Predominance of the Axial Conformation of 4-Methoxycyclohexanone

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Summary [1]H N.m.r. studies at 100 MHz show that for 4-methoxycyclohexanone in benzene solution at 31°, the axial:equatorial population ratio is 3:1; the chair conformation in which the methoxy-group is axial predominates contrary to the conclusion previously deduced from dipole moment studies.

Mateos *et al.*[1] recently reported determination of the dipole moment of 4-methoxycyclohexanone (1) in benzene solution at 25°. Using cyclohexanone and methoxycyclohexane as model compounds, their analysis of the data for 4-methoxy-cyclohexanone (1) gave an axial:equatorial ratio (1a) : (1e) of 36:64.

This ratio[1] was not consistent with our expectations based upon previous n.m.r. studies of 4-hydroxycyclo-hexanone (2).[2] For (2) the axial:equatorial population ratio (2a) : (2e) in benzene solution has been reported[3] to be 56:44. The predominance of the axial conformer (2a) was attributed to transannular electrostatic interactions involving the carbonyl- and hydroxy-groups stabilizing (2a) relative to (2e).[3] Since the hydroxy-group and the methoxy-group should exert comparable electrostatic effects in (1) and (2), and since the 'A-value' of methoxy-is smaller than that of hydroxy-,[4] one might expect 4-methoxycyclohexanone (1) to have a larger axial population than 4-hydroxycyclohexanone (2). Therefore, we prepared

[2,2,6,6-[2]H$_4$]-4-methoxycyclohexanone [[2]H$_4$]-(1) and determined its C-4 [1]H n.m.r. band width.[5] The n.m.r. results (Table) contradict the conclusions deduced from dipole moment measurements by Mateos *et al.*[1] The contradiction is particularly striking since according to the n.m.r. results, of all 4-substituted cyclohexanones which have been reported (Table), [[2]H$_4$]-(1) has the *greatest* axial population.
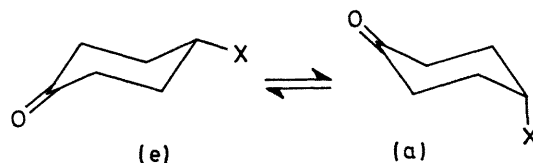
A similar contradiction exists for 4-chlorocyclohexanone (4). The axial:equatorial population ratio deduced from dipole moments by Mateos *et al.*, 32:68 (C$_6$H$_6$)[6] may be compared with n.m.r. data for (4) and [[2]H$_4$]-(4) (Table) which show predominance of the axial conformation (4a). Premuzic and Reeves[7] concluded that the n.m.r. spectrum of [[2]H$_4$]-(4) could be interpreted in terms of a *ca.* 60:40 mixture of (4a) : (4e). Recently, Loustalot *et al.*[8] repeated both the dipole moment[6] and the n.m.r. studies[7,9-11] and confirmed that the n.m.r. results contradict the dipole moment results for 4-chlorocyclohexanone (4). Furthermore, they showed that an almost identical contradiction

exists for 4-bromocyclohexanone (5).[8] They state that it is difficult to doubt the n.m.r. results and they discuss possible sources of error in the dipole moment method as applied to that the reported conformational populations deduced from dipole moments for 4-methoxycyclohexanone (1),[1] as well as for (4)[6,8] and (5)[8] are erroneous.‡

C-4 ^{1}H n.m.r. band width data for 4-substituted cyclohexanones (1)—(6) at 30 ± 3° showing predominance of the axial conformation (a)

Compound[a]	X	Solvent	W/Hz	% (a)	$\Delta G°$ kcal/mol	Ref.
[^{2}H$_4$]-(1)	MeO	C$_6$H$_6$	16·5 ± 0·1	73	−0·6	b,c
		CCl$_4$	17·0 ± 0·1	70	−0·5	b,c
		(CD$_3$)$_2$CO	17·5 ± 0·1	68	−0·5	b,c
[^{2}H$_4$]-(2)	HO	C$_6$H$_6$	19·7 ± 0·2	56	−0·15	3,9[d]
		CDCl$_3$	20·0	54	−0·1	2[d]
[^{2}H$_4$-](3)	BzO	C$_6$H$_6$	19·2 ± 0·2	60	−0·23	9
		(CD$_3$)$_2$CO	19·3 ± 0·1	59	−0·22	b,e
		PhMe	19·6 ± 0·1	59	−0·18	b,e
[^{2}H$_4$]-(4)	Cl	CCl$_4$	18·05 ± 0·05	67	−0·42	10
		FCCl$_3$	18·45 ± 0·02	65	−0·38	b,f
		CCl$_4$	19·4	60	−0·2	7
		(CD$_3$)$_2$CO	20·21 ± 0·03	57	−0·17	b,f
(4)	Cl	CCl$_4$	17·5	69	−0·5	11
		C$_6$H$_6$	19·0 ± 0·2	60	−0·2	9
		C$_6$H$_6$	19·7 ± 0·2	56	−0·2	8[d]
(5)	Br	C$_6$H$_6$	20 ± 0·2	54	−0·1	8[d]
(6)	I	C$_6$H$_6$	21 ± 0·5	55	−0·1	8[d]

[a] Deuterium substitution [2,2,6,6-^{2}H$_4$] should not affect the conformational equilibrium significantly.[10]

[b] This work; spectra were recorded at 31° with an 100 MHz Varian HA-100 n.m.r. spectrometer locked on internal tetramethylsilane. Model compounds were used to determine approximate values of W_e and W_a, the band widths of the individual chair conformations.[5]

[c] Since model compounds containing the methoxy-group were not available, benzoyloxy-model compounds (footnote e) were used to calculate % (a) from W. When hydroxy-model compounds[3] are used instead, calculated values of % (a) are slightly larger: C$_6$H$_6$, 74; CCl$_4$, 72; (CD$_3$)$_2$CO, 69. Methoxy-, hydroxy-, and benzoyloxy- model compounds would all be expected to give comparable results.

[d] This reference also reports values in other solvents.

[e] Model compounds: 4-benzoyloxy-2,6-dimethylcyclohexanones, W_e, 11·1; W_a, 31·0 Hz.

[f] Model compounds: 4-chloro-2,6-dimethylcyclohexanones,[10] W_e, 11·6; W_a, 31·4 Hz.

(4) and (5). The n.m.r. band width method of conformational analysis as applied to compounds (1)—(6) (Table) appears to be self-consistent and reliable.† We conclude

† The n.m.r. result for 4-hydroxycyclohexanone [56% of (2a) in benzene solution] and the chemical equilibration result for the related 2-t-butyl-4-hydroxycyclohexanones (53% axial isomer at equilibrium in benzene solution) are in excellent agreement.[12]

‡ Havinga and his co-workers have reported studies on tetrahydropyrans and other compounds for which conformational populations deduced from dipole moments and those determined by n.m.r. show good agreement.[13] If their approach were applied to compounds (1)—(6), i.e., use of closely related reference compounds, perhaps the agreement of the conformational populations deduced from dipole moments could be improved.

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