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CONFORMATIONAL EFFECTS IN COMPOUNDS WITH 6-MEMBERED RINGS—XI

STUDY OF A CONFORMATIONAL EQUILIBRIUM IN THE GAS PHASE AND IN SOLVENTS RANGING FROM NON-POLAR TO WATER: 4-METHOXYCYCLOHEXANONE

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Abstract—The conformation free energy difference ($\Delta G^\circ(1E \rightarrow 1A)$) for 4-methoxycyclohexanone (**1**) has been determined in 34 solvents, ranging in polarity from tetramethylsilile to trifluoracetic acid, using weighted average vicinal coupling constants and *two* pairs of anancomeric model compounds (**2–5**). The free difference in the gas phase has been estimated from the equilibrium in silicone oil (DC 550), itself derived by extrapolation from data for mixtures with hexamethyldisiloxane, together with the differential solvation energies from gas phase to silicone oil extrapolated from the solvation energies for **2–5** obtained from GLC retention data.

Calculations based on Abraham's reaction field theory of solvent effects on conformational equilibria correlate quite well with the general trend in $\Delta G^\circ(1E \rightarrow 1A)$ in "normal" solvents but fail to account even qualitatively for the difference in $\Delta G^\circ(1E \rightarrow 1A)$ between the gas phase and non-polar solvents.

Conformational equilibria in molecules with two or more polar substituents are in general sensitive to the effects of solvation. Many such molecules, notably di- and polyhalides and halo-ketones and -aldehydes (acyclic and 6-membered ring cyclic) have been studied, sometimes in a considerable range of solvents, but non-halogenated compounds have been studied much less widely. The very limited range of methods, mostly with rather low precision, for directly studying conformational equilibria in the gas phase and limitations of solubility, however, raise considerable difficulties in any attempt to investigate a conformational equilibrium in the gas phase *and* in a wide range of solvents (non-polar to water) and we do not know of any compound with two (or more polar) substituents that has been studied in this way. For this reason we have carried out a broad study of solvent effect on the equilibrium in 4-methoxycyclohexanone (**1**) (Fig. 1), using averaged coupling constants in **1** to measure equilibria in solution and gas-liquid chromatographic retention data for **2–5**, models for the conformers of **1**, to determine differences in solvation from the gas phase to one solvent for **1E** and **1A**.

The best, but not the most general method for the study of conformational equilibria is the use of NMR integration at (low) temperatures at which the equilibrium is slow on the NMR timescale[2] but this method is severely restricted in a number of respects, above all by the need for solvents with low freezing points and viscosities and for relatively high barriers to the interconversion of the conformers. A more widely applicable method is to relate the value of some property of a mobile system such as the coupling constant J for a specified pair of nuclei to the values J_e and J_a for the individual conformers:[3]

$$J = n_eJ_e + n_aJ_a \qquad (1)$$

where n_e and n_a are mole fractions and J_e and J_a are estimated by either freezing out the equilibrium at low temperatures,[4] which is not possible for 1, or curve fitting methods if J can be measured precisely over a wide temperature range[5] (this is subject to many sources of systematic errors resulting from assumptions such as $dJ_i/dT = 0$), or from model compounds,[6] as in this work.

Errors resulting from the use of eqn (1) are minimised if $K \sim 1$, and if J_e and J_a may be determined by extrapolation from *two* pairs of model compounds, e.g. by using 2–5 as anancomeric models for 1. The possible importance of flexible forms of 1 will be considered briefly later. We have used $S = (J_{AX} + J_{BX})$, which may be obtained directly from the separation of the outermost lines of the X multiplet of an AA'BB'X[7] spin system (see below), for **1** and anancomeric model compounds to derive values of S_E (for **1E**) and S_A (for **1A**) in order to obtain $K = n_A/n_E = (S_E - S)/(S - S_A)$.

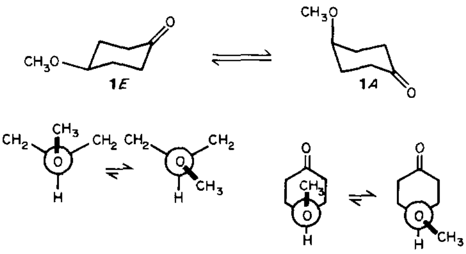


Fig. 1. Conformational equilibrium in 4-methoxycyclohexanone and rotameric equilibria for each ring conformer (only one enantiomeric form of each gauche rotamer is shown).

Our reasons for choosing 4-methoxycyclohexanone were as follows:

(a) The conformational equilibrium in **1** is known to be sensitive to solvation[8a] (a recent contrary conclusion[8b] is based on experiments with very low precision);

(b) $K \simeq 1$, presumably because dipole–dipole interactions oppose steric effects, and is therefore easy to measure with reasonable precision;

(c) Because $K \simeq 1$ for **1** relatively small alkyl groups such as methyl may be used in the anancomeric model compounds (with small corrections for conformational inhomogeneity), required both to provide estimates of coupling constants and for GLC measurements, thereby minimising distortion of the ring;

(d) **1** and the model compounds **2**–**5** may be readily deuteriated at the C-2 and C-6 positions, thereby reducing the absorption of the C-4 proton to the X part of an AA'BB'X spin system.

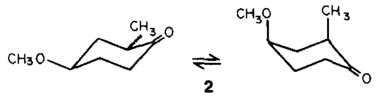
(e) **1**–**5** are soluble in a wide range of solvents to allow NMR spectra to be obtained with at most short accumulation times when using pulse Fourier-transform mode in the most unfavourable instances (continuous wave operation was possible for most solvents);

(f) **2**–**5** are sufficiently volatile for GLC measurements to be made over a considerable temperature range and for the use of two pairs of model compounds makes it possible to allow for the differential effect of a methyl group on the solvation of the conformers **1E** and **1A** to be detected and allowed for.

4-Methoxycyclohexanone has the disadvantages, shared by most non-halogenated compounds with polar substitutuents attached to rings by single bonds, that the equilibria between different rotameric arrangements of the methoxy-group are only qualitatively known and the torsion angles for some of these rotameric arrangements are uncertain so that it is difficult to estimate the electric dipole and quadrupole moments of the conformers **1E** and **1A** (see Results and Discussion).

The ketones **1**–**5** were readily prepared from 4-methoxyphenol (Scheme 1) and after deuteration the pairs of diastereomers, **2** and **3**, and **4** and **5**, were separated by chromatography. The third possible diasteromer, **10**, of 2,6-dimethyl-4-methoxycyclohexanone was neither isolated nor positively identified in mixtures of **4** and **5**.

The ketones **4** and **5** are adequately anancomeric so far as chair-chair equilibria are concerned so that no



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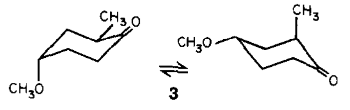
$\Delta G^\circ = \text{(i)} + \text{(ii)} + \text{(iii)} - \text{(iv)} - \text{(v)} = +10.6\ \text{kJ mol}^{-1}$		(CCl_4)
	11.4	(CH_2Cl_2)
	11.8	(Me_2CO)



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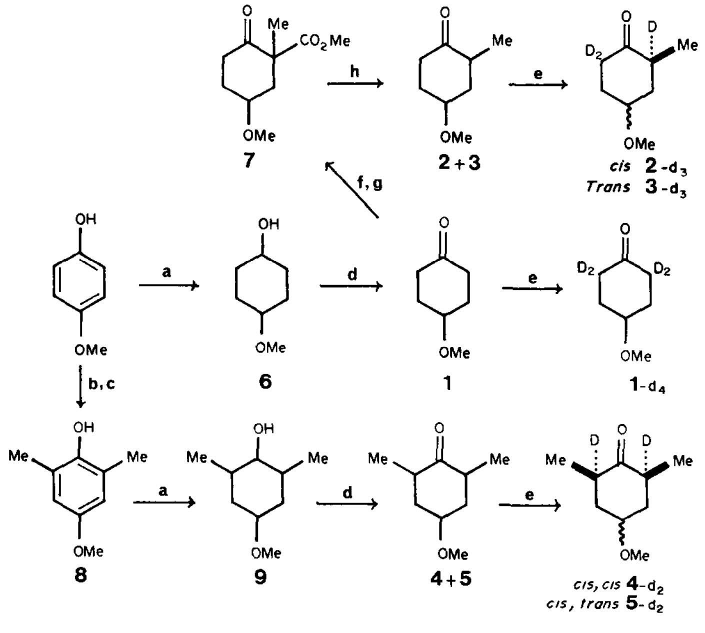
$\Delta G^\circ = \text{(i)} - \text{(ii)}$	$= +10.1$	(CCl_4)
	9.4	(CH_2Cl_2)
	9.1	(Me_2CO)

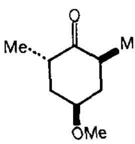
Interactions:

(i) $\Delta G^\circ_{e\to a}(\mathbf{11})^{10,11}$	+ 7.9	
(ii) $\Delta G^\circ_{e\to a}(\mathbf{1})$	2.2	(CCl_4)
	1.4	(CH_2Cl_2)
	1.0	(Me_2CO)
(iii) Interaction between Me and MeO (≡ **15**) taken as equal to corresponding Me—OH interaction in **12**	10.0[11]	
(iv) Gauche Me—CH_2 interaction ≃ $1/2\ \Delta G^\circ_{e\to a}(\mathbf{13})^{12}$	3.7	
(v) Gauche CH—OMe interaction ≃ $1/2\ \Delta G^\circ_{e\to a}$ $(\mathbf{14})^{12}$	1.2	

Scheme 2. Estimation of the free energy differences for the conformational equilibria in the ketones **2** and **3** needed to correct the observed values of S to give values of S_e and S_a.



Scheme 1. Synthesis of 1 and model compounds; a: N_2–Ni; b: $CH_2O + Me_2NH$: c: H_2–Pd/C; d: $CrO_3 + H_2SO_4/Me_2CO$; e: $D_2O + POCl_3$; f: NaH + Me_2CO; g: NaH + MeI; h: KOH/MeOH.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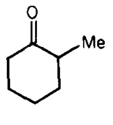
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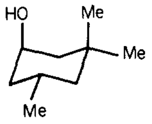
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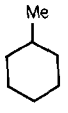
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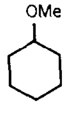
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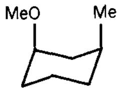
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correction for the alternative chair conformers are needed. For the ketones **2** and **3**, however, it is necessary *either* to make small corrections (Scheme 2) for the minor chair conformers, which requires an estimate of the conformational equilibrium in **1** in the various solvents, *or* to determine the temperature dependence of S for **2–5**. The corrections based on Scheme 2 are small (Table 1), however, and uncertainties in the other parameters used were far more important than the uncertainty about K for **1** even before carrying out an iterative correction. Compounds **2–5** were studied over a range of temperature (limited by the deterioration of resolution at low temperatures) in two solvents (Table 2). As expected [13] the solvent dependence of S for **4** and **5** is negligible (Table 1). The temperature dependence of S for **2** and **3** arises from two causes, the increasingly biased equilibria at low temperatures and the inherent temperature dependence of coupling constants in individual conformers. The constancy of S for **4** and **5** indicates that the latter is negligible for our purposes. After making corrections for the chair–chair equilibria as in Scheme 2, however, the temperature dependence of S for **2** and **3** are still significant compared with **4** and **5** and it seems likely that the calculated corrections are too small. The calculated corrections for **2** are clearly of uncertain accuracy (see Scheme 2) but are relatively simple for **3** for chair–chair equilibria. A likely source of the discrepancy is the neglect of twist conformers so that the limiting values of S at low temperatures (with very small corrections) for **2** and **3** are probably more reliable than the corrected values at 25°. Accordingly we have taken the average values of S at 25° from Table 1 for **4** (S = 15.09 Hz) and **5** (S = 5.45 Hz) and at low temperatures from Table 2 for **2** (S = 14.96 Hz) and **3** (S = 5.35 Hz) in order to derive S = 14.83 Hz for **1E** and S_A = 5.25 Hz for **1A** by simple extrapolation in order to calculate K for **1** in various solvents (Table 3).

The measurement of S for a wide range of solvents requires few comments. The solution in octafluorocyclobutane was saturated and the volatility of the solvent did not allow an accurate estimate of the concentration of **1**, which was estimated from the intensity of the spectrum to be about 0.1 M. Solutions of **1** in solvents of very low polarity have dielectric constants significantly different from the pure solvents but the effect on the equilibrium appears not to be important at concentrations $\ngtr$ 0.5 M and 0.5 M was adopted as a standard for most compounds.

For the measurement of gas-liquid equilibria by GLC it is necessary to establish that surface adsorption is not significant not only by eliminating tailing but also by

Table 1. Sums of coupling constants[a] (S) at 25° for **2–5**[b] (0.1 M) with corrections for conformational inhomogeneity[c]

Solvent[d]	Compound	Minor conformer[c]	S(Hz) obs.	S(Hz) corr.[e]
CCl_4[f]	2	1.5%	14.44	14.58
CH_2Cl_2		1.0	14.60	14.70
$(CH_3)_2CO$		1.0	14.54	14.63
CCl_4[f]	3	1.5	5.70	5.55
CH_2Cl_2		2.0	5.79	5.60
$(CH_3)_2CO$		2.5	5.85	5.61
CCl_4[f]	4	~0	15.15	
C_6H_6			15.04	
CH_2Cl_2			15.17	
$(CH_3)_2CO$			15.02	
CCl_4[f]	5	~0	5.55	
C_6H_6			5.40	
CH_2Cl_2			5.44	
$(CH_3)_2CO$			5.42	

[a] $S = J_{AX} + J_{BX}$ derived from first order analysis of AA'BB'X spectra; errors $\ngtr$ 0.05 Hz.
[b] Deuteriated at C-2 and C-6.
[c] Based on free energy differences derived in Scheme 2.
[d] Solvents containing hydrogen were > 99 atom% ^2H
[e] Iterative (see text).
[f] Run at 35° (Perkin Elmer R32) at 0.5 M.

Table 2. Temperature variation of sums of coupling constants[a] (S) for **2–5**[b] with corrections for conformational inhomogeneity[c]

Solvent[d]	Compound	Temp. (°C)	Minor conformer[c]	S(Hz) obs.	S(Hz) corr.[e]
CH_2Cl_2	2	+23	1.0%	14.60	14.70
		-20	0.4	14.88	14.91
		-70	0.1	14.98	14.99
	3	+20	2.0	5.79	5.60
		-30	1.0	5.63	5.53
		-70[f]	0.3	5.38	5.35
	4	+20	0	15.16	
		-30		15.15	
		-70		15.15	
	5	+25	0	5.44	
		-50		5.34	
		-70[f]		5.39	
$(CH_3)_2CO$	2	+25	0.8	14.54	14.63
		+ 2	0.5	14.63	14.69
		-60	0.1	14.92	14.93
	3	+21	2.4	5.85	5.62
		-30	1.1	5.56	5.46
		-60[f]	0.6	5.42	5.36
	4	+20	0	15.02	
		-30		15.02	
		-60		15.15	
	5	+21	0	5.42	
		-20		5.40	
		-60[f]		5.38	

[a] $S = J_{AX} + J_{BX}$ derived from first order analysis of AA'BB'X spectra; errors $\ngtr$ 0.05 Hz except at the lowest temperatures.
[b] Deuteriated at C-2 and C-6.
[c] Based on free energy differences, assumed to be independent of temperature, derived in Scheme 2.
[d] > 99 atom% ^2H.
[e] Iterative (see text).
[f] Decreased resolution at − 60 or − 70° increased the uncertainties in measurements of the narrow multiplets of **3** and **5** to ~ 0.1 Hz.

Table 3. Conformational free energy differences (ΔG°_{308} (**1E** → **1A**)) for 4-methoxycyclohexanone (**1**)[a] as a function of solvent using observed values of S[b] with $S_E = 14.83$ and $S_A = 5.25$ Hz (see text).

Solvent	Conc. (M)	S (Hz)	ϵ	ΔG°_{308} (kJ mol^{-1})
tetramethylsilane	0.5	7.82[c]		-2.28[c]
cyclohexane	0.5	8.09	2.023	2.21
trifluorochloromethane	0.5	8.13	2.28	2.16
cyclohexene	0.5	8.14	2.22	2.15
hexamethyldisiloxane	1.0 0.5 0.25	8.19 8.00 7.99	2.17	2.09 2.33 2.34
tetrachloroethylene	0.5	8.23	2.30	2.04
carbon tetrachloride	1.0 0.25	8.23 8.18	2.24	2.04 2.10
trichloroethylene	0.5	8.28	3.42	1.97
octafluorocyclobutane	satd.	8.28		1.97
cyclohexa-1,3-diene	0.5	8.30	2.35	1.95
1,1,1-trichloroethane	0.5	8.30	7.53	1.95
t-butyl chloride	0.5	8.42	9.7	1.80
t-butyl bromide	0.5	8.43	10.3	1.79
toluene[d]	0.5	8.50	2.38	1.71
dimethyl sulphide	0.5	8.55	6.2	1.65
chloroform[d]	0.5 0.1	8.57 8.54	4.64	1.62 1.66
benzene[d]	1.0 0.5 0.1	8.58 8.51 8.45	2.275	1.61 1.70 1.77
hexafluorobenzene	0.5	8.63		1.55
thiophene	0.5	8.73	2.71	1.44
furan	0.5	8.75	2.94	1.41
quinoline	0.5	8.75	9.00	1.41
dibromomethane	0.5	8.77	6.9	1.39
dichloromethane	0.5	8.79	8.93	1.37
pyridine	0.5	8.83	12.3	1.32
isoquinoline	0.5	8.84	10.7	1.31
methyl alcohol[d]	0.5	8.99	32.6	1.14
acetone[d]	0.5	9.08	20.7	1.04
acetonitrile[d]	0.5	9.35	37.5	0.74
acetic acid[d]	0.5	9.36	6.17	0.73
dimethylsulphoxide[d]	0.5	9.52	46.68	0.56
formamide	0.5	9.53	111.0	0.55
pyrrole	0.5	9.64	8.13	0.43
water[d]	0.5	10.09	80.0	+0.05
trifluoroacetic acid[d]	0.5	10.27	8.55	0.25

[a] Deuteriated at C-2 and C-6.

[b] $S = J_{AX} + J_{BX}$ derived from first order analysis of AA'BB'X spectra; errors $\ngtr 0.05$ Hz.

[c] Run at 273 K.

[d] > 99 atom% ^{2}H.

Table 4. GLC retention data for **2**–**5** on silicone oil (DC 550; 3% w/w) on Chromosorb G

Tmep. (°C)	Adjusted retention times (s)[a]				$\delta\Delta G^\circ$ (kJ mol^{-1})[b]	
	2	**3**	**4**	**6**	(**3**–**2**)	(**5**–**4**)
+50	2758	2982	3700	4211	-0.209	-0.347
70	943	1006	1255	1418	0.188	0.348
90	415[c]	440[c]	490	545	0.180	0.320
110	205[c]	216[c]	-	-	0.170	-
130	100[c]	104[c]	124[c]	135[c]	0.131[d]	0.294[d]
(35	Extrapolated values:				-0.22±0.02	-0.36±0.02
					-0.08±0.03 for **1E**-**1A**)	

[a] Means of $\nless 3$ measurements at each temperature.

[b] $\delta\Delta G^\circ = -RT \ln r$, where r is the ratio of adjusted retention times for the specified pair of diastereomer: a negative sign implies that the first member of each pair is the *more* strongly solvated; uncertainties $\ngtr \pm 0.015$ kJ mol^{-1} at $\ngtr 90°$.

[c] Determined relative to 4-t-butylcyclohexanone as a common standard rather than by direct comparison.

[d] These values were subject to rather large experimental errors and were given low weightings.

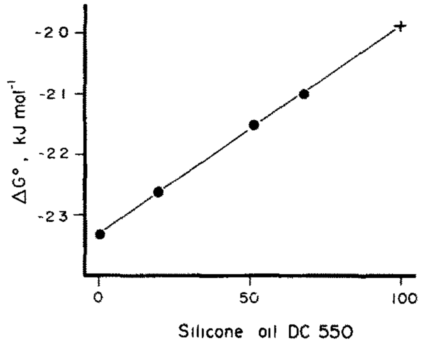

Fig. 2. Linear extrapolation of $\Delta G^\circ_{e \to a}$ (**1**) for mixtures of $(Me_3Si)_2O$ and silicone oil DC550 to 100% silicone oil DC550 (●, observed; +, extrapolated).

varying the ratio of liquid stationary phase to solid support.[14] This was done for a variety of pairs of diasteromeric compounds varying from non-polar to hydroxylic[15] and it was found that 3% (w/w) or more was suitable under our conditions and data was obtained for **2**–**5** for 50 to 130° using 3% (w/w) silicone oil in order to allow extrapolation to the temperature used for NMR. Once more an extrapolation using two pairs of models was clearly better than using a single pair of models and ignoring the possible effect of the biasing substituents. Silicone oil suitable for GLC, however, is far too viscous for NMR measurements of coupling constants and the equilibrium for **1** in silicone oil was determined by extrapolation from a series of mixtures of silicone oil and hexamethyldisoloxane, the most similar solvent of low viscosity available to us (Fig. 2). From this extrapolated value together with the differential solvation effect of silicone oil derived from the GLC measurements on the model compounds we obtained an estimate of the gas phase equilibrium for **1**. We believe that this is the first time that conformational equilibria in solution have been related to the equilibrium in the gas phase in this simple and relatively precise way.

EXPERIMENTAL

NMR spectra were measured using Perkin–Elmer R32 and Bruker WH 90 (pulse Fourier transform) spectrometers (90 MHz). Solvents were commercial samples purified by distillation apart from deuteriated solvents which were not purified. The R32 spectrometer used Me_4Si as lock (except for $(Me_3Si)_2O$ and its mixtures with silicon oil when the solvent absorption was used) and several sweeps in both directions were measured at the widest possible sweep width (9 mm Hz^{-1}) for each sample, with calibration provided by a frequency counter. The WH 90 spectrometer was locked to a solvent resonance (^{2}H). Using a sweep width of 400 Hz the FID was accumulated into 4K memory addresses, 4K zeros were added[16] and no exponential weighting was applied before Fourier transform, giving a digital resolution of 0.097 Hz with plotting at 12 mm Hz^{-1}. The variable temperature systems of both spectrometers were checked with a methanol thermometer.[17]

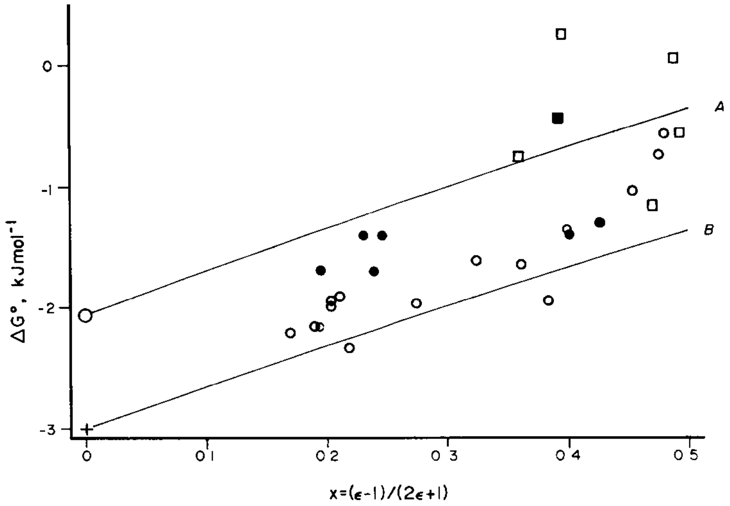

Fig. 3. $\Delta G^\circ_{e\to a}$(1) as a function of solvent polarity x = (ε − 1)(2ε + 1); *A*, calculated solvent effect using experimental value (○) for vapour phase; *B*, calculated solvent effect using experimental values for solvents of low polarity, with extrapolated value (+) for vapor phase (○, "normal" solvents; ●, aromatic solvents; □, hydrogen bonding solvents; ■, aromatic hydrogen bonding solvent).

GLC measurements were made with Pye Series 104 chromatographs fitted with mass flow controllers. The retention times of the ketones 2–5 were measured with a glass column 5 ft × 1/8 in. filled with Chromosorb G coated with 3% silicone oil (DC 550), with the "air peak" determined by extrapolation from the retention times of the first five n-alkanes. The retention times of each pair of model compounds were so similar that at the higher temperatures used (110–130° for 4 and 5; 90–130° for 2 and 3) it was not possible to measure them simultaneously and 4-t-butylcyclohexanone was used as a reference compound.

Preparation of ketones **1–5**

4-*Methoxycyclohexanone*. 4-Methoxyphenol (1 mole) was reduced over W4 Raney Ni[18] with H_2 to **6**, b.p. 92–100°/11 mm, n_D^{20} = 1.4681 (lit.[19] b.p. 90–99°/11 mm, n_D^{20} = 1.4650), which was oxidised in acetone with Jones chromic acid[20] to give **1**, b.p. 80°/11 mm, n_D^{20} = 1.4568 (lit.[21] b.p. 82°/11 mm, n_D^{20} = 1.4560[22]). **1** was deuteriated by treatment (20°, 3 day) with D_2O (13 g) in which had been dissolved $POCl_3$ (12 mmole). The soln was treated with $KHCO_3$ (10 g) and **1** was extracted into CH_2Cl_2 (4 × 10 ml), the extracts were dried ($MgSO_4$) and concentrated. The deuteriation was repeated and the 2,2,6,6-d_4-**1** was distilled, b.p. 87–90°/17 mm.

cis- *and* trans-2*Methyl*-4-*methoxycyclohexanone* (**2**, **3**). **1** (50 g) was added slowly to a stirred mixture of NaH (20 g) and dry Me_2CO_3 (400 ml) with a few drops of MeOH and the stirred mixture was boiled under reflux (1 day), treated with MeI (225 g), and boiled (1 day). The product was worked up with H_2O and Et_2O and distilled giving nearly pure **7**, b.p. 124–125°/12 mm, n_D^{20} = 1.4612 (Found: C, 60.58; H, 8.30. Calc. for $C_{10}H_{16}O_4$; C, 59.98; H, 8.05%), which was hydrolysed (5 hr) with boiling KOH (20 g) in MeOH (200 ml) to give a mixture of **2** and **3** (16 g), b.p. 95–101°/15 mm, n_D^{20} = 1.4550 (lit.[23] b.p. 92–97°/15 mm). This mixture was deuteriated by the method used for **1** giving a mixture of 2,6,6-d_3-**2** and -**3**, b.p. 93–99°/16 mm, which was separated by chromatography over silica gel using pentane-Et_2O (4:1), from which the pure stereoisomers were recovered by evaporation. The samples so obtained were apparently pure and stereochemically homogenous as judged from ^{1}H NMR spectra in 3 solvents (Table 1).

2,6 - *Dimethyl* - 4 - *methoxycyclohexanone* (**4**, **5**). 4 - Methoxyphenol (1 mole) reacted (1 hr, 100°) with CH_2O (40% in H_2O, 300 ml) and Me_2NH (25% in H_2O, 500 ml) to give 2,6 - di(dimethylaminomethyl) - 4 - methoxyphenol (166 g), b.p. 170°/10 mm, n_D^{20} 1.5229 (lit.[24] b.p. 143–152°/3 mm). The latter in AcOH (400 ml) was reduced over 5% Pd on charaoal (10 g) with H_2 at 100°/70 atm giving **8** (50 g), b.p. 148°/30 mm, m.p. 77° after crystallisation from pentane followed by vacuum sublimation at 40°/25 mm (lit.[24] m.p. 77°). This phenol was reduced[24] to **9**, b.p. 118–140° (lit.[24] 119–124°/24 mm), which was oxidised using Jones' chromic acid giving a mixture of **4** and **5**, b.p. 90–98°/15 mm, n_D^{20} 1,4570 (lit.[24] b.p. 106–111°/24 mm, n_D^{20} 1.4520). This mixture was deuteriated by the method used for **1** giving a mixture of 2,6-d_2-**4** and -**5** which was separated in the same way as the mixture of **2** and **3**. The samples so obtained were apparently pure and stereochemically homogeneous as judged from ^{1}H NMR spectra in 4 solvents (Table 1).

RESULTS AND DISCUSSION

The conformational equilibrium in **1** shows a marked sensitivity to solvent (Table 3 and Fig. 3), with the axial conformer **1A** being the more stable in all but the most polar hydroxylic solvents. Our results are reasonably consistent with the earlier measurements by Stolow and Giants using three solvents (the results for C_6H_6 and CCl_4 in the published Table[8] should be interchanged[25]) and indicate that **1E** is more polar than **1A**, a relationship that is not obvious, e.g. from any simple inspection of models. In order to estimate what solvent effects would be expected from "normal" solvents we have attempted to apply Abraham's reaction field theory[1] to **1**. For this purpose it is necessary to calculate the electric dipole and quadrupole moments of the two conformers. In previous applications[1] axially symmetric groups such as halogen have been studied almost exclusively and in the present instance there are several sources of uncertainty in the calculation. We have assumed that (a) the methyl "inside" rotamer of **1A**, can be neglected completely, (b) the two methyl-methylene interactions in the s-*trans* rotamer of **1E**, by analogy with the large *trans-gauche* energy difference for methyl ethyl ether (~6 kJ mol^{-1}),[26] make the s-*trans* rotamer, in which the Me group cannot rotate away from the methylene groups, much less stable than the two *gauche* rotamers, (c) the electric moments of **1A** and **1E** can be approximated adequately by assuming ϕ (H–C–O–Me) = 0° rather than attempting to estimate the *gauche* torsion angles, which must be considerably less than 60° if it is correct that CH_2–C–O–Me *gauche* interactions are large, (d) the group dipole moments, derived from cyclohexanone[27] and dimethyl ether,[28] act along the C=O bond and the C–O–Me bisector respectively, (e) the centre of the molecule, which is not easily defined for these relatively unsymmetrical molecules, could be taken as the mid-point of the line joining the two point dipoles, located halfway along the C=O and at the ether oxygen respectively, and (f) the geometry of the conformers could be calculated adequately from standard bond lengths and angles,[29] which seems probable in the absence of serious steric strains. The values of Abraham's solvation parameter h and k are $+8.53$ and $+1.81\,\mathrm{kJ\,mol^{-1}}$. Clearly the approximations involved make the present application of Abraham's theory very tentative but the calculated slope of ΔE^s against $x = (\epsilon - 1)/(2\epsilon + 1)$ agrees quite well with the observed differences for solvents of low to moderate polarity (excluding the aromatic solvents). On the other hand the change in the equilibrium between the gas phase and solvents of low polarity is not consistent with the theory because **1A** is most favoured in solvents of low polarity and there is no monotonic change in equilibrium with increase in x. Clearly there is a factor, relatively favourable to **1A** in solvents of low polarity, that is not included in simple measures of solvents polarity such as dielectric constant. In work concerned with the solvation of conformers with a single polar substituent we have found that whereas the equilibrium in **14** is little affected by change of solvent there is a marked difference in the equilibrium in the gas phase and in solvents of low polarity, with **14E** relatively favoured by solvation,[15] exactly the opposity of the result for **1** for such solvents. It appears, therefore, that if **14** can be accepted as a normal solute the anomaly in **1** is even greater than at first appears. At present we have no explanation for this difference but we are studying other compounds with a single polar substituent for comparison with **14**.

The general effects of different classes of solvents follow the usual pattern. Benzene and some other aromatic compounds without hindering alkyl groups (furan, thiophene) are much more effective than would be expected from their dielectric constants (Fig. 3) although pyridine and quinoline show no abnormality. It is interesting to note, however, that in the series cyclohexane, -ene, -1,3-diene, benzene, the effects of successive double bonds are *not* additive and benzene indeed appears to be about as effective as might be expected by extrapolating from earlier members of the series. The well known "benzene effect",[1a] therefore, may properly be called a "polyene effect" and we hope to be able in the future to study polenes as solvents in conformational equilibria. Hydrogen bonding solvents are extremely effective but atoms with high polarisability (Table 3: compare CH_2Cl_2 and CH_2I_2, or Me_3CCl and Me_3CBr) do not lead to any anomalies.

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