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CONCERNING THE CONFORMATIONS OF HIGHLY SUBSTITUTED CYCLOHEXANONES AND DERIVATIVES[1,2]

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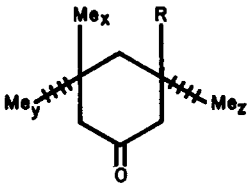
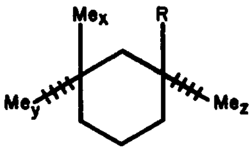
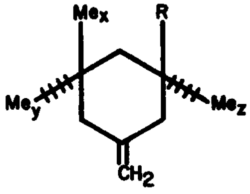
Recent dipole moment studies on aryl-substituted cyclohexanones (e.g., ketone Ia) (1) prompt us to make this preliminary report on our NMR investigations of this ketone, related cyclohexanones Ib and Ic and derivatives II and III. (2).



Ia, R = C_6H_5
Ib, R = α-$C_{10}H_7$
Ic, R = p-F-C_6H_4



IIa, R = C_6H_5
IIb, R = α-$C_{10}H_7$



IIIa, R = C_6H_5
IIIb, R = α-$C_{10}H_7$

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NMR peak assignments were made with the aid of selectively deuterated analogs, in conjunction with spin-decoupling techniques. The plots of methyl proton chemical shifts of Ia and Ib vs. concentration in solvents of differing polarity and magnetic properties are summarized in Fig. 1.

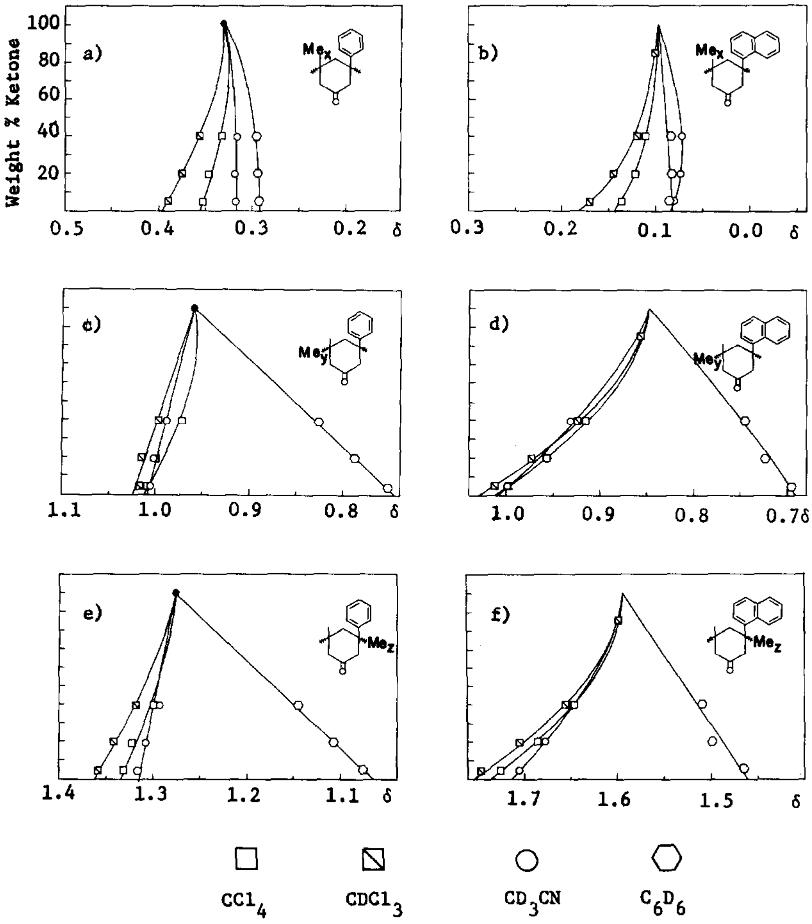

Fig. I Methyl Proton Chemical Shifts of 3-Phenyl-3,5,5-trimethylcyclohexanone (Ia) and 3-(α-Naphthyl)-3,5,5-trimethylcyclohexanone (Ib): Dilution and Solvent Dependence

The anomalous, high-field chemical shift attributed to Me$_x$ (Figure Ia, Ib) is considered to arise from a 1,3-diaxial relationship of Me$_x$ protons in a plane perpendicular to and near that of the aromatic ring, and therefore in the shielding region of the aromatic ring current effects. It seems most difficult to accommodate the observed low frequency (high field) shift on the basis of an equatorial aryl moiety. Methyl shifts similar to ours have recently been reported in more complicated, less flexible systems by Ireland and co-workers (3).

From the chemical shift data for the cyclohexanones (data for the representative examples Ia, Ib and Ic given in Figure I and Table I) and derived cyclohexanes (II) and exomethylene cyclohexanes (III), the structural requirements for the observation of the anomalously shielded methyl proton shifts have been delineated as: (a) the cyclohexanone (or derivative) must be tetrasubstituted at C-3 and C-5, (b) at least one substituent must be aryl, and (c) the carbonyl function (or indeed, any sp^2-hybridized carbon) at C-1 is not essential.

The aromatic solvent-induced shifts (ASIS) (4) of the methyl protons in the ketones provide strong support of an axial position for the aromatic substituent. Methyl groups at C-3 and C-5 carbon atoms of simpler, substituted cyclohexanones have been shown (4) to have ASIS values (i.e., $\Delta^{CCl_4}_{C_6H_6} = \delta(CCl_4) - \delta(C_6H_6)$) of ca. 0.2 ppm (axial) to 0.3 ppm (equatorial). The methyl ASIS values of ketones can be readily separated into two types (Table I): (a) values for Me_x ranging from 0.0 to 0.13 ppm and (b) values for Me_y and Me_z, ranging from 0.25 to 0.37 ppm. The Me_y and Me_z values agree well with those obtained by Laszlo and colleagues (5) for equatorial methyl protons.

Table I Methyl ASIS Values in ppm for cyclohexanones I

$\Delta^{i}_{j} = \delta(i) - \delta(j)$ (for solvents i and j)

Cyclohexanone (Substituents)	Methyl group	$\Delta^{CCl_4}_{C_6D_6}$	$\Delta^{CDCl_3}_{C_6D_6}$	$\Delta^{CD_3CN}_{C_6D_6}$
I	Me_x	0.065	0.103	0.017
(3-Phenyl-3,5,5-trimethyl)	Me_y	0.276	0.282	0.265
	Me_z	0.270	0.294	0.250
Ib	Me_x	0.059	0.099	-0.003
(3-(α-Naphthyl)-3,5,5-trimethyl)	Me_y	0.318	0.335	0.318
	Me_z	0.271	0.295	0.251
Ic	Me_x	0.10	0.13	0.07
(3-(p-fluorophenyl)-3,5,5-trimethyl)	Me_y	0.25	0.31	0.27
	Me_z	0.34	0.37	0.33

The Me_x ASIS values observed are much smaller than those obtained previously for axial groups, but explicable on the basis of the proposed 1,3-diaxial Me_x-aryl relationship. This aromatic ring can be expected to protect Me_x sterically from the approach of solvent molecules of all types: the relative constancy of the Me_x shifts (see Fig. I) is thus compatible with its indifference to effects of solvent. ASIS values obtained for methylene protons also support this conclusion. The constancy of chemical shift and coupling constant values as solvent polarity and nature is varied is consistent with the very high predominance of a single conformer. This conclusion is supported by preliminary variable temperature NMR studies.

Studies of long-range (4-bond) couplings in the cyclohexane ring in these and related compounds support the view that the cyclohexanones exist in essentially chair-like conformations (undoubtedly somewhat flattened to alleviate 1,3-diaxial interactions) rather than twist-boat or other flexible forms. Carbon-13 chemical shifts (to be published) in the ketones and related bicyclo[3.2.1]octenes (6) lend further support to the view that these highly substituted cyclohexanone rings exist predominantly in a single, chair-like conformation.

Our conclusion that an aryl substituent in these 3-aryl-3,5,5-trimethylcyclohexanones occupies an axial position is contrary to previous conclusions (1). We feel that our more recent and extensive data is compelling, and that the earlier experimental results can be accommodated on an axial-aryl formulation.

REFERENCES

1. a) M. Balasubramanian and A. D'Souza, Tetrahedron, 24, 5399 (1968); b) Ibid., 25, 2973 (1969).
2. The preparation, physical properties and complete NMR data of these compounds are found in the Ph.D. dissertation of M.J.G., and will be reported in a later paper. The NMR spectra were recorded on Varian A-60 and HA-100 spectrometers.
3. R. E. Ireland, P. S. Grand, R. E. Dickerson, J. Bordner, and D. R. Rydjeski, J. Org. Chem., 35, 570 (1970).
4. For an excellent review see P. Laszlo, "Progress in Nuclear Magnetic Resonance Spectroscopy", Vol. 3, pp 231-402, Pergamon Press, New York, 1967.
5. M. Fétizon, J. Goré, P. Laszlo, and B. Waegell, J. Org. Chem., 31, 4047 (1966).
6. See following paper for preparation and proton NMR studies.