THE PREDOMINANCE OF AXIAL CONFORMERS FOR TRANS-4-SUBSTITUTED CYCLOHEXENE OXIDES

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A ^{1}H NMR conformational study of *cis*- and *trans*-4-substituted cyclohexene oxides revealed an increased predominance, as compared with the parent 4-substituted cyclohexenes, of the equatorial conformer for *cis*-isomers and a preference of the axial conformer for *trans*-isomers. These conformational shifts can be rationalized in terms of intramolecular dipole–dipole and/or steric interactions. However, molecular mechanics calculations failed to reproduce the relative stability of the axial conformer in *trans*-4-substituted cyclohexene oxides.

INTRODUCTION

Equatorial conformers of substituted six-membered cyclic compounds are generally more stable than axial conformers and violations of this rule attract special attention ('conformational effects'[1]). In particular, all conformational equilibria studied so far for both *trans*- and *cis*-4-substituted cyclohexene oxides 1 and 2 (X = COOR, CN, NO$_2$, SO$_2$Ph, CH$_2$OR) were biased towards an equatorial form E.[2-4] Only *trans*-4-(benzyloxy)cyclohexene oxide was considered to possess almost equally populated E- and A-conformations.[4] We report here the first example of a *reversed* conformational preference for compounds of type 1.

2A   2E

3A   3E

X = Cl (a), OCD$_3$ (b), OOCCH$_3$ (c), CN (d)

1A   1E
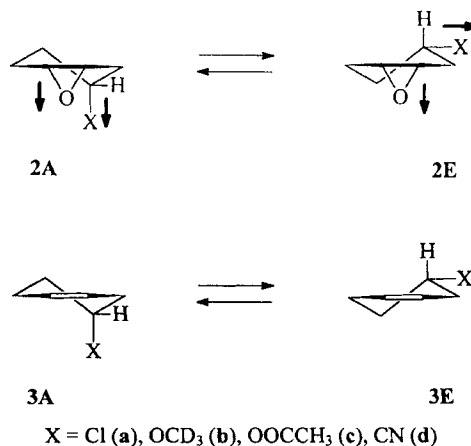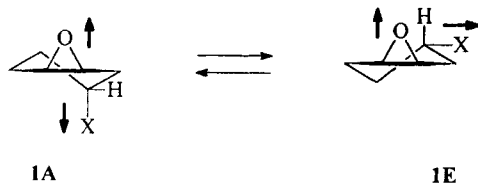
RESULTS AND DISCUSSION

The conformer populations (n_A, n_E) for epoxides 1 and 2, and parent cyclohexenes 3 were determined by ^{1}H NMR spectroscopy (360 MHz) using Eliel's equation for H$_X$ signal widths ($W = \Sigma J_{HH}$) measured as the distance between the terminal peaks of this multiplet:

$$W = W_A n_A + W_E n_E \qquad (1)$$

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The determination of the limiting parameters W_A and W_E was a key problem in the method (see below). The results of measurements and the corresponding free energy differences ΔG_{E-A} are summarized in Table 1.

To obtain ΔG_{E-A} values free of solvent effects, we estimated ΔG_{E-A}^{vapour} by the 'parabolic extrapolation' method[5] using the following linear relationship between the equilibrium free energy and a function of solvent dielectric constant:[5,6]

$$\Delta G = A + B[0\cdot5 - (\varepsilon - 1)/(2\varepsilon + 1)]^{1/2} \qquad (2)$$

The energy difference between conformers was also calculated by molecular mechanics using (a) an MM2 force field[7] amplified with epoxide ring parameters from Ref. 8 and (b) an MMX force field (PCMODEL program) (Table 2).

The parameter W for the *cis*-isomers **2** evidently includes two large *trans* coupling constants $^3J_{HH}$ corresponding to the equatorial orientation of substituent X. It does not noticeably depend on solvent polarity. Taking into account the substantial difference in the dipole moments of **2A** and **2E** (Table 2), such independence on solvation energy points to a very strong preference for the **2E** conformation (except for **2d**).

Indeed, the *cis*-axial form **2A** should be destabilized both by electrostatic and steric $O \cdots X$ repulsion (see below) leading to a completely biased equilibrium. Thus the observed W values (Table 1) can be used as W_E limiting parameters. The W_A limiting parameters (and both W_E and W_A for **1d–3d**) were chosen so that (a) the estimated ΔG_{E-A} values for **3a** and **d** fit the previously reported experimental data (see Table 1) and (b) the variation of these parameters with a change of the X substituent was the same as in the cyclohexane series.[9] We used the following set of parameters for both epoxides **1** and **2** and cyclohexenes **3**: $W_E/W_A = 33\cdot1/13\cdot0$ Hz $(X = Cl)$, $31\cdot7/12\cdot5$ Hz (OCD_3), $32\cdot6/12\cdot5$ Hz (OAc) and $33\cdot5/14\cdot3$ Hz (CN).

The parameter W for *trans*-isomers **1** is solvent dependent indicating a small but definite increase in the population of **1E** with increasing of the medium polarity. This could be easily explained for chloroepoxide **1a** and cyanoepoxide **1d** by the larger dipole moment of the **1E** conformer compared with **1A** (Table 2). However, this explanation is insufficient for the methoxy derivative **1b** because of the reversed order of the polarity of the conformers. This regularity is not valid for formamide-d_3, possibly owing to specific solvation (*e.g.* hydrogen bonding).

Table 1. ^1H NMR data (360 MHz) and conformational parameters for epoxides **1** and **2** and cyclohexenes **3**[a]

X	Solvent	ε	**1** (*trans*)				**2** (*cis*)				**3**			
			δH_X	W	n_A	ΔG_{E-A}	δH_X	W	n_A	ΔG_{E-A}	δH_X^{b}	W^b	n_A	ΔG_{E-A}
Cl (**a**)	Vapour[c]	1·00				1·8[c]				⩽−10				−1·3[c]
	C_6D_{12}	2·02	3·98	20·2	64	1·5	3·56	32·9	~0		4·04	25·2	39	−1·1
	CCl_4	2·23	4·08	19·9	66	1·7	3·65	33·0	~0		4·13	25·0	40	−1·0[d]
	CS_2	2·64	4·01	20·4	63	1·4	3·62	32·9	~0		4·06	25·2	39	−1·1[e]
	CD_3I	7·00	4·12	20·8	61	1·1	3·78	33·2	~0		4·20	24·9	41	−0·9
	$(CD_3)_2CO$	20·7	4·17	21·1	60	1·0	3·91	33·2	~0		4·29	24·3	44	−0·6
	CD_3CN	36·2	4·17	21·2	59	0·9	3·88	33·0	~0		4·32	24·0	45	−0·5
	$DCOND_2$	110	4·21	20·6	62	1·2	3·92	32·6	~2·5	~−9				
OCD_3 (**b**)	Vapour[c]	1·00				2·7[c]				⩽−10				−1·7[c]
	C_6D_{12}	2·02	3·17	17·8	72	2·4	2·96	31·7	~0		3·32	25·3	33	−1·7
	$(CD_3)_2CO$	20·7	3·24	18·7	68	1·9	3·10	31·6	~0		3·39	25·3	33	−1·7
OAc (**c**)	Vapour[c]	1·00				3·0[c]								−1·3[c]
	C_6D_{12}	2·02	4·78	17·9	73	2·5	4·54	32·6	~0		4·92	24·8	39	−1·1
	$(CD_3)_2CO$	20·7	4·78	19·6	65	1·5	4·58	32·3	~0		4·92	24·3	41	−0·9
CN (**d**)	Vapour[c]	1·00				0·1[c]								−0·4[c]
	C_6D_{12}	2·02	2·53	24·2	48	−0·2[f]	[g]	[g]		[h]	2·62	24·4	47	−0·3[i]
	CD_3I	7·00	2·71	25·0	44	−0·6	2·50	30·9	14	−4·6	2·87	24·3	48	−0·2
	$(CD_3)_2CO$	20·7	2·77	25·2	43	−0·7	2·66	30·6	15	−4·3	2·97	23·9	50	0·0

[a] The error of measurements was ±0·3–0·4 Hz for W; the estimated error was ±5% for n_A and ±0·5 kJ mol^{-1} for ΔG.
[b] 100 MHz.[10a].
[c] Estimated by the parabolic extrapolation method.[5]
[d] −1·3 kJ mol^{-1} (CF_2Cl_2, 128 K).[11b]
[e] −2·2 kJ mol^{-1} (CS_2–$CDCl_3$, 300 K),[12] −0·8 kJ mol^{-1} (CS_2, 303 K),[13] −1.0 kJ mol^{-1} (CS_2, 213 K).[13]
[f] −0·8 kJ mol^{-1} (CCl_4, 303 K).[3]
[g] Overlapped.
[h] −3·8 kJ mol^{-1} (CCl_4, 303 K).[3]
[i] −0·6 kJ mol^{-1} (CF_2Cl_2, 128 K),[11b] −0·4 kJ mol^{-1} (CS_2, 303 K),[13] 0·0 kJ mol^{-1} (CCl_4, 303 K).[13]

Table 2. Energy differences (kJ mol^{-1}) and dipole moments (D) for the conformers of epoxides **1** and **2** and cyclohexenes **3**

Compound	X	Method	ΔE_{E-A} Total	Dipolar	μ μ_A	μ_E
1a	Cl	Exp.[a]	1·8			
		MM2	−1·9	0·2	0·65	2·1
		MMX	−3·1	0·6	0·5	2·2
1b	OMe	Exp.[a]	2·7			
		MMX	−1·8[b]	1·5[b]	2·0[b] (2·1; 1·6)	1·0[b] (1·6; 3·0)
1d	CN	Exp.[a]	0·1			
		MM2	−2·9	−1·2	1·7	3·1
		MMX	−2·8	−1·3	3·0	4·5
2a	Cl	Exp.	≤−10			
		MM2	−6·0	−3·1	3·8	2·6
		MMX	−6·4	−2·2	3·9	2·7
2b	OMe	Exp.	≤−10			
		MMX	−3·6[b]	−3·0[b]	3·1[b] (2·7; 2·2)	2·9[b] (2·9; 1·0)
2d	CN	Exp.	−4 ÷ −5			
		MM2	−3·2	−1·1	5·2	3·7
		MMX	−3·6	−1·0	6·7	5·1
3a	Cl	Exp.[a]	−1·3			
		MM2	−1·4	−0·4	2·0	1·5
		MMX	−3·1	−0·3	2·0	2·3
3b	OMe	Exp.[a]	−1·7			
		MM2[c]	−2·1[b]		1·7[b] (1·5; 0·9)	1·1[b] (1·4; 1·1)
		MMX	−2·1[b]	−0·3[b]	1·0[b] (1·3; 1·6)	1·5[b] (1·3; 1·5)
3d	CN	Exp.[a]	−0·4			
		MM2[c]	−1·2		3·4	3·0
		MMX	−1·6	0·2	4·9	5·1

[a] Estimated by the parabolic extrapolation method.[5]
[b] Data for conformers with optimal torsional position of the MeO group.
[c] See Ref. 10b.

In contrast to the 'normal'[2,9] solvent dependence of the conformational equilibrium for the epoxides **1**, the parent cyclohexenes **3** (except **3b**) demonstrate a weak 'axial shift' of the equilibrium in polar solvents as first described in Ref. 10a (see also Refs 10b, 11b and 12). An analogous anomaly was observed for the 3-OR-methylenecyclohexanes.[11] This phenomenon did not correlate with a difference in dipole moments for the conformers **3A** and **3E**,[10b] so it was attributed to a difference in either their quadrupole moments or/and in their molecular volumes.[10] The uncertainty in calculated dipole moments of the cyclohexenes **3** (Table 2) should be mentioned: $\mu_A > \mu_E$ according to MM2, but $\mu_E > \mu_A$ according to MMX. This discrepancy complicates the interpretation of the results.

The most interesting feature of the equilibrium **1A** ⇌ **1E** is an unusual predominance of the axial conformer for *trans*-substituted epoxides **1a–c**, especially in non-polar solvents and vapour, whereas for

the corresponding cyclohexenes **3a–c** the equatorial form predominates. This effect is more pronounced for more electronegative RO substituents than for Cl. At the same time, *cis*-substituted epoxides **2a–c** are completely equatorial.

In the case of *trans*-cyanoepoxide **1d** the relative stabilization of the axial conformer is not so strong. It can be detected only by extrapolation to the vapour phase. For the *cis*-isomer **2d** (and also its structural analogues **2a–c**), the equatorial conformation is much more preferred than for its parent 4-cyanocyclohexene **3d**.

The greater equatorial preference of the conformational equilibrium for *cis*-4-substituted cyclohexene oxides **2a–d** compared with **3a–d** can be predicted both by qualitative considerations, as a result of electrostatic and steric O···X repulsion, and by molecular mechanics calculations (Table 2). Intramolecular electrostatic (dipolar) interactions destabilize the axial conformer

2A, and this contribution constitutes up to 80% (X = OMe) of the total energy difference. Surprisingly, the van der Waals repulsion seems to be of little importance: even in the case of the bulky chlorine substituent (**2a**) this term is of equal value for the axial and equatorial conformers (MMX). To reveal the real importance of non-bonded interactions for the destabilization of axial conformer **2A** we used a method of 'preoptimal structures.'[14] In the calculated structure of cyclohexene oxide (MMX), the appropriate axial hydrogen atom was replaced by chlorine with corresponding lengthening of the C—X bond and keeping other geometry parameters unchanged. The energy of this preoptimal structure (POS) was $8 \cdot 2$ kJ mol^{-1} higher than the energy of the axial conformer of **2a** with optimized structure (OS). Van der Waals interactions in this POS exceeded those in OS by $10 \cdot 4$ kJ mol^{-1}, thus proving their hidden importance for the conformational peculiarities of *cis*-substituted epoxides **2**.

Molecular mechanics calculations on *trans*-4-substituted cyclohexene oxides **1** predict the same or even a more pronounced predominance of equatorial conformers as for cyclohexenes **3** (Table 2). This result is in contradiction with the experimental data. A qualitative consideration suggests the dipole–dipole repulsion between the polar C—X bond and the epoxide fragment in the equatorial form **1E** or/and the dipole–dipole attraction in the axial form **1A** as the main reason for the observed predominance of axial conformers **1A**. However, the calculated electrostatic interactions account for only a small part of the axial conformer's stabilization and thus support this idea also only qualitatively. Moreover, the calculation shows the resultant dipolar stabilization of the equatorial conformer for **1d** (Table 2).

On the basis of a structural resemblance, it seems reasonable to compare the conformational effect for compounds **1** with a preference for the axial conformers of *trans*-1,4-disubstituted cyclohexanes[9b,15] or 4-substituted cyclohexanones[9c,d] bearing electronegative substituents. This effect was explained both by dipolar interactions[9b,15] and by long-range orbital interactions[16] between two electronegative groups across the cyclohexane ring. The orbital interactions transmit an electron withdrawal caused by the equatorial substituent through a sequence of *antiperiplanar* σ-bonds to the second equatorial electronegative substituent and vice versa, and thus destabilize this conformation.[16] However, the epoxide moiety cannot play the role of a (quasi)equatorial electron withdrawing group such as the carbonyl group in cyclohexanones. In both the E and A conformers the C-1—O and C-2—O bonds are rather (quasi)axial, and so their electronegativity cannot destabilize the equatorial orientation of the substituent at C-4 by means of orbital interactions. Thus, to explain the difference between the experimental and calculated data one should either suggest a new mechanism of the

effect or assume that the intramolecular dipolar interactions in these structures are much stronger than those predicted by molecular mechanics.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker WH 360 (360 MHz) spectrometer for $0 \cdot 1 - 0 \cdot 2$ M solutions at 295 K. Owing to the good resolution of H_X signals in the ^{1}H NMR spectra, separation of isomers **1** and **2** was not necessary.

The epoxides **1** and **2** were obtained from the corresponding cyclohexenes **3** by standard procedures:[3] by treatment with *m*-chloroperbenzoic acid (chlorides **1a** and **2a**) or *via* bromohydrins (**1b–1d** and **2b–2d**). The *trans*-isomers **1** were predominant in both cases (2:1–3:1). The cyclohexenes **3a**,[17] **3b**,[18] **3c**[19] and **3d**[20] were prepared according to literature procedures.

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