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Conformational analysis of *trans*-2-halocyclohexanols and their methyl ethers: a ^{1}H NMR, theoretical and solvation approach

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ABSTRACT: The conformational equilibria of *trans*-1-methoxy-2-chloro- (**1**), *trans*-1-methoxy-2-bromo- (**2**) and *trans*-1-methoxy-2-iodocyclohexane (**3**), and their corresponding alcohols (**4**–**6**), were studied through a combined method of NMR, theoretical calculations and solvation theory. They can be described in terms of the axial–axial and equatorial–equatorial conformations, taking into account the main rotamers of each of these conformations. From the NMR experiments at 183 K in CD_2Cl_2–CS_2, it was possible to observe proton H_2 in the ax–ax and eq–eq conformers separately for **1** and **2**, but not for **3**, which gave directly their populations and conformer energies. In the alcohols the proportion of the ax–ax conformer was too low to be detected by NMR under these conditions. Those HH couplings together with the values at room temperature, in a variety of solvents allowed the determination of the solvent dependence of the conformer energies and hence the vapor state energy difference. The ΔE (E_{ax}–E_{eq}) values in the vapor state for **1**, **2** and **3** are −0.05, 0.20 and 0.55 kcal mol^{-1}, respectively, increasing to 1.10, 1.22 and 1.41 kcal mol^{-1} in CD_3CN solution (1 kcal = 4.184 kJ). For **4**–**6** the eq–eq conformation is always much more stable in both non-polar and polar solvents, with energy differences ranging from 1.78, 1.94 and 1.86 kcal mol^{-1} (in CCl_4) to 1.27, 1.49 and 1.54 kcal mol^{-1} (in DMSO), respectively. Comparison of the hydroxy and methoxy compounds gives the intramolecular hydrogen bonding energy for the alcohols as 1.40, 1.36 and 1.00 kcal mol^{-1} (in CCl_4) for **4**, **5** and **6**, respectively. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: *trans*-1,2-disubstituted cyclohexanes; conformational analysis; NMR; density functional theory

INTRODUCTION

1,2-Disubstituted cyclohexanes are useful models to rationalize the interactions which control the conformational equilibria.[1–3] Conformational preferences of this class of compounds have been the subject of several investigations, including one of pharmacological interest, reported by Kay *et al.*[4] They concluded that the *trans* isomer of 2-*N*,*N*-dimethylaminecyclohexyl acetate methiodide is active as an acetylcholinesterase substrate, whereas the *cis* isomer is inactive.[4]

The conformational behavior of *trans*-1,2-disubstituted cyclohexanes has been explained mainly in terms of steric effects involving the substituents. In the case of *trans*-2-methycyclohexanol, the equilibrium is shifted towards the eq–eq conformation, probably due to 1,3-diaxial interaction in the ax–ax isomer, whereas for *trans*-1,2-dibromocyclohexane, the ax–ax population is 68% in CCl_4 (from dipole moment measurements) owing to the large repulsive steric interaction in the eq–eq conformation.[5]

However, the nature of the substituent interactions is not limited to electrostatic and steric factors only. Additional effects, repulsive or attractive, have been proposed and in particular the '*gauche* effect' has been invoked to explain the extra stability of two *gauche* electronegative atoms.[1,2]

The methodologies that have been employed in studies of conformational equilibria of molecules include, mainly, infrared[6,7] and NMR spectroscopy, and in the latter low-temperature or rigid derivatives are often used.[8,9] Infrared spectroscopy is not always an adequate technique for conformational analysis, because an absorption should not present the same molar absorptivities for all conformers.[10,11] Use of *tert*-butyl derivatives as model compounds is not possible for aliphatic systems, and for cyclic molecules the bulky group can cause distortions in the ring's geometry.[12]

Based on these considerations Abraham and Bretschneider[13] developed an NMR, theoretical and solvation calculation method, which has now been extensively applied to aliphatic systems.[14–16] An analysis of 2-bromocyclohexanone using this methodology was re-

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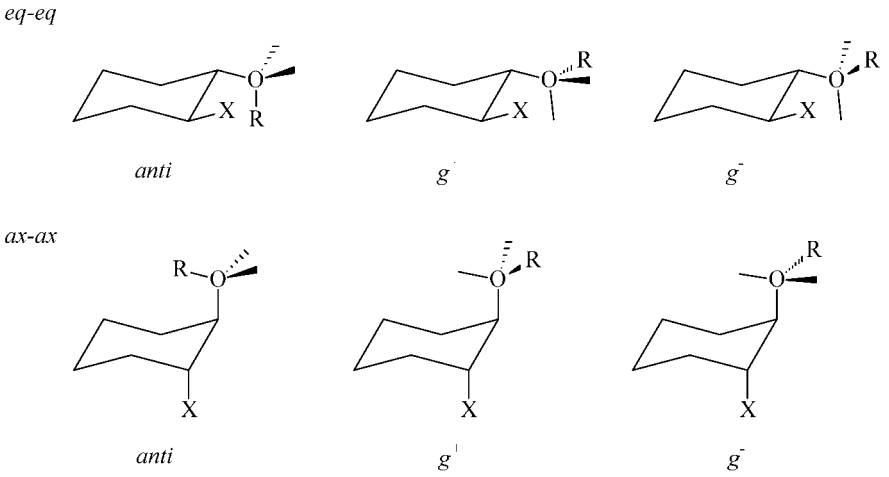

R = Me X = Cl(**1**), Br(**2**), I(**3**)
R = H X = Cl(**4**), Br(**5**), I(**6**)

Figure 1. Stable conformers of compounds **1**–**6**. For compounds **1**–**3**, the eq–eq g^- form was not characterized as a stable form

cently performed, which reviewed and refined previous data[6–9] giving very satisfactory results.[17] Abraham *et al.*[18] have also studied the conformational behavior of *trans*-2-fluorocyclohexanol and its methyl ether. They obtained the OH···F hydrogen bonding attraction in the eq–eq conformer as 1.6 kcal mol^{-1} (1 kcal = 4.184 kJ), and also that the OMe···F interaction was neutral, neither attractive nor repulsive. Bodot *et al.*[10] concluded that OH···Cl hydrogen bonding occurred in *trans*-2-chlorocyclohexanol from infrared studies, but this was not definite for the corresponding bromo and iodo derivatives.

The challenge of this work is apply the joint NMR, theoretical and solvation calculation method to six *trans*-1,2-disubstituted cyclohexanes (Fig. 1): *trans*-1-methoxy-2-chloro- (**1**), *trans*-1-methoxy-2-bromo- (**2**) and *trans*-1-methoxy-2-iodocyclohexane (**3**) and *trans*-2-chloro- (**4**), *trans*-2-bromo- (**5**) and *trans*-2-iodocyclohexanol (**6**), where the stable conformations of **1**–**6** present several degrees of freedom, due to rotation of the methoxy and hydroxy groups. In this method, calculated geometries for the ax–ax and eq–eq conformations are introduced in the MODELS program,[13–18] the theory of which follows, and the reaction field parameters obtained, together with the behavior of NMR coupling constants in solvent of varying polarities, lead to calculated couplings and the difference in energies between the conformers.

THEORY

The DFT calculations were performed using the Gaussian 98 program[19] and the solvation calculations using the MODELS program[13] (available on request from Professor R. J. Abraham, University of Liverpool). The solvation theory has been described fully elsewhere,[13] so only a brief description is given here. The solvation energy of any molecule in state A is the difference between the energy in the vapor (E_A^V) and in any solvent (E_A^S) of relative permittivity ε. This is given in terms of the dipolar (k_A) and quadrupolar (q_A) reaction field terms plus a direct dipole–dipole term to take account of the breakdown of the Onsager reaction-field theory in very polar media.[13] The input for the program is simply the dipole and quadrupole moments plus the solute radius and refractive index, both of which are calculated in the program. In state B a similar equation is obtained, differing only in the values of the dipole and quadrupole terms. Subtraction of the two equations gives ΔE^S ($E_A^S - E_B^S$), the energy difference in any solvent of given relative permittivity in terms of ΔE^V and calculable parameters. The theory has been given in detail previously[14–16] and shown to give an accurate account of the solvent dependence for a variety of conformational equilibria. The calculations were performed with the MODELS program, using as input the geometries from Gaussian. The dipole and quadrupole moments of the molecules are calculated directly from the partial atomic charges in the molecule obtained from the CHARGE routine.[20]

RESULTS AND DISCUSSION

Geometry calculations

The stable conformers of compounds **1**–**6** were obtained by calculating the potential energy surface (PES) through the AM1 method. The geometries for the most stable conformers were then optimized using DFT calculations with the B3LYP method and 6–311 + g(d,p) (**1**, **2**, **4** and

Table 1. Dihedral angles H—C—O—CH_3 (θ,°), conformer energies (E_{rel}, kcal mol^{-1}) and dipole moments (μ, D) for *trans*-1-methoxy-2-halocyclohexanes (**1**–**3**)

		Methyl ether								
		Cl[a]			Br[ab]			I[bc]		
	Conformer	θ	E_{rel}	μ	θ	E_{rel}	μ	θ	E_{rel}	μ
Eq–eq	g^+	−31.6	0	3.14	−32.8	0	3.24	−36.8	0.16	3.28
	anti	169.6	2.55	3.34	171.6	2.67	3.40	177.4	2.04	3.41
Ax–ax	g^+	−31.8	0.28	1.66	−32.6	0.50	1.72	−37.1	0	2.08
	g^-	42.0[d]	0.30	2.16	40.9	0.59	2.22	43.9	0.18	2.48
	anti	149.9	6.67	2.89	149.2	6.76	2.99			

[a] Values obtained using the B3LYP/6–311 + g** level.
[b] Blank lacunas represent no local minimum.
[c] Values obtained using the B3LYP/3–21g level.
[d] g^- conformation for the chlorine derivative is not a minimum when using MP2 or HF methods.

5) or 3–21 g (**3** and **6**) basis set, available in the Gaussian 98 program.[19] Zero-point energy corrections were also performed at these levels. Some geometric parameters, energies and dipole moments for the most stable conformers of **1**–**6** are shown in Tables 1 and 2.

Conformational analysis

For the halocyclohexanols (**4**–**6**), the ax–ax g^+ and g^- (Fig. 1) conformations are of approximately equal energy and are always more stable than the respective *anti* conformations. For the eq–eq conformations the g^- conformation is much more stable than the other forms, which may be neglected (Table 2).

For the methoxy derivatives (**1**–**3**) the situation is different (Table 1). Although for the chloro compound (**1**) three minima (g^+, g^- and *anti*) could be located for each conformation (ax–ax and eq–eq), for the bromine (**2**) and iodine derivatives (**3**) only two minima for the eq–eq conformation are observable, since the g^- conformer was not an energy minimum in the potential energy surface. Further analysis for the chloro compound revealed that the minimum corresponding to the eq–eq g^- conformation ($\theta = 6.5$; $E_{re} = 0.01$; $\mu = 2.55$; see Table 1 for the meaning of these properties) is not characterized when other theoretical levels (HF and MP2/6–311G**) were applied, and its odd convergence at the B3LYP/6–311 + g(d,p) level was therefore neglected. Moreover, the *anti* conformers are more than 2 kcal mol^{-1} higher in energy when in an eq–eq conformation, and therefore they may also be neglected. The same is true for the ax–ax conformation, whose *anti* conformations are all of much higher energy (>6 kcal mol^{-1}). The remaining g^+ and g^- conformers, for the ax–ax conformation, are of almost equal energies. All these results show that the statistical possibility of the eq–eq conformers is one (g^+) and that for the ax–ax conformers is two (g^+ and g^-).

Thus the populations of the ax–ax and eq–eq conformers in solution are obtained through

$$J_{obs} = n_{ax}J_{ax} + n_{eq}J_{eq}$$

$$n_{ax} + n_{eq} = 1$$

$$n_{ax}/n_{eq} = 2\exp(-\Delta E/RT)$$

$$\Delta E = E_{ax} - E_{eq}$$

The most stable geometries for **1**–**3** (ax–ax g^+ and g^-

Table 2. Dihedral angles H—C—O—H (θ,°), conformer energies (E_{rel}, kcal mol^{-1}) and dipole moments (μ,D) for *trans*-2-halocyclohexanols (**4**–**6**)

		Halohydrin								
		Cl[a]			Br[a]			I[b]		
	Conformer	θ	E_{rel}	μ	θ	E_{rel}	μ	θ	E_{rel}	μ
Eq–eq	g^+	−51.0	2.86	3.71	−52.8	2.90	3.80	−52.4	2.51	3.70
	g^-	63.2	0	2.43	63.6	0	2.52	60.0	0	2.15
	anti	179.9	3.15	3.80	179.6	3.21	3.82	178.3	2.04	3.68
Ax–Ax	g^+	−46.4	2.95	2.95	−47.1	3.12	1.36	−54.0	1.84	1.78
	g^-	63.0	2.96	2.96	63.7	3.35	2.28	66.6	2.12	2.45
	anti	161.3	3.64	3.64	162.6	3.90	2.69	156.9	3.15	2.68

[a] Values obtained using the B3LYP/6–311 + g** level.
[b] Values obtained using the B3LYP/3–21 g level.

Table 3. Reaction field parameters from MODELS, using B3LYP/6–311 + G(d,p) or 3–21G geometries

Compound	Conformer	k	h	l	V_M	μ
1	Ax–ax	0.8638	1.8483	0.5417	143.445	1.85
	Eq–eq	2.0872	2.4618	0.5417	143.445	2.87
2	Ax–ax	0.7651	1.6977	0.5645	147.925	1.76
	Eq–eq	1.8276	2.2640	0.5645	147.925	2.73
3	Ax–ax	0.5664	1.3370	0.6115	154.053	1.55
	Eq–eq	1.4328	1.8261	0.6115	154.053	2.46

Table 4. Relative permittivities (ε) and experimental (for **1**–**6**) and calculated[a] (for **1**–**3**) coupling constants ($^3J_{H_1,H_2}$, Hz)

Solvent	ε	**1**	**2**	**3**	**4**	**5**	**6**
CCl_4	2.24	6.97	7.04	7.64	8.98	9.17	9.56
		6.79	6.86	7.48			
Pure liquid	—[b]	7.36	7.48	8.08	8.13	8.65	9.00
		7.59	7.69	8.28			
Pyridine-d_5	12.40	7.88	8.07	8.64	8.55	8.71	9.17
		7.92	8.07	8.63			
Acetone-d_6	20.70	7.90	8.14	8.72	8.58	8.73	9.08
		—[c]	8.26	8.81			
CD_3CN	37.50	8.40	8.60	9.11	8.95	9.12	9.48
		8.31	8.46	8.99			
DMSO-d_6	46.70	8.20	8.42	8.90	8.47	8.63	9.02
		—[c]	—[c]	—[c]			

[a] Second entries
[b] $\varepsilon = 6.23$ for **1**, 5.98 for **2** and 5.95 for **3**, and they were obtained through interpolating in a graphic of $^3J_{H_1,H_2}$ vs $\varepsilon_{solvent}$
[c] Calculated data are not available, owing to the abnormal behavior of acetone and DMSO for these systems.

and eq–eq g^+), calculated at the B3LYP/6–311 + G(d,p) (**1** and **2**) and 3–21 g (**3**) levels, were applied in the MODELS program[13] to determine the reaction field parameters (Table 3).

When combined with the experimental coupling constants in Table 4, the results obtained from MODELS give the calculated coupling constants, also presented in Table 4. A detailed discussion of this methodology was presented recently.[14,15,17] Relative energies in several solvents and the molar fractions for the ax–ax conformations of **1**–**3** obtained in this work are presented in Table 5. The conformational trend (the eq–eq population increases from **1** to **2** and to **3**) agrees with the literature[21] and the low-temperature NMR data obtained here corroborate the joint methodology applied in this work.

Low-temperature studies were performed for compounds **1**–**3** in CS_2–CD_2Cl_2 (1:1). The two separate conformers were observed at 183 K. The integration of the H_{2ax} proton signal gave directly the conformer populations. The intrinsic $^3J_{H_{1ax},H_{2ax}}$ couplings measured at 183 K (1:1 CS_2–CD_2Cl_2) for **1**–**3** were 9.58, 9.83 and 10.30 Hz, respectively, and were in a good agreement with the values obtained using the joint NMR, theoretical and solvation calculations method, which were 9.58, 9.85 and 10.41 Hz, respectively. $^3J_{H_{1eq},H_{2eq}}$ couplings could not be measured owing to the low percentages of ax–ax

Table 5. Energy differences ($E_{ax-ax} - E_{eq-eq}$) in kcal mol^{-1}, mole fraction of ax–ax conformation for **1**–**6** and hydrogen bond energies in kcal mol^{-1} for **4**–**6**

	ΔE						n_{ax-ax}						OH···X energy		
Solvent	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**	**4**	**5**	**6**
Vapor	−0.05	0.20	0.55				0.68	0.59	0.44						
CCl_4	0.38	0.58	0.86	1.78	1.94	1.86	0.51	0.43	0.32	0.09	0.07	0.08	1.40	1.36	1.00
Pure liquid	0.72	0.87	1.10	1.06	1.49	1.49	0.37	0.31	0.23	0.25	0.14	0.14	0.34	0.62	0.39
Pyridine	0.89	1.04	1.25	1.35	1.54	1.59	0.30	0.26	0.19	0.17	0.13	0.12	0.46	0.50	0.34
Acetone	0.88	1.12	1.33	1.35	1.54	1.54	0.31	0.23	0.17	0.17	0.13	0.13	0.53	0.42	0.21
CD_3CN	1.10	1.22	1.41	1.71	1.94	1.86	0.23	0.20	0.15	0.10	0.07	0.08	0.61	0.72	0.45
DMSO	1.06	1.19	1.39	1.27	1.49	1.54	0.25	0.21	0.16	0.19	0.14	0.13	0.22	0.35	0.17

conformations at 183 K (5–6%), and the couplings were too small and superimposed owing to long-range couplings (*W*). However, these couplings could be estimated by the method above and the intrinsic $^3J_{H_{1eq},H_{2eq}}$ calculated values for **1**–**3** were 4.14, 2.88 and 1.18, respectively. The values of 5 and 6% of ax–ax conformation for **1** and **2**, respectively, gave a ΔG for **1** of 1.07 and for **2** of 1.00 kcal mol^{-1}, the eq–eq being the most stable, which are in agreement with solvation theory (Table 5). For the iodo compound **3**, the H_2 proton of the ax–ax conformer was obscured by the signal corresponding to the *cis* isomer.

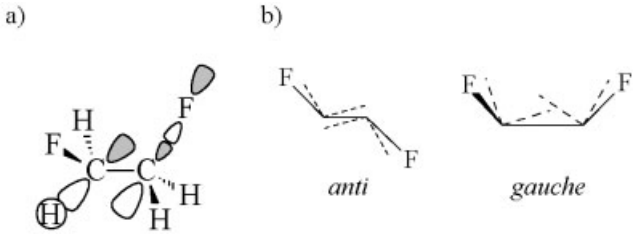

Figure 2. Interactions favoring the *gauche* conformation. (a) Hyperconjugation and (b) bent-bond

trans-2-Halocyclohexanols

Despite the structural similarity of *trans*-2-halocyclohexanols to their methyl ethers, the governing interactions of these systems are significantly different. Intramolecular hydrogen bonding between halogen and hydroxyl hydrogen should drive the conformational equilibrium towards the eq–eq conformation in the halohydrins. In order to obtain the conformational preferences and the hydrogen bonding energies in halohydrins, intrinsic couplings of the methyl ethers, and also their energies, were needed, since the application of the MODELS program to the alcohols was not possible, as their couplings do not vary sufficiently with change in solvent (large preference for the eq–eq conformation). The intrinsic $^3J_{H_{1eq},H_{2eq}}$ couplings of the halohydrins were taken to be the same as the $^3J_{H_{1eq},H_{2eq}}$ couplings of the methoxy derivatives, and this approximation is reasonable, since the intrinsic $^3J_{H_{1ax},H_{2ax}}$ couplings of the methoxy derivatives obtained at 183 K (1:1 CD_2Cl_2–CS_2) are close to the corresponding couplings for the halohydrins obtained at the same conditions [$^3J_{H_{1ax},H_{2ax}} = 9.48$, 9.61 and 10.26 Hz for chloro- (**4**), bromo- (**5**) and iodohydrin (**6**), respectively]. Furthermore, for the estimation of the intramolecular hydrogen bonding energies, we took into account only the most stable conformations (see Table 2 for the relative stabilities) and assumed that the steric effect of the methoxyl group is similar to that of the hydroxyl group. By subtracting the ΔE values of the ethers from those for the halohydrins, the values of the hydrogen bonding energies in any solvent for halohydrins were obtained (Table 5).

Experimental evidence for the occurrence of intramolecular hydrogen bonding in these 2-halohydrins is the fact that the observable couplings in CD_3CN, for example, are larger than those in the corresponding methyl ethers. Obviously, larger $^3J_{H_1,H_2}$ values correspond to larger eq–eq conformer populations. Moreover, theoretical evidence for hydrogen bonding in the bromo- and iodohydrin comes from the fact that its eq–eq g^- conformation is stable, whereas for the methyl ether this conformation is not a minimum in the PES.

Certainly, hydrogen bonding is not the only existing interaction on the halohydrins.[11] Zefirov *et al.*[1] found an attractive interaction in some 1,2-disubstituted cyclohexanes, called the '*gauche* effect.' Epiotis[22] attributed this '*gauche* effect' to an attractive interaction between n_O and n_X via the σ^*_{CC} orbital, when the molecules are disposed in the eq–eq conformation, which decreases in the order F > Cl > Br > I, for both the halohydrins and their methyl ethers. More recent interpretations to the '*gauche* effect' were detailed elsewhere,[23–28] namely hyperconjugation and bent bond, as follows. In 1,2-difluoroethane, for instance, the better σ donors follow the order C—H > C—C > C—F, thus the *gauche* form is stabilized by the $\sigma_{CH} \rightarrow \sigma^*_{CF}$ hyperconjugation [Fig. 2(a)]. Another interaction, which favors the *gauche* over the *trans* form, is an *anti* destabilization due to poorer overlap between the C—C σ-bond orbitals caused by bond bending at the carbon nuclei [Fig. 2(b)].

Lastly, two other effects also play an important role in defining the conformational preferences of the 2-halohydrins: dipole–dipole and steric repulsion. The classical 1,3-diaxial interactions present in the ax–ax conformers shift the studied equilibria towards the eq–eq conformers, which are predominant. However, the increase in the halogen volume, on going from Cl to Br and to I, leads to a strong *gauche* repulsion between the oxygen and halogen atom lone pairs, which results in a decrease in the eq–eq conformer population for the bromo or iodo derivative in comparison with the chloro derivative.

Solvent effects

The conformational equilibrium of a system can change with the medium. The solvent may also interact with the solute, not only in terms of electrical field, but also in some other ways. It is known, for example, that chloroform, a proton donor solvent[29] as well as methylene chloride, leads to an anomalous behavior in the conformational equilibrium of *trans*-2-fluorocyclohexanol as described by Abraham *et al.*,[18] where the eq–eq conformer was much more stable in $CDCl_3$ than in CD_3CN, for instance.

In this work, it was observed that for **4**–**6** the eq–eq

conformer (a more polar conformer than the average of ax–ax conformers) population is higher in CCl_4 than in more polar solvents. This unexpected behavior can be understood by taking into account that **4–6** may not be well solvated by CCl_4 (which is a non-polar solvent) at the concentration at which the NMR experiments were performed (0.1–0.2 mol cm^{-3}) and this favors the intramolecular hydrogen bonding stabilizing the eq–eq conformer. The observation that the spectrum of *trans*-2-chlorocyclohexanol (**4**), at two different concentrations (6 and 30 mg cm^{-3}) in CCl_4, with no significant changes in the $^3J_{H_1,H_2}$ values (9.05 and 8.98 Hz, respectively) indicates that there is no relevant self-association, i.e. the possibility of intermolecular hydrogen bonding, for this conformer, can be excluded.

Intermolecular hydrogen bonding may occur just in the ax–ax conformation, which presents smaller $^3J_{H_1,H_2}$ coupling constants. However, as the couplings in the halohydrins, in all solvents, are larger than in the corresponding ethers (meaning a higher eq–eq population), it can be concluded that only intramolecular hydrogen bonding is occurring. Therefore, in the remaining solvents, the behavior displayed by the coupling constants and the calculated hydrogen bonding energies (Table 5) indicated that **4–6** present intramolecular hydrogen bonding, which is weaker than in CCl_4 solution.

The self-association phenomenon has already been described for some other compounds in non-polar solvents, as for 2-bromocyclohexanone in n-hexane,[7] which stabilizes greatly the equatorial conformation, and also for the acetic anhydride in cyclohexane,[30] but 2-bromocyclohexanone showed 'normal' behavior in CCl_4.[17]

The data in DMSO, and in acetone, show that the **4–6** ax–ax conformer population is larger than expected. However, DMSO with properties as a proton acceptor solvent,[29] and also acetone, may lead to an interaction between the ax–ax conformation of the halohydrin hydroxyl hydrogen with these solvents rather than for the corresponding eq–eq conformation, or there may be competition between the possible intramolecular hydrogen bonding (in the eq–eq conformation) and hydrogen bonding with the solvent (in the ax–ax conformation). Nevertheless, the ethers (**1–3**) show a very similar conformational behavior in DMSO, which cannot be attributed to hydrogen bonding. Moreover, in CD_3CN, which is also a proton acceptor, the coupling constants show the expected behavior. These facts seem to suggest that the extra and specific stabilization of the ax–ax conformer in DMSO must be related to the intrinsic properties of this solvent, and to some extent of acetone also. DMSO exhibits a large negative charge density on the oxygen atom which prevents the solvation of the eq–eq conformer. This repulsive effect is enhanced by the repulsive interaction between the halogen atom of the eq–eq conformer and the solvent methyl groups.

Conformational preferences

In the methoxy compounds, the eq–eq conformation is always the most stable form in solution. The energy difference between the conformations should not be explained only in terms of dipole–dipole and steric effects, but also as being due to an attractive interaction between the two heteroatoms, known as the '*gauche* effect.'[1,11,22–28] For the halohydrins, the main factor governing the conformational equilibrium is intramolecular hydrogen bonding, mainly when the compounds are diluted in non-polar solvents, such as in CCl_4 solution.

EXPERIMENTAL

Syntheses

The compounds studied here are known and were synthesized according to the literature procedures.[10,21,31–33] Methyl ethers were obtained by the reaction between cyclohexene and the corresponding *N*-halosuccinimide, in methanol, at room temperature for bromine and iodine derivatives and under reflux for chlorine. The halohydrins were obtained similarly, but water was used instead of methanol. The NMR assignments are also known,[21] but a suitable interpretation is given as follows.

NMR experiments

^1H NMR spectra were obtained on a Varian Gemini 300 spectrometer operating at 300.07 MHz. Spectra were of ca 30 mg cm^{-3} solutions with a probe temperature of 296 K. The ^1H NMR spectra at low temperature were obtained at 183 K in CS_2–CD_2Cl_2 (1:1). [$^2H_{12}$]Cyclohexane was used as the deuterium lock for the CCl_4 solutions and pure liquid. All spectra were referenced to Me_4Si and the typical conditions were spectral width 2000 Hz with 32K data points and zero filled to 128K to give a digital resolution of 0.03 Hz.

For the ^1H–^1H-gCOSY experiment, a Varian standard pulse sequence was used. Typical conditions were 16 transients, accumulated into 2K data points with 128 experiments, with a pulse width 12.9 μs, sweep width of ca 5800 Hz and AT of 0.17 s. The FID was zero filled to 2K data points (F_2) and 2K data points (F_1). Solutions contained ca 20 mg ml^{-1} of sample.

trans-1-Methoxy-2-chlorocyclohexane. ^1H NMR (CCl_4, 300.07 MHz), δ 1.34 (2H, m, H_4 and H_5), 1.40 (1H, m, H_6), 1.66 (2H, m, H_3 and $H_{5'}$), 1.71 (1H, m, $H_{4'}$), 2.00 (1H, m, $H_{6'}$), 2.12 (1H, m, $H_{3'}$), 3.13 (1H, dt, 7.08, 3.59, H_1), 3.37 (3H, s, OCH_3), 3.82 (1H, ddd, 7.26, 7.08, 4.08, H_2); ^{13}C NMR (CCl_4, 75.45 MHz), δ 22.1 (C_5), 23.8

(C_4), 28.2 (C_6), 33.4 (C_3), 53.0 (C_2), 56.9 (OCH_3), 81.7 (C_1).

trans-*1-Methoxy-2-bromocyclohexane.* ^{1}H NMR (CCl_4, 300.07 MHz), δ 1.35 (2H, m, H_4 and H_5), 1.38 (1H, m, H_6), 1.69 (1H, m, $H_{4'}$), 1.79 (1H, m, H_3), 1.99 (1H, m, $H_{5'}$), 2.07 (1H, m, $H_{6'}$), 2.24 (1H, m, $H_{3'}$), 3.22 (1H, dt, 7.00, 3.21, H_1), 3.36 (3H, s, OCH_3), 3.96 (1H, ddd, 7.34, 7.00, 4.04, H_2); ^{13}C NMR (CCl_4, 75.45 MHz), δ 22.0 (C_5), 22.8 (C_4), 27.8 (C_6), 32.6 (C_3), 56.9 (OCH_3), 60.2 (C_2), 81.6 (C_1).

trans-*1-Methoxy-2-iodocyclohexane.* ^{1}H NMR (CCl_4, 300.07 MHz), δ 1.29 (3H, m, H_4, H_5 and H_6), 1.53 (1H, m, $H_{4'}$), 1.75 (1H, m, $H_{5'}$), 1.86 (1H, m, H_3), 2.11 (1H, m, $H_{6'}$), 2.25 (1H, m, $H_{3'}$), 3.20 (1H, dt, 7.32, 4.04, H_1), 3.31 (3H, s, OCH_3), 4.04 (1H, ddd, 8.91, 7.32, 4.10, H_2); ^{13}C NMR (CCl_4, 75.45 MHz), δ 22.7 (C_5), 25.9 (C_4), 29.0 (C_6), 33.5 (C_2), 36.0 (C_3), 56.4 (OCH_3), 82.8 (C_1).

trans-*2-Chlorocyclohexanol.* ^{1}H NMR (CCl_4, 300.07 MHz), δ 1.29 (3H, m, H_4, H_5 and H_6), 1.60 (1H, m, H_3), 1.74 (2H, m, $H_{4'}$ and $H_{5'}$), 2.03 (1H, m, $H_{6'}$), 2.16 (1H, m, $H_{3'}$), 2.47 (1H, m, OH), 3.43 (1H, dt, 8.98, 4.61, H_1), 3.64 (1H, ddd, 11.30, 8.98, 4.39, H_2); ^{13}C NMR (CCl_4, 75.45 MHz), δ 23.8 (C_5), 25.4 (C_4), 32.6 (C_6), 34.8 (C_3), 66.8 (C_2), 74.8 (C_1).

trans-*2-Bromocyclohexanol.* ^{1}H NMR (CCl_4, 300.07 MHz), δ 1.28 (3H, m, H_4, H_5 and H_6), 1.62 (1H, m, $H_{4'}$), 1.72 (1H, m, $H_{5'}$), 1.75 (1H, m, H_3), 2.16 (1H, m, $H_{6'}$), 2.27 (1H, m, $H_{3'}$), 2.44 (1H, s, OH), 3.48 (1H, dt, 9.17, 4.58, H_1), 3.78 (1H, ddd, 11.70, 9.17, 4.37, H_2); ^{13}C NMR (CCl_4, 75.45 MHz), δ 23.9 (C_5), 26.4 (C_4), 33.1(C_6), 35.8 (C_3), 61.2 (C_2), 74.7 (C_1).

trans-*2-Iodocyclohexanol.* ^{1}H NMR (CCl_4, 300.07 MHz), δ 1.27 (2H, m, H_4 and H_6), 1.38 (1H, m, H_5), 1.52 (1H, m, $H_{4'}$), 1.84 (1H, m, $H_{5'}$), 1.88 (1H, s, OH), 2.03 (1H, m, H_3), 2.08 (1H, m, $H_{6'}$), 2.45 (1H, m, $H_{3'}$), 3.57 (1H, dt, 9.56, 4.39, H_1), 3.98 (1H, ddd, 12.18, 9.56, 4.18, H_2); ^{13}C NMR (CCl_4, 75.45 MHz), δ 24.3 (C_5), 27.8 (C_4), 33.2 (C_6), 38.2 (C_3), 43.2 (C_2), 75.5 (C_1).

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