

Conformational Analysis of *cis*-2-Halocyclohexanols; Solvent Effects by NMR and Theoretical Calculations

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Conformational problems often involve very small energy differences, even low as $0.5 \text{ kcal mol}^{-1}$. This accuracy can be achieved by theoretical methods in the gas phase with the appropriate accounting of electron correlation. The solution behavior, on the other hand, comprises a much greater challenge. In this study, we conduct and analysis for cis-2-fluoro-, cis-2-chloro-, and cis-2bromocyclohexanol using low temperature NMR experiments and theoretical calculations (DFT, perturbation theory, and classical molecular dynamics simulations). In the experimental part, the conformers' populations were measured at 193 K in CD_2Cl_2 , acetone- d_6 , and methanol- d_4 solutions; the preferred conformer has the hydroxyl group in the equatorial and the halogen in the axial position (ea), and its population stays at about 60-70%, no matter the solvent or the halogen. Theoretical calculations, on the other hand, put the ae conformer at a lower energy in the gas phase (MP2/ 6-311++G(3df,2p)). Moreover, the theoretical calculations predict a markedly increase in the conformational energy on going from fluorine to bromine, which is not observed experimentally. The solvation models IEF-PCM and C-PCM were tested with two different approaches for defining the atomic radii used to build the molecular cavity, from which it was found that only with explicit consideration of hydrogens can the conformational preference be properly described. Molecular dynamic simulations in combination with ab initio calculations showed that the ea conformer is slightly favored by hydrogen bonding.

Introduction

Six-membered rings constitute the classical problem in conformational analysis and are closely connected to the birth of modern stereochemistry.¹ The conformational preference is usually rationalized as a delicate compromise among the so-called stereoelectronic effects, which in this context means repulsion between the substituent and the axial hydrogens (1,3-diaxial repulsions) and hyperconjugation.^{1,2} These effects are intrinsic to each molecule and have been extensively investigated in the gas phase through theoretical calculations.^{3–6} Often, the energy difference between

DOI: 10.1021/jo101819u Published on Web 12/01/2010 © 2010 American Chemical Society the possible conformers lies below 1 kcal·mol⁻¹, and it is not rare to find cases in which this conformational energy stays as low as 0.2 kcal·mol⁻¹.^{7,8} Attaining such a level of accuracy in solution is one of the greatest challenges for contemporary computational chemistry.

Much of what we know about conformational analysis came from the study of substituted cyclohexanes.^{1,2,9–12}

⁽¹⁾ Eliel, E. L.; Wilen, S. H.; Mander, L. N. Stereochemistry of Organic Compounds; Wiley: New York, 1994.

⁽²⁾ Wiberg, K. B.; Hammer, J. D.; Castejon, H.; Bailey, W. F.; DeLeon, E. L.; Jarret, R. M. *J. Org. Chem.* **1999**, *64*, 2085–2095.

⁽³⁾ Ribeiro, D. S.; Rittner, R. J. Org. Chem. 2003, 68, 6780-6787.

⁽⁴⁾ Pophristic, V.; Goodman, L. Nature 2001, 411, 565–568.

⁽⁵⁾ Goodman, L.; Gu, H.; Pophristic, V. J. Phys. Chem. A 2005, 109, 1223-1229.

⁽⁶⁾ Basso, E. A.; Oliveira, P. R.; Caetano, J.; Schuquel, I. T. A. *J. Braz. Chem. Soc.* **2001**, *12*, 215–222.

⁽⁷⁾ Freitas, M. P.; Tormena, C. F.; Rittner, R.; Abraham, R. J. J. Phys. Org. Chem. **2003**, *16*, 27–33.

⁽⁸⁾ Oliveira, P. R. O.; Rittner, R. Magn. Reson. Chem. 2008, 46, 250–255.
(9) Bjornsson, R.; Arnason, I. Phys. Chem. Chem. Phys. 2009, 11, 8689–8697.
(10) Jensen, F. R.; Bushweller, C. H.; Beck, B. H. J. Am. Chem. Soc. 1969, 91, 344–351.

⁽¹¹⁾ Schneider, H. J.; Hoppen, V. J. Org. Chem. 1978, 43, 3866-3873.

⁽¹²⁾ Aliev, A. E.; Harris, K. D. M. J. Am. Chem. Soc. 1993, 115, 6369-6377.

SCHEME 1. Conformational Equilibrium of *trans*-2-Halocyclohexanols and *cis*-2-Halocyclohexanols



Cyclohexane rings and analogous heterocyclics appear in the structure of innumerous biologically important molecules and, of course, the role played by these molecules depends on how the substituents interact among themselves and with the solvent media. In this respect, several research groups devoted considerably efforts to dissect the solvent effects on conformational equilibria.^{7,8,13-15}

A typical case of solvent effect on conformational equilibria was provided by Wiberg et al.¹⁵ while studying *trans*-1,2difluorocyclohexane. In the gas phase, the most stable conformer has both fluorine in the axial position (diaxial), but in solution this preference is completely reversed, i.e., the diequatorial conformer becomes progressively more stable as the medium polarity increases. In other cases, the proximity of two substituents allows the formation of intramolecular hydrogen bonds, as for instance in trans-2-fluorocyclohexanol.¹³ Moreover, the presence of the OH group leads to strong interactions with some solvents, such as CDCl₃ and CD₂Cl₂, that can affect the conformational trend. Abraham et al.¹³ suggested that an equatorial OH group is solvated differently than an axial one, with direct consequences to the conformational behavior. Oliveira and Rittner⁸ investigated the conformational equilibrium of *trans*-3-X-cyclohexanols, finding that the most stable conformer is the one with the halogen in the axial position, even for a bulky substituent like bromine.

Rationalizing the conformational preference is usually easier for the *trans*-1,2-configuration because in most cases both substituents act in the same direction to make the diequatorial conformer more stable by avoiding 1,3-diaxial interactions, Scheme 1. On the other hand, in the *cis* configuration the substituents work in opposite ways, i.e., whereas one substituent directs the preference to the **ae** conformer, the other tend to lead to **ea**. Surprisingly, there is a silence in the literature about the conformational behavior of the *cis* isomers for 1,2-disubistituted halocyclohexanols.

Another crucial question in the study of conformational equilibrium is the choice of an appropriate theoretical model. Density functional theory became very popular since the 1990s, mostly because of the success of Becke's three parameter method¹⁶ with correlation by Lee, Young, and Parr (B3LYP).¹⁷ However, recent analyses showed that this functional,





FIGURE 1. Variable-temperature spectra for *cis*-2-chlorocyclohexanol in CD_2Cl_2 . (Atom numbering follows from Scheme 1.)

among others, failed sometimes in the calculation of reliable energy differences for six-membered rings. Bjornsson and Arnason⁹ evaluated the performance of a class of functionals that include dispersion interactions and concluded that this kind of correction is essential for obtaining reliable conformational energies. On the other hand, perturbation theory up to second order is enough to achieve results comparable to the highly accurate CCSD(T) method. However, the solvent has not been considered in those studies.

As mentioned above, trans-2-halocyclohexanols as well as trans-3-halocyclohexanols have been investigated by NMR spectroscopy and theoretical calculations.7,8,13,14 In contrast, the cis isomer was left aside over the years, maybe because of the experimental difficulties in preparing some of the halo derivatives as well as by the need of a very refined theoretical approach to correctly reproduce and interpret the experimental data in solution. As we go from fluorine to bromine, it is expected that the ae conformer becomes more stable because it has a much more bulky substituent in the equatorial position. Moreover, since the two conformers have different dipole moments, we expect some sort of solvent effect. Our present NMR data for cis-2-X-cyclohexanols (X = F, Cl, and Br) shows no such trends but rather an apparent insensitivity while changing the solvent and the substituent, with the halogen always being in the axial position. In the following, we report the conformational analysis of cis-2-halocyclohexanols by a combination of experimental and theoretical approaches.

Results and Discussion

Measuring the Conformational Populations by Low Temperature Experiments. Figure 1 illustrates the variable temperature

⁽¹³⁾ Abraham, R. J.; Smith, T. A. D.; Thomas, W. A. J. Chem. Soc., Perkin Trans. 2 1996, 1949–1955.

⁽¹⁴⁾ Duarte, C. J.; Freitas, M. P. J. Mol. Struct. 2009, 930, 135–139.

⁽¹⁵⁾ Wiberg, K. B.; Hinz, W.; Jarret, R. M.; Aubrecht, K. B. J. Org. Chem. 2005, 70, 8381–8384.

⁽¹⁶⁾ Becke, A. D. J. Chem. Phys. 1993, 98, 1372-1377.

⁽¹⁷⁾ Lee, C.; Yang, W.; Parr, R. G. Phys. Rev. B 1988, 37, 785-789.

ΓABLE 1.	NMR Measurements of Conformers'	Populations and Relative	Conformational Energies at -80	°C for <i>cis</i> -2-Halocyclohexanols
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	$^{1}\mathrm{H}$			¹³ C average		average
	% of ea	$\Delta G^{\circ} \left(\mathbf{ea} - \mathbf{ae} \right)^a$	% of ea	$\Delta G^{\circ} \left(\mathbf{ea} - \mathbf{ae} \right)^a$	% of ea (±2%)	$\Delta G^{\circ} \left(\mathbf{ea} - \mathbf{ae} \right) \left(\pm 0.04 \right)$
			Flu	orine		
CD_2Cl_2	70	-0.33	75	-0.42	73	-0.38
acetone- d_6	66	-0.26	70	-0.33	68	-0.22
methanol- d_4	76	-0.44	74	-0.40	75	-0.19
			Chl	orine		
CD_2Cl_2	63	-0.20	65	-0.24	64	-0.29
acetone- d_6	64	-0.22	62	-0.19	63	-0.20
methanol- d_4	69	-0.31	69	-0.31	69	-0.24
			Bro	mine		
CD_2Cl_2	62	-0.19	62	-0.19	62	-0.42
acetone- d_6	65	-0.24	64	-0.22	65	-0.31
methanol- d_4	74	-0.40	70	-0.33	72	-0.36
^{<i>a</i>} In kcal·mol ⁻	⁻¹ . A negative val	lue means that the ea co	nformer is more	stable		

¹H NMR spectra of *cis*-2-chlorocyclohexanol in CD₂Cl₂. Generally, we could observe well-resolved signal split at -80 °C for all of the studied compounds, and the populations were determined by integration of the spectra at this temperature using both ¹H and ¹³C spectra. The individual conformers are identified by their coupling constants and chemical shifts. In Figure 1, for instance, we see three sets of signals at -80 °C. The left one (4.56 ppm) must belong to an equatorial H2 (geminal to chlorine) since it has the largest chemical shift and is unresolved, i.e., has small coupling constants because of the $\sim 60^{\circ}$ arrangement relative to the vicinal hydrogens. The H1 signal is expected to present a more resolved shape, a lower chemical shift and the same integral as H2. The signal that meets these requirements appears at 3.71 ppm and, together with the previous one, identifies the ea conformer. By a similar analysis, the signals in the vicinity of 4.1 ppm are attributed to the H1 and H2 hydrogens of the ae conformer, and after integration we get 63% of ea and 37% of ae. These values can be inserted into the thermodynamical equation bellow to give the experimental conformational energies:

$$\Delta G^{\circ} = -RT \ln K \tag{1}$$

where *R* is the gas constant, *T* is the absolute temperature (in this case 193.15 K), and *K* is the equilibrium constant, $K = n_{ea}/n_{ae}$, where n_{ea} and n_{ae} are the ea and ae conformer populations, respectively. Table 1 presents the experimental populations and conformational energies determined from the above analysis for the remaining compounds.

Generally, the results from ¹H and ¹³C spectra are coherent to one another, and in every case the ea conformer is found to be the more stable. A rough estimate of the uncertainties involved in these determinations can be done by regarding the ¹H and ¹³C spectra measurements as replicates. This gives an error of 2% in the populations for the average population calculated from ¹H and ¹³C. The observed variations are in most cases too close to the experimental errors to allow the identification of clear trends, from which we conclude that neither the solvent nor the halogen seems to modify the conformer's populations significantly. This is quite surprising, since the bulky bromine atom would be expected to prefer the equatorial position on the basis of steric repulsions. In other words, for a given solvent we would expect the population of the ae conformer to become increasingly larger while passing from F to Br. A similar axial preference of the halogens was

observed in the past for 2-halocyclohexanones,¹⁸ and in that case the conformational preference was justified on the basis of the hyperconjugative effect. For the cyclohexanones, however, the populations were significantly more sensible to the solvent polarity. More recently, Oliveira and Rittner⁸ found the same axial preference for *trans*-3-halocyclohexanols. Before trying to propose any explanation to this behavior, it is crucial to establish the conformational preference in the gas phase, given the decisive role the solvent can play. Since we cannot measure the conformers' populations in the gas phase, this answer has to be obtained through theoretical calculations, which we are going to describe.

Theoretical Study. Conformational Preference in the Gas **Phase.** In order to determine the lowest energy orientation for the OH group in each conformer, we built a potential energy surface (PES) by varying the H1-C1-O-H dihedral angle, Figure 2. The three minimum candidates that appear in the PES (g-, trans, and g+) were optimized using both B3LYP/6-311+G(2d,p) and MP2/6-311+G(2d,p) levels of theory, Table 2. Although MP2 is probably the best choice to obtain accurate conformational energies,9 it has the drawback of being very expensive for vibrational frequencies. In this way, thermal corrections were obtained from the B3LYP calculations. The three rotamers from the PES resulted in converged geometries with MP2. With B3LYP the grotamer was not found to be stable and converged to g+ in ae. In each case, the minimum energy conformer has the OH bond directed to the halogen, which are g+ for **ae** and *trans* for ea. These arrangements are not completely adequate for a hydrogen bond between OH and the halogen, but they still lead to a strong interaction requiring ca. 2.6 kcal \cdot mol⁻¹ to be broken by a rotation in the ea conformer and more than 3.0 kcal·mol⁻¹ for **ae**. In the gas phase, the rotamers labeled as g- and *trans* for **ae** and g- and g+ for **ea** contribute practically nothing to the conformers' populations. Therefore, we initially confined our analysis in solution to the lowest energy rotamers (ae-g+ and ea-trans).

The relative energies calculated with the larger basis set, 6-311++G(3df,2p), are in most cases smaller than those obtained with 6-311+G(2d,p). For instance, the energy difference between the most stable conformers of the bromine

⁽¹⁸⁾ Basso, E. A.; Kaiser, C.; Rittner, R.; Lambert, J. B. J. Org. Chem. **1993**, 58, 7865–7869.



FIGURE 2. Potential energy surfaces (PESs) for the hydroxyl group rotation at the B3LYP/6-311++G(d,p) for F (blue), Cl (red), and Br (yellow): **ae** (top) and **ea** (bottom).

 TABLE 2.
 Relative Energies^a Obtained after Optimizing the Possible

 Minima in the PES for Rotation over the H1-C1-O-H Dihedral

		ae			ea	
	g-	trans	g+	g+	trans	g-
		В	3LYP/6-3	11+G(2d,	p)	
F	_b	4.022	0.000	2.617	-8.1×10^{-4}	2.674
Cl	b	4.117	0.000	3.249	0.514	3.428
Br	_b	4.155	0.000	3.367	0.636	3.563
			MP2/6-31	1+G(2d,p))	
F	3.203	4.284	0.000	2.890	0.431	2.833
Cl	3.270	4.278	0.000	3.132	0.684	3.218
Br	3.197	4.213	0.000	3.148	0.813	3.254
	MP	2/6-311+-	+G(3df,2p)// MP2/6	-311+G(2d,p)	
F	3.030	3.935	0.000	2.886	0.453	2.807
Cl	3.243	4.069	0.000	2.966	0.450	3.037
Br	3.197	4.053	0.000	3.107	0.640	3.174
^{a}I	n kcal•mo	l^{-1} , without	ut thermal	correction	s. ^b Not stable at t	his level.

derivative decreases from 0.813 to 0.640 kcal mol⁻¹ with the MP2 method; this seemingly small variation has indeed important consequences for the quantitative calculation of the conformer's populations. The variation is much less important for the fluorine derivative, which suggests that the correct description of the conformational equilibrium of compounds bearing the heavier atoms chlorine and bromine requires a basis set of the 6-311++G(3df,2p) quality.



FIGURE 3. ¹H NMR signal of the OH proton of *cis*-2-chloro-cyclohexanol in acetone- d_6 at -80 °C.

It is noteworthy that the lower energy structures are coherent with the experimental NMR results. More specifically, in the ae conformer the H1-C1-O-H dihedral angle is calculated to be about 64°, whereas for the ea conformer it is about 180°. Hence, we expect to observe two OH proton resonances, one with a low coupling (3.18 Hz, for ae) and another with a large coupling constant (6.13 Hz, for ea), which is exactly what the ¹H spectrum shows in the solvents where the OH resonance could be recorded, Figure 3. As mentioned above, the ea conformer is the most stable in solution according to the NMR measurements on the cyclohexane ring nuclei. The OH resonance also shows the ea conformer in greater proportion (Figure 2), but more than this, it strongly suggests that the solvent effect originates from the medium polarity (and maybe from short-range interactions) and not from a substantial structural modification, since the optimized gas phase geometries have structural parameters compatible with the experimental results. It must be noted, however, that the OH group of the cyclohexane ring is probably involved in hydrogen bonding when the solvent is methanol. The question is if this interaction provides some advantage to one or the other conformer. More about this point will be discussed in the next sections.

According to the gas phase calculations, Table 2, the **ae** conformer is the more stable (except for fluorine in B3LYP), as someone could anticipate on the basis of steric hindrance. Moreover, the preference for the **ae** conformer, which has the halogen in the equatorial position, is intensified while passing from fluorine to bromine, except for the higher basis set (6-311++G(3df,2p)), which shows the fluorine and chlorine derivatives with about the same conformational energy. These results suggest (at least comparing F to Br) that 1,3-diaxial repulsions operate to allocate the bulky bromine atom in the equatorial position. Since this conclusion has the support of MP2 results with a sufficiently large basis set, we can trust in the gas phase calculations, so that agreement with experiments has to be searched in the solvent effects.

TABLE 3.Differences in Conformational Energies^a in Solution for theMost Stable Rotamers (ae-g+ and ea-trans) of cis-2-HalocyclohexanolsCalculated Using the Solvation Models IEF-PCM and C-PCM at theMP2/6-311++G(3df,2p)//MP2/6-311+G(2d,p) Level

	IEF-	IEF-PCM		СМ
	UAHF	Bondi	UAHF	Bondi
		Fluorine		
CHaCla	+0.139	-0.167	+0.128	-0.219
acetone	+0.101	-0.223	+0.096	-0.223
methanol	-0.249	-0.181	-0.262	-0.175
		Chlorine		
CH ₂ Cl ₂	+0.189	-0.269	+0.202	-0.257
acetone	+0.168	-0.353	+0.175	-0.345
methanol	-0.009	-0.264	-0.007	-0.254
		Bromine		
CH ₂ Cl ₂	+0.231	-0.103	+0.225	-0.086
acetone	+0.196	-0.119	+0.195	-0.107
methanol	+0.112	-0.127	+0.114	-0.118
^{<i>a</i>} In kcal mostable.	ol ⁻¹ . Negative	values mean tha	it the ea conform	ner is more

Conformational Preference in Solution with the Polarizable Continuum Model. One of the most complete approaches to deal with solvent effects is the polarizable continuum model (PCM),^{19,20} which breaks the solvation free energy into electrostatic and nonelectrostatic contributions. The former describes how the solute electron density is affected by the electric field created by the bulk of solvent molecules, whereas the latter takes into account the energy required for building a molecular cavity within the liquid (cavitation), as well as solute-solvent dispersion and repulsion energies. There are several ways to construct the molecular cavity, which basically consist in selecting a set of atomic radii and a method for defining the molecular surface from those radii. While selecting atomic radii, it is possible to describe hydrogens explicitly or to include them implicitly into a single sphere together with heavy atoms (united atom models). Our first choice for this work was the well-known UAHF atomic radii method, which treats hydrogens implicitly. This option, however, gave conformational trends opposing the NMR experiments. Since we are dealing with solute-solvent systems in which hydrogen bonds can effectively occur, we could be tempted to attribute the divergence to theses interactions. Nevertheless, before judging these deviations from experiments as a real phenomenon, we also considered the possibility of an inadequacy of the theoretical model to treat a so delicate case of conformational equilibrium. In this way, we performed a series of calculations in which the cavity was build with explicit hydrogen atoms, more specifically, using Bondi's radii. Additionally, we carried out calculations using two versions of the PCM approach, namely, the integral equation formalism (IEF-PCM)¹⁹ and the conductor-like polarizable continuum model (C-PCM).²⁰ Table 3 lists the conformational energies for the most stable rotamers of each conformer (ae-g+ and ea-*trans*). We present here only the MP2/6-311++G(3df,2p) results, whereas the complete set of calculations including B3LYP and MP2 with the smaller basis set are collected as Supporting Information. The B3LYP

TABLE 4. Gas Phase Dipole Moments^{α} Calculated at the MP2/6-311++G(3df,2p) Level

	· · · · ·					
	ae			ea		
	<i>g</i> -	trans	g+	g+	trans	g-
			Vacuum			
F	3.25	3.77	1.90	3.02	2.27	3.26
Cl	3.45	3.85	2.02	3.08	2.41	3.56
Br	3.63	3.96	2.11	3.15	2.51	3.71
<i>a</i> In	debyes.					

results, although qualitatively correct, overestimate too much the conformational preference for fluorine and underestimate it for the heavy atoms. MP2 with the 6-311+G(2d,p) basis set improves the results over B3LYP for fluorine to a quantitative level when using Bondi's radii, but for chlorine and bromine the agreement with experiments was still unsatisfactory.

Regarding the efficiency of the solvation models, IEF-PCM and C-PCM are essentially equivalent. It is evident that UAHF, with includes hydrogens implicitly in the heavy atom spheres, cannot capture the molecular cavity nuances with the accuracy required for this problem. With the use of the larger basis set, the IEF-PCM results using Bondi's radii are quantitatively correct. Probably, a basis set like 6-311+ G(2d,p) is enough to deal with second raw elements, but for the heavier atoms we could only obtain quantitative agreement using the 6-311++G(3df,2p) basis set. In conclusion, the correct description of the conformational preference in this system requires the use of explicit hydrogens to build the molecular cavity in the PCM model and a sufficiently large basis set to describe the heavier halogens.

Let us now consider the reasons for the conformational preference in solution. As we said above, the gas phase calculations show that the ae conformer (with the halogen in the equatorial position) is the more stable, and this preference is intensified for bromine because of its large volume. On the other hand, the experimental conformational populations show that the ea conformer, which has the halogen in the axial position, is more stable even for bromine and, moreover, that this preference is practically unchanged. The quantity most easily associated to the solvation energy is the dipole moment. Table 4. Fixing our attention only on the most stable rotamers (ae-g+and ea-trans), we see that the dipole moment of ea is a little larger than that of ae in the gas phase, and as the solvent effect is proportional to $\mu^{2,21}$ it is expected that the ea conformer will be more stabilized in solution than ae, which is actually what the PCM calculations showed. However, then we have to ask why the conformers' populations, for a given solvent, remain almost unaffected by the size of the substituent in solution. For instance, the ea populations in acetone are 66%, 64%, and 65% for fluorine, chlorine, and bromine, respectively (¹H results, Table 1). Again, the dipole moments are the key. As we go from fluorine to bromine, the dipole moment increases (Table 4), and thus the solvent effect is expected to be the largest for bromine, then chlorine and fluorine. Therefore, there are two effects acting in opposite directions, namely, the steric repulsions (pushing the halogen to the equatorial position) against the solvent effect (that stabilizes the halogen in the axial position). In this way, as we go from fluorine to

⁽¹⁹⁾ Cances, E.; Mennucci, B.; Tomasi, J. J. Chem. Phys. **1997**, 107, 3032– 3041.

⁽²⁰⁾ Barone, V.; Cossi, M. J. Phys. Chem. A. 1998, 102, 1995–2001.

⁽²¹⁾ Onsager, L. J. Am. Chem. Soc. 1936, 58, 1486-1493.

TABLE 5. Relative Conformational Energies Calculated at the IEF-PCM-MP2/6-311++G(3df,2p) Level a

	ae			ea		
	g-	trans	g+	g+	trans	g-
		Ε	oichloromet	hane		
F	0.920	1.161	0.167	0.716	0.000	0.673
Cl	0.968	1.107	0.305	0.500	0.000	0.574
Br	1.196	1.450	0.103	0.803	0.000	0.893
			Acetone			
F	0.630	0.803	0.223	0.389	0.000	0.395
Cl	1.076	1.203	0.353	0.557	0.000	0.631
Br	0.858	1.169	0.119	0.376	0.000	0.433
			Methano	1		
F	0.682	0.941	0.181	0.239	0.000	0.206
Cl	0.959	1.180	0.309	0.405	0.000	0.456
Br	0.663	0.935	0.127	0.414	0.000	0.527

^{*a*}In kcal mol⁻¹; single-point over the optimized MP2/6-311+G(2d,p) structure. Thermal corrections (at 193.15 K) are taken from the gas phase B3LYP/6-311+G(2d,p) frequencies; for the g- rotamer of **ae**, which is not stable at B3LYP, we used the same thermal correction of the *trans* rotamer.

bromine, there should be a decrease in the preference of **ea** due to the greater size of this latter, but this trend is actually counterbalanced by the solvent effect, which tends to make the **ea** conformer of bromine more stable relative to **ae** in comparison to fluorine, since the dipole moment of the bromine derivative is larger.

Now, if we want to be able to make a close comparison between measured and calculated data, it is necessary to take into account the small contributions of the other rotamers. In this way, the optimized structures that generated the energies in Table 2 were submitted to single-point calculations at the MP2/6-211++G(3df,2p) level with the IEF-PCM solvation model, giving the energies in Table 5. It is interesting to note that the higher energy rotamers all have dipole moments (Table 4) larger than those of the lowest energy ones (ae-g+ and ea-trans), so they will become more stable as the solvent polarity increases. This is exactly what the data of Table 5 shows. For instance, the g-rotamer of ea is 3.17 kcal·mol⁻¹ above the *trans* rotamer in the gas phase for the bromine derivative (Table 2). In methanol, this difference falls to 0.53 kcal·mol⁻¹ (Table 5), since the grotamer has a dipole moment of 3.71 D against only 2.51 D of the trans rotamer. As the relative energy of many rotamers fall bellow 1.0 kcal·mol⁻¹ in solution, they begin to make important contributions to the total population of each conformer (ae or ea). In Table 6 we compare the experimental and calculated conformers' populations in solution taking into account the contribution of all rotamers. The calculated and experimental values can be considered in very good agreement, since the energy differences for this problem are in the vicinity of $0.2 \text{ kcal mol}^{-1}$, and this was actually achieved by the theoretical method.

Effect of Hydrogen Bonding. In order to get a more detailed insight about the solute-solvent interactions, we ran a set of molecular dynamics simulations. Basically, we are looking for hydrogen bonding patterns that could affect the individual conformers in different ways. The solvent arrangement around the solute molecule can be investigated through the radial distribution functions (RDFs). These functions are constructed with the aim of recognizing structured

TABLE 6. Experimental and Calculated Conformers' Populations^{*a,b*}

	% ea		$\Delta G^{\circ}_{193} (\mathrm{kcal} \mathrm{mol}^{-1})$	
	$expt^{c}(\pm 2\%)$	$calc^d$	expt (±0.04)	calc
		Dichlorometh	ane	
F	73	63	-0.38	-0.20
Cl	64	72	-0.22	-0.36
Br	62	60	-0.19	-0.16
		Acetone		
F	68	66	-0.29	-0.26
Cl	63	74	-0.20	-0.40
Br	65	66	-0.24	-0.26
		Methanol		
F	75	71	-0.42	-0.34
Cl	69	74	-0.31	-0.40
Br	72	62	-0.36	-0.19
<i>a</i> -	too Tr brown			

 ${}^{a}T = 193$ K. b IEF-PCM-MP2/6-311++G(3df,2p)//MP2/6-311+ G(2d,p) with thermal corrections at the B3LYP/6-311+G(2d,p) level in the gas phase at T = 193 K. c Average from ¹H and ¹³C. d Calculated by taking into account the contributions of all rotamers.



FIGURE 4. Radial distribution functions (RDFs) for *cis*-2-chlorocyclohexanol (blue line for the **ae** conformer and red line for **ea**).

portions of the solution, presenting a unitary value in the bulk liquid (distant from the solute) and peaks differing from unity (close to the solute) whenever there is a high degree of organization among the solvent molecules. A hydrogen bonding, for instance, can be identified by a sharp peak at about 2 Å (for $O \cdots H$ RDFs).

For most cases, both conformers interact in very similar ways with the solvent molecules. In Figure 4 we present the



FIGURE 5. Solute-methanol complexes. The energy differences were obtained with IEF-PCM-MP2/6-311++G(3df,2p)//MP2/6-31+G(d,p); distances are in angstroms.

RDFs for cis-2-chlorocyclohexanol, and the remaining ones are included as Supporting Information. The interaction of the OH hydrogen with methanol molecules, for instance, gives rise to marked peaks that identify hydrogen bonds. Despite that, there is no appreciable difference in the solvation pattern for the OH group in the axial or in the equatorial arrangement. Nonetheless, Figure 4 shows that the differences in the hydrogen bond peaks for the two conformers are substantially different for the chlorine derivative in acetone. The ae conformer has more hydrogen bonds than ea and hence is more stabilized by this kind of interaction. As a result, hydrogen bonds are expected to decrease somewhat the ea population, which is evidently not reproduced by a continuum model like PCM. Note that, in Table 6, the calculated ea populations for chlorine in acetone is larger than those of the other two derivatives, whereas the experimental values behave in the opposite way. If we take into account the behavior evidenced in the RDFs, we can suppose that part of this difference comes from these specific interactions. There are other differences in the calculated and observed population, like that of the fluorine derivative in dichloromethane, but in this case we found no evidence in the RDFs that these difference come from distinct solvation patterns.

The halogen is not involved in hydrogen bonding. The $X \cdots D$ RDFs actually show a slight protruberance that suggests some kind of complexation; the same happens to the HO $\cdots D$ RDFs but with a somewhat more intense peak. In both cases, there is no substantial difference between the two conformers so that, again, this interaction is not expected to affect the conformational preference. It is interesting to note that the OH acts as a better hydrogen bonding acceptor in dichlorometane than in methanol, which should be in principle a better hydrogen donor. In this case, there is an intense OH \cdots O interaction, i.e., the OH hydrogen binds

TABLE 7. Relative Conformational Energies for the Most Stable Rotamers of ae and ea Obtained at the IEF-PCM-MP2/6-311++ G(3df,2p)//MP2/6-31+G(d,p) Level

	$\Delta E (\text{kcal mol}^{-1})^{a}$		
	complexed	isolated	
F	-0.252	-0.036	
Cl	-0.366	-0.232	
Br	-0.131	-0.021	
an 1:41			

"Without thermal corrections, including nonelectrostatic contributions in the solvation energies.

to the methanol oxygen. Apparently, there is no space to accommodate two methanol molecules complexing to the cyclohexane, so that only the strongest interaction prevails. In the case of dichloromethane, for which there is no such strong interaction, we observe complexations at both the OH oxygen and at the halogen, but these interactions happen with the solvent molecules more distant from the cyclohexane ring than the previous one.

Now, classical force fields are parametrized in a process in which agreement with the majority of available experimental data is pursued. Nonetheless, we always must keep in mind that these parameters may eventually be unable to correctly describe a new situation. In order to better understand the solute-solvent interactions, we took advantage of the statistical information provided by the classical simulations and combined it with a refined ab initio treatment. This approach was adopted for the solvent methanol. From the RDFs (Figure 4), we see that the OH of the cyclohexane ring acts essentially as a proton donor in hydrogen bonding between the solute and the methanol molecules. Moreover, integration of the OH····O(methanol) RDFs gives about one molecule of methanol complexed to the solute. On the basis of these data, we optimized the geometries of solute-methanol complexes for the lowest energy conformers, Figure 5.

The optimized structures for the complexes were obtained in the gas phase using MP2 with a smaller basis set (6-31+G(d,p)) and further used for a IEF-PCM single point calculation with the larger basis set (6-311++G(3df,2p)). For comparison, we also calculated the relative conformational energies for the isolated molecules at the same level of theory, Table 7. Complexation with a methanol molecule, according to the above combination of methods, favors the ea conformer for the three compounds. This complexation is more important for the F and Br derivatives and is helpful in understanding the small differences between the calculated and experimental values of Table 6 for methanol. For the chlorine derivative, on the other hand, hydrogen bonding as calculated above tends to accentuate the slightly overestimated relative conformational energy (Table 6). Even so, it is important to say that these relative energies are calculated to within 0.2 kcal mol⁻¹ compared to experiments, which is a more than acceptable deviation for condensed phase calculations.

Conclusions

Despite the marked differences from one halogen to another, the experimental conformers' populations are very close for the three substituents in the solvents tested. Theoretically, the conformational equilibrium of *cis*-2-halocyclohexanols requires a careful account of each possible rotamer generated by rotation of the hydroxyl group, while solvation effects are crucial for the correct description of the conformational equilibrium in these compounds. The solvent model has to be applied with the due care in order to capture the detailed features of the solute-solvent interactions in each conformer. The united atom model (UAHF) fails to predict the correct conformational trend, whereas the use of Bondi's radii with explicit consideration of all hydrogens brings experiment and theory very close. Molecular dynamics simulations show that in most cases the solute complexes with about the same number of solvent molecules. This information, in conjunction to MP2 calculations, shows that complexation to a methanol molecule is likely to favor the ea conformer. After all, cis-2-halocyclohexanols can be taken as a good example of the richness still hidden in the conformational analysis of small molecules.

Experimental Section

Compound Preparations. 2-Bromocyclohexanone²². Prepared by dropping liquid bromine in a mixture of water and cyclohexanone as described in ref 20. Yields were about 58% (bp 45 °C/ 0.5 mmHg). The product was protected from light and stored at low temperature to avoid decomposition.

2-Chlorocyclohexanone. Obtained commercially and purified by distillation through a Vigreux column (bp 60–64 °C/10 mmHg).

trans-2-Fluorocyclohexanol²³. Cyclohexene oxide (6.4 mL), KHF₂ (7.4 g), and di(ethylene glycol) (13.0 mL) were placed on a round-bottom flask and kept at 175 °C with magnetic stirring for 1 h. The solid residue was separated on a Büchner funnel, and the collected liquid was distilled under reduced pressure in a Vigreux column, yielding 4.3 g (58%) of a colorless liquid (bp 69–71 °C/15 mmHg).

2-Fluorocyclohexanone²³. *trans*-2-Fluorocyclohexanol (3.0 g) was dissolved in acetone (50 mL, free of isopropyl alcohol) in a round-bottom flask. Chrome VI oxide (3,0 g) was dissolved in sulfuric acid (2.4 mL) and water (6.0 mL), and this mixture was added dropwise from a addition funnel while keeping the temperature at about 35 °C. The mixture was then allowed to react for 24 h under magnetic stirring at room temperature. Isopropyl alcohol was subsequently added until the solution became green. After filtration of the solid and removal of the remaining acetone, the product was dissolved in methylene dichloride and washed with distilled water. The organic phase was dried with Na₂SO₄, and the solvent was removed on a rotary evaporator. Distillation through a Vigreux column gave 1.43 g (48%) of a colorless liquid (bp 65–69 °C/13 mmHg). *cis*-2-Halocyclohexanols^{24,25}. The halogenated ketone (17 mmol)

cis-2-Halocyclohexanols^{24,25}. The halogenated ketone (17 mmol) was dissolved in dried THF (25 mL) in a round-bottom flask under N₂ atmosphere and magnetic stirring. After the temperature was lowered to -78 °C, K-selectride (20 mL) was added, and the reactor was kept under stirring for 4 h. The reaction mixture was allowed to attain ambient temperature, after which it was hydrolyzed with water (3.0 mL) and ethanol (11.5 mL). The organoborane was oxidized with NaOH 6.0 mol/L (7.5 mL) and 30% H₂O₂ (11.5 mL). The aqueous phase was than saturated with CaCO₃ and extracted with ethyl ether. The two organic portions were joined, dried with MgSO₄, and carried to a rotary evaporator where the solvent was removed. Distillation through a Vigreux column under reduced pressure gave the pure compounds with yields of about 50%

(*cis*-2-fluorocyclohexanol, bp 69 $^{\circ}$ C/14 mmHg; *cis*-2-chlorocyclohexanol, bp 75 $^{\circ}$ C/8 mmHg; *cis*-2-bromocyclohexanol, bp 55 $^{\circ}$ C/2 mmHg).

cis-2-Fluorocyclohexanol: ¹H NMR (CDCl₃, 300.06 MHz) δ 3.77 (1H, m, H₁), 4.68 (1H, m, H₂), 2.03 (1H, m, H_{3e}), 1.80–1.48 (5H, m, H_{3a}, H_{4e}, H_{5e}, H_{6a}, H_{6e}), 1.46–1.24 (2H, m, H_{4a}, H_{5a}), 2.10 (1H, s, OH). ¹³C (CDCl₃, 75.46 MHz, σ): 70.0 (C₁), 92.87 (C₂), 28.5 (C₃), 20.9 (C₄), 22.0 (C₅), 30.1 (C₆).

cis-2-Chlorocyclohexanol¹H NMR (CDCl₃, 300.06 MHz) δ 3.83 (1H, m, H₁), 4.30 (1H, m, H₂), 2.04 (1H, m, H_{3e}), 1.90–1.60 (5H, m, H_{3a}, H_{4e}, H_{5e}, H_{6a}, H_{6e}), 1.46–1.28 (2H, m, H_{4a}, H_{5a})), 2.10 (1H, d, OH). ¹³C (CDCl₃, 75.46 MHz, σ): 70.6 (C₁), 66.21 (C₂), 31.9 (C₃), 21.6 (C₄), 22.4 (C₅), 30.7 (C₆).

cis-2-Bromocyclohexanol¹H NMR (CDCl₃, 300.06 MHz) δ 3.70 (1H, m, H₁), 4.51(1H, m, H₂), 1.92 (1H, m, H_{3a}), 2.12 (1H, m, H_{3e}), 1.82–1.58 (4H, m, H_{4e}, H_{5e}, H_{6a}, H_{6e}), 1.50–1.30 (2H, m, H_{4a}, H_{5a}). ¹³C (CDCl₃, 75.46 MHz, σ): 70.6 (C₁), 62.3 (C₂), 33.3 (C₃), 22.4 (C₄), 23.8 (C₅), 32.2 (C₆).

NMR Measurements. NMR spectra were acquired on a Varian Mercury Plus BB Spectrometer, operating at 300.059 MHz for ¹H and 75.457 MHz for ¹³C, in solutions of 20 mg/mL in CD₂Cl₂, acetone- d_6 , and methanol- d_4 using TMS as internal reference. Typical ¹H NMR pectra were ran with spectral width of 4000 Hz and 32 K data points, which was further zero filled to 128 K to give a digital resolution of 0.03 Hz. COSY and HSQC experiments were also run in order to aid signal attributions. Variable temperature experiments were conducted at intervals of about 30 °C down to -80 °C, which was enough the get the conformers signals well split apart for all solvents.

Theoretical Calculations. The potential energy surfaces (PES) were constructed by varying the H1-C1-O-H angle in increments of 10° through 360° at the B3LYP/6-311++G(d,p) level. The minimum structures we optimized at the at B3LYP/ 6-311+G(2d,p) and MP2/6-311+G(2d,p) levels with tight convergence criterium and ultrafine grid for DFT. Frequency calculations were performed over the B3LYP geometries to characterize the stationary points according to the number of imaginary frequencies (which must be zero for true minima). All thermochemistry analysis was conducted at 193.15 K to match the NMR experimental conditions. Solvation effects were included with the IEF-PCM and C-PCM models using T = 193.15 K and dielectric constants stored in the program database. Molecular cavities were constructed using the GEPOL protocol combined with two different choices of atomic radii, namely, UAHF (united atoms optimized for Hartree-Fock) and Bondi. All electronic structure calculations were performed with the GAUSSIAN 03²⁶ suite of programs.

Molecular dynamics simulations were performed with the TINKER^{27,28} package of programs using the OPLS-AA²⁹ force field. This force field was applied since it has been successful in

⁽²²⁾ Allinger, J.; Allinger, N. L. Tetrahedron 1958, 2, 64-74.

⁽²³⁾ Wittig, G.; Mayer, U. Chem. Ber. 1963, 96, 335.

⁽²⁴⁾ Akiyama, T.; Nishimoto, H.; Kuwata, T.; Ozaki, S. Bull. Chem. Soc. Jpn. 1984, 67, 180–188.

⁽²⁵⁾ Vogel, A. I. Vogel's Textbook of Practical Organic Chemistry, 5th ed.; Longman Scientific and Technical, 1989; p 526.

⁽²⁶⁾ Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., J.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision E; Gaussian, Inc.: Wallingford, CT, 2004.

⁽²⁷⁾ Ponder, J. W. *TINKER: Software Tools for Molecular Design*, Version 5.1; Washington University School of Medicine: St. Louis, 2010.
(28) Ren, P.; Ponder, J. W. J. Phys. Chem. B 2003, 107, 5933–5947.

reproducing the properties of liquid alcohols.³⁰ Boxes containing 300 solvent molecules were minimized and used to accommodate the solute under investigation, with further minimization to rms = 0.01 before starting the molecular dynamics simulations. Simulations used flexible models (solute and solvent) and deuterated solvent molecules with T = 193 K. The box dimensions were $(31.7765)^3$ Å³ for CD₂Cl₂-d₂, $(33.2367)^3$ Å³ for acetone-d₆, and $(27.2298)^3$ Å³ for methanol-d₄. Simulations

ran in the *NVT* ensemble with time step of 0.25 fs. Equilibration periods last 25 ps with accumulations for more 250 ps.

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Supporting Information Available: Cartesian coordinates for the optimized structures, complementary energy tables and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

⁽²⁹⁾ Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. J. Am. Chem. Soc. **1996**, 118, 11225–11236.

⁽³⁰⁾ Lehtola, J.; Hakala, M.; Hämäläinen, K. J. Chem. Phys. B 2010, 114, 6426–6436.