significance of shift centres well removed from the coordinating site should not be over-estimated. For instance, the position of C-7 with respect to the acetyl group in **4** is similar to the position of the methoxy carbon with respect to the acetyl in one conformation of **5**. Fig. 2 shows that the use of either Lu(fod)$_3$ or La(fod)$_3$ produces the same solution (68% of *E* conformation). However the definition obtained through the use of Lu(fod)$_3$ is remarkably better (R_{cryst} 0.4% *vs.* 1.6%, see Fig. 2). If the experimental errors correspond to an uncertainty in R_{cryst} of 100%, this corresponds to an error in the *E* value of ±4% for the Lu(fod)$_3$ experiment and from −12% to +16% for the La(fod)$_3$ experiment. In the former case the average absolute error in reproducing the 20 pseudocontact shifts ranging from 133 to 4 ppm was only 0.1 ppm. The hypothesis of a single distorted solution is discarded by our analysis, as R_{cryst} was never lower than 5.1% even when using Lu(fod)$_3$. The precise agreement between the present result, that of NOE experiments of Kruse and Kha[11c] and that obtained by Taddei and coworkers[11a] using a much simpler LIS analysis is noticeable; it is possible that, in relatively large and asymmetrical molecules like this one, proton shift centres are sufficient to define the problem. The prevalence of the *E* conformer can be related[11a] to the *s-trans* relation between the carbonyl double bond and C(1)–C(2), which exhibits a higher degree of double bond than C(2)–C(3). The present result compares with 75%–80% of *Z* conformation that we obtained by the analysis of the ($\Delta M - \Delta D_{La}$) values exhibited by 2-naphthaldehyde,[2f] possibly exhibiting a greater conjugative interaction between the carbonyl and the aryl moiety.

In 2-methylacetophenone **6** the substantial ΔD values obtained for *ortho* and *para* carbons support essentially planar structures. The analysis of ($\Delta M - \Delta D_{Lu}$) data, assuming two planar conformers gave an unsatisfactory R_{cryst} value of 1.6% for *ca.* 90% of *Z* conformer. This outcome can be related to incorrect bond lengths and angles of the examined conformers, as in this sterically hindered molecule standard geometrical



(Z)-6 (E)-6

(Z)-6	TORSION ANGLES	(E)-6
0.68	C(2)-C(1)-C-O	144.67
-0.45	Ha-C-C-O	24.57
119.25	Hb-C-C-O	145.85
239.74	Hc-C-C-O	266.89
179.67	Hd-C-C(2)-C(1)	191.42
-59.94	He-C-C(2)-C(1)	-49.36
59.27	Hf-C-C(2)-C(1)	72.13

Fig. 3 Structural parameters of the two conformers of 2-methylacetophenone **6** from RHF 6-31G* full optimization

parameters are probably inadequate. Thus we have run an *ab initio* RHF full optimization of the geometrical parameters of the *E* and *Z* conformer with a 6-31G* basis set (program GAUSSIAN 92),[16] obtaining the results shown in Fig. 3; while the *Z* conformer was found to be essentially planar, the *E* conformation exhibited a 35° rotation of the acetyl group out of the ring plane. With these starting geometries LIS analysis produced a better solution at 92% of *Z* conformation (R_{cryst} 0.75%, see Fig. 2). The use of La(fod)$_3$ gave as usual the same solution with a poorer definition (R_{cryst} 1.5%).

The lanthanide positions calculated with either diamagnetic reagents for compounds **2**–**6** (see Table 7) are in the normal range for methyl ketones. Of the four sites around the carbonyl oxygen (see Theory), the lanthanide populates essentially the couple of sites closer to the acetyl methyl group, significantly out of the carbonyl plane.

Conclusions

The patterns of diamagnetic complexation shifts produced by Lu(fod)$_3$ and La(fod)$_3$ on aromatic ketones are always qualitatively similar, reflecting predominantly π-electron-density transmission. The lutetium reagent appears better to reproduce the diamagnetic contribution in several cases, which seem to be related more to the strength of the electronic interaction with the carbonyl than to a different steric demand of the two lanthanide ions. For these molecules the experiment with La(fod)$_3$ appears to over-estimate the diamagnetic correction for nuclei close to the coordinating site. In all the cases examined the lutetium experiment supported the results obtained through the use of La(fod)$_3$. However, with strongly coordinating substrates, the use of Lu(fod)$_3$ significantly improved the definition of the results. In this way it has been possible to run accurate conformational studies of acetophenone, 2-acetylnaphthalene, 2,6-dimethyl-4-nitro-, 3-methoxy- and 2-methyl-acetophenone. The particularly good fit obtained for **2**, **4** and **5** can be attributed to the lack of steric hindrance in the substrate, so that standard bond lengths and angles could be safely adopted, and leaves little significance to the many possible caveats about the background theory of LIS analysis. The only surviving problems regard the possible influence of complexation on conformational solutions and how to get a good starting geometry for sterically hindered substrates. These points are now being studied in our laboratories.

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