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THE SOLVENT EFFECT ON THE CONFORMATIONAL EQUILIBRIA OF 4-SUBSTITUTED CYCLOHEXENES

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Conformational preferences have been measured for 4-X-cyclohexenes (X = Br, Cl, CHO, COOH) in a series of solvents with increasing polarity. The conformational equilibrium exhibits a very weak solvent dependence. ΔG varies at most by 0·25 kcal mol^{-1} (1 kcal = 4·184 kJ) shifting from a non-polar mixture (CS_2–$CDCl_3$) to highly polar $(CD_3)_2SO$. The reaction field theory was used to calculate the variation of ΔG with solvent polarity. The calculated solvent shifts $\delta\Delta G$ are small and in agreement with the values determined experimentally.

INTRODUCTION

There has been no systematic study on the conformational effects of the double bond in cyclohexene derivatives. The experimental data available for some 4-substituted cyclohexenes,[1–3] 3-substituted methylenecyclohexanes[4,5] and 4-substituted-6,7,8,9-tetrahydro-5*H*-benzocycloheptenes[6] suggest that steric interactions in these compounds are reduced compared with the corresponding substituted cyclohexanes. Still, it was found that the equatorial isomer is favoured over the axial isomer in non-polar solvents (CS_2, CF_2Cl_2).[5,7,8] This preference was claimed to be due to an electrostatic interaction between the double bond and the polar substituent,[5,7] and the noticeable increase in the axial conformation population in moderately polar solvents ($CHFCl_2$, CHF_2Cl) seems to support this conclusion. The relative decrease in ΔG_{a-e} of 0·33 and 0·32 kcal mol^{-1} (1 kcal = 4.184 kJ) ($\Delta G_{a-e} = G_a - G_e$, where a and e stand for axial and equatorial, respectively) were observed for 4-chlorocyclohexene (**2**) and 4-chloro-1,2-dimethylcyclohexene[1], respectively, on shifting from non-polar CF_2Cl_2 ($\varepsilon = 2.13$) to moderately polar CHF_2Cl ($\varepsilon = 6{\cdot}11$). A decrease in ΔG_{a-e} of 0·46 kcal mol^{-1} was observed for 4-chloro-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[6] (solvents: CS_2, $\varepsilon = 2{\cdot}6$, and $CHFCl_2$, $\varepsilon = 5{\cdot}34$), suggesting a further increase in the population of the axial conformation with increasing solvent polarity.

On the other hand, molecular mechanics calculations[9] led to the conclusion that electrostatic interactions do not play an important role in determining the conformational preference of the above-mentioned compounds. The solvent effect on conformational equilibria was also calculated to be small.[9]

In this paper, we report a ^{1}H NMR study of conformational equilibria of four 4-X-cyclohexenes (X = Br, Cl, CHO, COOH) in solvents of varying polarity, together with calculations based on the molecular mechanics method coupled with the reaction field theory.

RESULTS AND DISCUSSION

The conformational equilibria of 4-X-cyclohexenes (X = CHO, COOH) (3-cyclohexen-1-yls; for the sake of uniformity we use the numeration shown in Figure 1) have been studied previously by ^{1}H NMR in $CDCl_3$ solution[10].

The coupling constants J_{ax} and J_{bx} and ΔG values in $CDCl_3$ solution are available[10] and are presented in Tables 1 and 2, together with the corresponding values determined in this work. The first-order 600 MHz ^{1}H NMR spectra of the H^X pattern recorded in this work permitted direct analysis of the H^X signal and the determination of its coupling constants.

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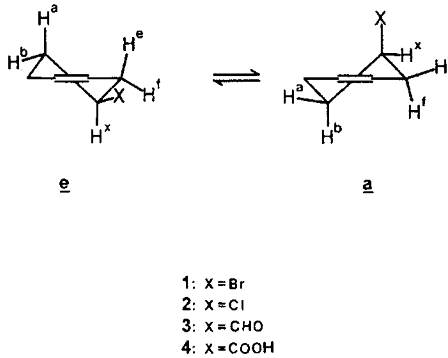

Figure 1. Conformational equilibrium of 4-X-cyclohexenes

The coupling constants and signal widths of individual conformers were calculated using the empirical equation proposed by Haasnoot *et al.*[12]

The procedure used for the determination of ΔG values will be exemplified on the H^X portion of the ^1H NMR spectrum of 4-formylcyclohexene (**3**) (3-cyclohexencarbaldehyde) in acetone (Figure 1; X = CHO), shown in Figure 2.

The conformer populations (n_a, n_e) were determined from coupling constants or line widths using the following equations:

$$n_e = (J - J_a)/(J_e - J_a) \qquad (1)$$

$$n_e = (W - W_a)/(W_e - W_a) \qquad (2)$$

We used the J_{ax}. (Figure 1) coupling constant in equation (1) for the following reasons: (i) it has sufficiently different values in two conformations and (ii) the data set, used by Haasnoot *et al.* in the empirical generalization of the Karplus equation for the calculation of coupling constants, is biased towards torsional angles of *ca* 60° and 180°. This makes the J_{xe} and J_{xf} calculated constants less reliable for the precise determination of n_e and n_a values. The determined n_e values for compound **3** are 0·70 [J_{xa} based, equation (1)] and 0·77 [W based, equation (2)] in $CDCl_3$ and 0·71 (J_{xa} based), and 0·76 (W based) in acetone. These and the corresponding ΔG_{a-e} values for compounds **1** to **4** in different solvents are presented in Table 2 and compared with the calculated values.

The calculations of ΔG for the conformational equilibrium in solution are based on the method described earlier.[9,15] The gas-phase free-energy difference of the two conformers, ΔG^v, is the sum of steric energy difference calculated with the MM2 program[11] and the charge interaction energy difference calculated with the IDME program.[15] Based on the reaction field theory, this program also calculates the solvation energy (*SE*), and yields the value of free energy difference ΔG^s_{a-e} in solution (Table 2):

$$\Delta G^s_{a-e} = \Delta G^v_{a-e} - SE.$$

There are three possible minimum energy rotamers around the C-4—C=O bond for each ring conformation (a, e) of 3, corresponding to the carbonyl oxygen eclipsing either H—C-4 or the ring carbons C-3 or C-5. In both ring conformations, the rotamers with the carbonyl oxygen eclipsing H—C-4 are of high energy (1·72 kcal mol^{-1} in the axial conformation and 1·54 kcal mol^{-1} in the equatorial conformation, relative to the energy minimum corresponding to the equatorial conformation rotamer with carbonyl oxygen eclipsing C-3), so do not contribute significantly to the conformational mixture. The other two rotamers are of about equal steric and electrostatic energies in the equatorial conformation of **3** (the relative energies are 0·00 and 0·19 kcal mol^{-1} for the rotamers with carbonyl oxygen eclipsing C-3 and C-5, respectively). In the axial conformation, the rotamer with the carbonyl oxygen eclipsing C-5 is more stable than that eclipsing C-3 by *ca* 0·6 kcal mol^{-1} owing to favourable electrostatic interactions. However, the two rotamers have very similar geometries. The geometries of the rotamers with carbonyl oxygen eclipsing C-3 were

Table 1. Dihedral angles, θ (°) and coupling constants, J (Hz), in 4-formylcyclohexene (**3**)

	Axial		Equatorial		$J_{exp.}$		
	θ^a	$J_{calc.}$	θ^a	$J_{calc.}$	$(CD_3)_2CO$	$CDCl_3$	
$J_{x,a}$	−55·5	3·9	−176·6	12·3	9·9	9·8	9·9[b]
$J_{x,b}$	61·6	3·0	65·7	2·4	3·3	3·3	2·7[b]
$J_{x,e}$	70·4	1·9	−168·1	11·9	7·0	7·3	
$J_{x,f}$	−47·4	5·2	−49·2	4·9	7·1	6·9	
$J_{x,CHO}$		1·0		1·0	1·0	1·0	
W^c		15·0		32·6	28·3	28·6	

[a] Dihedral angle between vicinal hydrogens, MM2 values.[11]
[b] Taken from Ref. 10.
[c] Signal width.

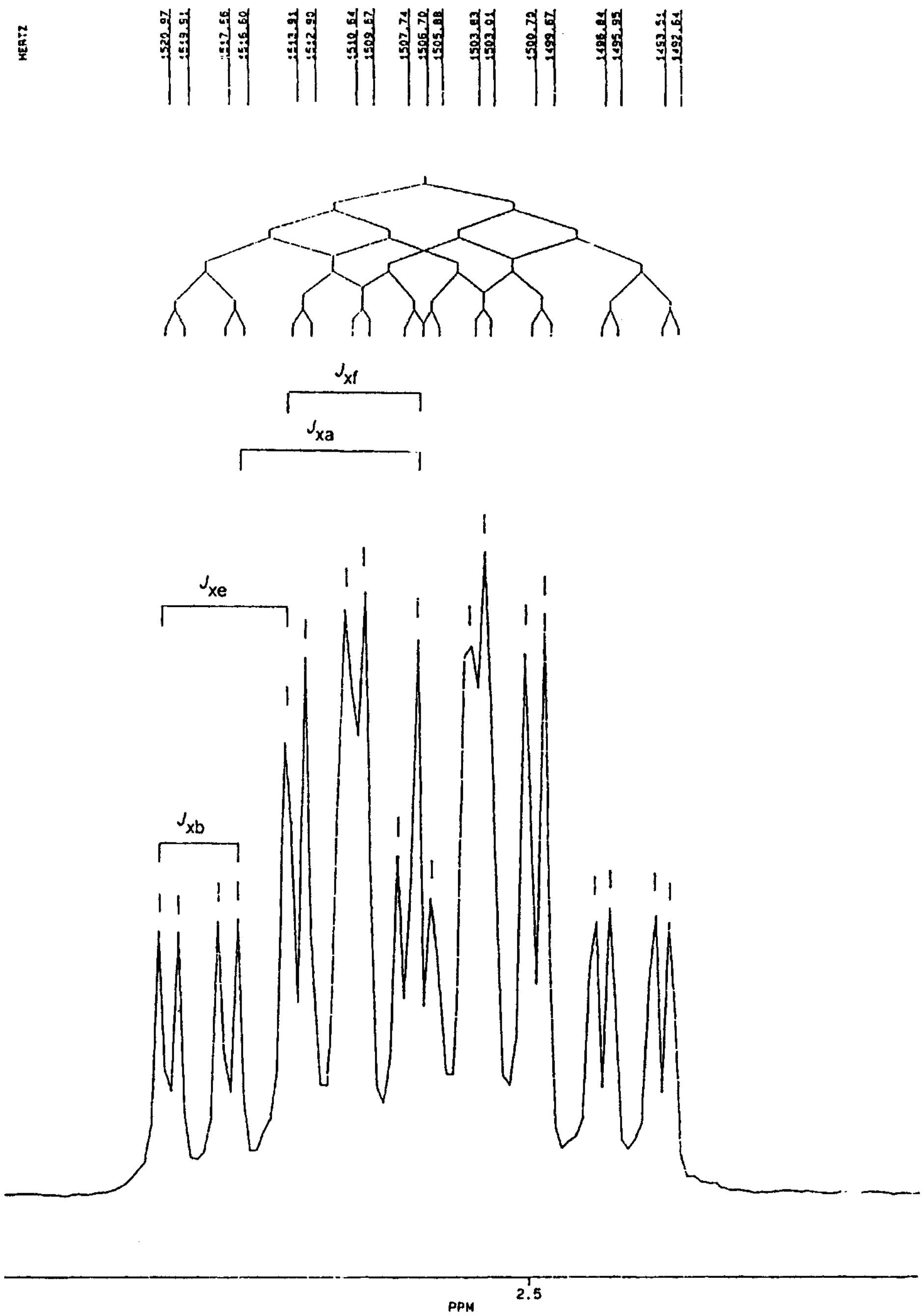

Figure 2. Signal of H^x proton of **3** in $(CD_3)_2CO$, $\delta 2{\cdot}51$ ppm

Table 2. Spectroscopic data and conformational distribution[a]

Compound		$J_{x,a}$[b]	W	n_e^J	n_e^W	ΔG^J_{exp}	ΔG^W_{exp}	ΔG_{calc}
4-Bromocyclohexene (**1**)								
Axial conf.		3·6	14·3					
Equatorial conf.		11·9	30·5					
Solvent[c]	ε							
CS_2–$CSCl_3$ (9 : 1)	2·6	9·6	25·1	0·72	0·67	0·56	0·41	0·45
$CDCl_3$	4·8	9·6	25·0	0·72	0·66	0·56	0·38	0·48
C_6D_6	7·5[d]	9·2	24·7	0·67	0·64	0·42	0·35	0·49
$(CD_3)_2CO$	20·2	9·3	24·5	0·68	0·63	0·45	0·31	0·50
$(CD_3)_2SO$	44·0	8·9	23·7	0·63	0·58	0·32	0·19	0·51
4-Chlorocyclohexene (**2**)								
Axial conf.		3·4	14·2					
Equatorial conf.		11·7	29·6					
Solvent[c]	ε							
CS_2–$CDCl_3$ (9 : 1)	2·6	9·3	25·2	0·71	0·71	0·53	0·53	0·55
$CDCl_3$	4·8	9·5	24·9	0·73	0·69	0·60	0·49	0·56
C_6D_6	7·5[d]	9·3	24·7	0·71	0·68	0·53	0·45	0·57
CD_2Cl_2	9·1	9·4	24·7	0·72	0·68	0·56	0·45	0·57
$(CD_3)_2CO$	20·2	9·3	24·6	0·71	0·67	0·53	0·42	0·59
$(CD_3)_2SO$	44·0	8·9	23·7	0·66	0·61	0·39	0·28	0·59
4-Formylcyclohexene (**3**)								
Axial conf.		3·4	15·0					
Equatorial conf.		12·3	32·6					
Solvent[c]	ε							
CS_2–$CDCl_3$ (9 : 1)	2·6	9·8	28·3	0·70	0·75	0·51	0·66	0·78
$CDCl_3$	4·8	9·8	28·6	0·70	0·77	0·51	0·72 (0·4–0·5)[e]	0·82
C_6D_6	7·5[d]							0·83
CD_2Cl_2	9·1	9·8	28·4	0·70	0·76	0·51	0·70	0·85
$(CD_3)_2CO$	20·2	9·9	28·3	0·71	0·75	0·54	0·66	0·86
$(CD_3)_2SO$	44·0	9·8	27·9	0·70	0·73	0·51	0·60	0·89
4-Carboxycyclohexene (**4**)								
Axial conf.		3·8	13·9					
Equatorial conf.		12·3	31·8					
Solvent[c]	ε							
CS_2–$CDCl_3$ (9 : 1)	2·6	11·4	29·4	0·89	0·87	1·25	1·12	0·74
$CDCl_3$	4·8	11·2	29·3	0·87	0·86	1·11	1·07 (1·00)[e]	0·74
C_6D_6	7·5[d]	10·9	28·9	0·83	0·84	0·95	0·99	0·74
$(CD_3)_2CO$	20·2	11·3	29·5	0·88	0·87	1·18	1·12	0·73
$(CD_3)_2SO$	44·0	11·1	29·3	0·86	0·86	1·05	1·07	0·73

[a] The equational conformation populations, n_e^J and n_e^W were determined with equation (1) or (2) using coupling constants and signal widths, respectively (estimated error ±0·04 in n_e, ±0·11 in ΔG).

[b] Literature values in $CDCl_3$ are $J_{x,a}$ = 9·90 Hz (compound **3**) and $J_{x,a}$ = 11·39 Hz (compound **4**); see Ref. 10.

[c] In benzene solution of **3**, the H^x signal was not observed at 2·50 ppm but at higher field (*ca* 1·90 ppm) as a result of solvent anisotropy.[13] It could not be resolved from the signals of other protons.

[d] It was found that benzene behaves as a more polar solvent than its bulk dielectric constant of 2·30 would suggest.[14]

[e] See Ref. 10

used for the calculation of coupling constants in both conformations (Table 1).

The calculated solvation energies of the individual rotamers varies from *ca* 1·0 kcal mol^{-1} in $CDCl_3$ to 2·5 kcal mol$^-$ in $(CD_3)_2SO$. The net solvent effect on the conformational equilibrium was calculated to be very small, however, since the solvation energy is nearly equal for all the rotamers in both conformations (axial and equatorial with respect to aldehyde group). The calculated free energy difference in the gas phase ($\Delta G^v = 0{\cdot}75$ kcal mol^{-1}) was almost equal to that found for the non-polar solvents [$\Delta G^s = 0{\cdot}78$ kcal mol^{-1} in CS_2–$CDCl_3$ (9 : 1)] favouring the equatorial conformation, and it changed very little on shifting to polar solvents (see Table 2). This is in agreement with the experimental results.

The three rotamers around the C-4—C$=$O bond have been considered in both ring conformations of **4**, all with hydroxyl proton *cis* to the carbonyl group. The calculated and experimental results show that the equatorial conformation strongly predominates in all solvents studied (see Table 2).

The conformational equilibria in 4-bromo- and 4-chlorocyclohexenes (**1** and **2**, respectively) exhibit a weak solvent dependence resulting in a decrease in ΔG_{a-e} in polar solvents. However, this effect is small with respect to the polarity range of the solvents used, and supports the calculated invariance of conformational population with the solvent polarity. The equatorial conformation remains dominant in all the solvents studied.

Finally, we conclude that for the compounds studied, **1–4**, the equatorial conformation predominates in all the solvents examined. The observed and calculated solvent effects are small, similar to those observed for monosubstituted cyclohexane derivatives, and unlike those found in disubstituted cyclohexane derivatives with polar groups, suggesting that the double bond does not introduce significant electrostatic forces into the molecule.

EXPERIMENTAL

4-Formylcyclohexene (cyclohexene-3-carbaldehyde) (**3**) was purchased from Aldrich and distilled before use. 4-Carboxycyclohexene (cyclohexene-3-carboxylic acid) (**4**) and 4-chlorocyclohexene (**2**) were synthesised according to Ref. 1 and 4-bromocyclohexene (**1**) according to Ref. 2. All compounds were shown to be >99·7% pure by GC prior to use. The ^{1}H NMR spectra were taken on a Bruker AM 600 (600 MHz) spectrometer equipped with Aspect 3000 computer, in the indicated solvents using the following solvent shifts (δ) for lock: CS_2–$CDCl_3$ (9 : 1) 7·24, $CDCl_3$ 7·24, C_6D_6 7·15, $(CD_3)_2CO$ 2·04 and $(CD_3)_2SO$ 2·49. All the calculations were performed on a IBM 3090 computer.

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