Tetrahedron Letters, Vol.22, No.29, pp 2807 - 2810, 1981
Printed in Great Britain

0040-4039/81/292807-04$02.00/0

THE CONFORMATION OF 4-PHENYLCYCLOHEXANONE IN SOLUTION BY ^{1}H- AND ^{13}C-LANTHANIDE INDUCED SHIFT (L.I.S.) ANALYSIS : EVIDENCE IN FAVOUR OF PHENYL OVER t-BUTYL AS A CONFORMATIONAL LOCK

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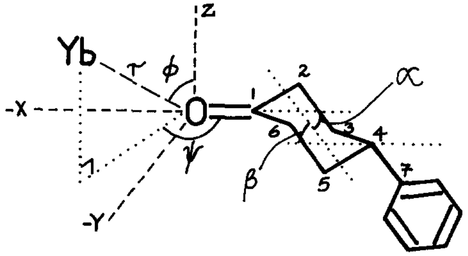
Summary. The degree of pucker of the cyclohexanone ring in 4-phenylcyclohexanone has been refined by L.I.S. analysis. The results indicate puckering intermediate between that in cyclohexanone and 4-t-butylcyclohexanone, suggesting that phenyl may be preferable to t-butyl as a locking group in conformational analysis. The Yb $(fod)_3$ shift reagent, although binding primarily at the carbonyl oxygen atom, also complexes weakly with the phenyl group.

Lanthanide-induced n.m.r. shifts, if accurately measured and correctly interpreted, contain sufficient information to allow the refinement of solution molecular conformation. As a result, we have obtained reliable estimates of the extent of ring pucker in cyclohexanone,[1] 4-t-butylcyclohexanone,[1] and bicyclo[3.1.0]hexan-3-one.[2] We now present the results of an extension of this work to 4-phenylcyclohexanone (1) which demonstrate the importance of a mathematically rigorous approach to data processing and reveal features of lanthanide ion binding hitherto unrecognised.

(1)



2-site binding model:
reflect Yb in XZ plane;
4-site binding model:
reflect Yb in XZ and XY
planes.

Unlike single-crystal X-ray diffraction where, typically, several thousand measured 'reflection' intensities permit simultaneous refinement of often hundreds of atomic coordinates, the information content of the L.I.S. experiment is low; it is not feasible, therefore, to attempt wholesale structure solution in the X-ray sense based on L.I.S. data. In conformational analysis, however, the problem is not one of gross structure determination (bond lengths and angles can usually be reliably estimated either by literature analogy or theoretical methods) but rather accurate determination of torsional (dihedral) angles. Our approach to the study of the conformation of (1) in solution has therefore been to use molecular mechanics calculations on 4-methylcyclohexanone[3] to furnish a starting geometry, with the equatorial methyl replaced by phenyl, oriented perpendicular to the mean plane of the cyclohexanone ring (in agreement with the calculations of Allinger and Tribble on the conformation of phenylcyclohexane[4]). L.I.S. data then permit refinement of this geometry *via* systematic variation of the cyclohexane ring pucker angles α and β.

L.I.S.'s were measured for all carbon (XL-100, 25.2 MHz) and hydrogen atoms (R-34, 220 MHz) (on the same solutions) by incremental addition of Yb $(fod)_3$ to solutions of (1) (0.736 M) and phenylcyclohexane (2) (0.711 M) in $CDCl_3$. Commercial (1) was used as purchased; (2) was purified by distillation *in vacuo* and preparative g.l.c.; Yb $(fod)_3$ was dried *in vacuo* over P_4O_{10} for 24 h prior to use; $CDCl_3$ was stored over molecular sieves and passed through alumina immediately before use. The slopes of the least-square linear plots of induced shift *versus* the molar ratio of shift reagent to substrate [correlation coefficients 0.996 or better for (1) and 0.984 or better for (2)] are assumed to correspond to the bound shifts (ΔM values, see Tables).

TABLE 1

Observed and calculated ΔM's for 4-phenylcyclohexanone-Yb $(fod)_3$

	$C_{2,6}$	$C_{3,5}$	C_4	C_7	$C_{\underline{o}}^{\underline{a}}$	$C_{\underline{m}}^{\underline{a}}$	$C_{\underline{p}}^{\underline{a}}$
$\Delta M_{obs.}$	48.25	22.81	17.60	8.94	6.78	4.62	3.76
corr. coeff.	.998	.998	.998	.996	.996	.996	.999
$\Delta M_{calc.}^{\underline{b}}$	48.0	22.8	17.6	8.6	5.8	3.2	2.6

	$H_{2,6}$eq.	$H_{2,6}$ax.	$H_{3,5}$eq.	$H_{3,5}$ax.	H_4	$H_{\underline{o}}^{\underline{a}}$	$H_{\underline{m}}^{\underline{a}}$	$H_{\underline{p}}^{\underline{a}}$
$\Delta M_{obs.}$	41.7	30.2	13.1	19.3	14.5	5.9	2.8	2.4
corr. coeff.	.999	.999	.999	.999	.999	.999	.999	.999
$\Delta M_{calc.}^{\underline{b}}$	41.8	30.3	13.1	19.2	14.7	6.0	2.3	1.7

$\underline{a}$ these nuclei were not included in the refinement of α and β (see text)

$\underline{b}$ calculated for that lanthanide ion position and molecular geometry giving global minimum R-factor

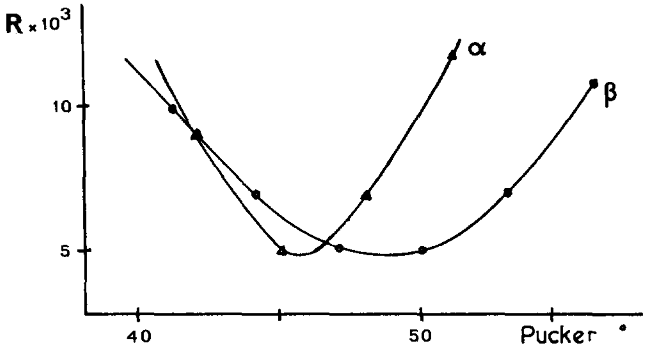
Computer program LIRAS 3[5] was used to calculate (from the McConnell-Robertson equation) theoretical ΔM's at each nucleus 'i' as a function of Yb-ion position (defined by the polar variables r, ϕ, ψ) and molecular geometry and to compare these with observed ΔM's through calculation of an R-factor [equation (1)] where f is a normalisation factor defined by equation (2). We have

$$R = \left\{ \sum_i (\Delta M_{i,obs} - f\Delta M_{i,calc.})^2 \Big/ \sum_i \Delta M_{i,obs.}{}^2 \right\}^{1/2} \qquad (1)$$

discussed previously[6] the two- and four-site models for Yb-ion binding at the carbonyl oxygen and shown that the latter gives better definition of the substrate geometry. Thus we use the four site model for these comparative studies. The *o*, *m*- and *p*-nuclei of the phenyl ring were excluded

$$f = \sum_i (\Delta M_{i,obs.} . \Delta M_{i,calc.}) \Big/ \sum_i \Delta M_{i,calc.}^2 \qquad (2)$$

from the analysis since, being remote from the lanthanide binding site, they have only small Δ M's, and the carbonyl carbon was excluded because of its vulnerability to contact and diamagnetic shift effects. Pucker angle α was varied in 3° increments and, for each geometry, that position of the lanthanide ion was located (by variation of r, ϕ, ψ) at which disagreement between observed and calculated Δ M's was minimised. Angle α was then held constant at the value found to give the overall minimum R-factor and pucker angle β was similarly refined. Re-refinement of α at constant β, and β at constant α, was continued until neither angle changed significantly. The results are summarised graphically in the Figure.



The four-site model yields minima in the R-factor versus pucker curves which are well-defined. The lanthanide polar coordinates (r = 2.85-2.90 Å, ϕ = 60-65° and 120-115°, ψ = 145-150° and 215-200°) for global minimum R-factors indicate binding into oxygen lone-pair electron density (as expected) and demonstrate that the four-site model allows the lanthanide ion greater freedom to minimise steric interactions with (1)'s ketonic α-hydrogen atoms than is possible in the two-site case. We have observed this effect in our studies on bicyclo [3.1.0] hexan-3-one and adamantanone.[6] The angles of pucker so obtained (α = 45°, β = 47-50°) are intermediate between those that we have measured previously by the L.I.S. technique for cyclohexanone (49° and 51°) and 4-t-butylcyclohexanone (42° and 50°).[1] We are therefore led to the important conclusion that the 4-phenyl substituent distorts the cyclohexanone ring to a lesser extent than does the 4-t-butyl group: phenyl is thus a better 'locking group' than t-butyl for conformational analyses requiring rigid cyclohexanone models.

Detailed inspection of the $\Delta M_{i,calc.}$ values (Table) reveals that although the agreement with $\Delta M_{i,obs.}$ is excellent for the cyclohexanone ring, the calculated values for the phenyl ring are much too low. This, coupled with the recognition that shift reagents are Lewis acids and that L.I.S.'s recorded on substrates dissolved in benzene are usually lower than when CCl_4 is the solvent,[8] suggested the possibility of secondary binding between the shift reagent and the 4-phenyl substituent, and prompted a further experiment in which phenylcyclohexane was used as substrate in the L.I.S. study

The results (carbon-13 data, Table 2) show that although the ΔM's are small, the correlation coefficients and intercepts are entirely acceptable. The ΔM's are largest (and similar) for the aromatic carbon atoms and decrease through the cyclohexane ring with increasing distance from the phenyl group. This suggests that the ytterbium ion is associated specifically and symmetrically with the aromatic ring, presumably above (and below) the ring plane. In the 4-phenylcyclohexanone case, of course, the ytterbium ion is coordinated predominantly to the region of highest Lewis basicity (the carbonyl oxygen); nonetheless, the results with phenylcyclohexane imply the probability of further complex formation, albeit to a lesser (and unknown) extent, with the phenyl ring, an effect which has not been observed previously.

TABLE 2

Observed (δ) and bound shifts (Δ M) for phenylcyclohexane-Yb(fod)$_3$

	C_1	$C_{2,6}$	$C_{3,5}$	C_4	C_7	$C_{\underline{o}}$	$C_{\underline{m}}$	$C_{\underline{p}}$
δ(p.p.m.)	44.61	34.49	26.95	26.19	147.87	126.65	128.11	125.61
ΔM	1.18	0.88	0.41	0.45	1.63	1.81	1.74	1.85
intercept	44.62	34.49	26.95	26.19	147.89	126.67	128.13	125.63
corr. coeff.	.989	.999	.996	.989	.984	.988	.985	.991

It is important to stress that subtle effects of this kind can only be recognised if the raw L.I.S. data are collected with scrupulous attention to possible sources of experimental error and mathematical rigour is maintained throughout the computational analysis. By this approach, comparatively small differences between observed and calculated induced shifts, which might otherwise be dismissed as experimental or theoretical shortcomings, take on a new significance, suggesting new experiments and extending knowledge and understanding in this fascinating and important field.

Acknowledgements - We thank the SRC for a fellowship (to H.A.B.) and for grants towards the purchase of NMR spectrometers.

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(Received in UK 15 April 1981)