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Conformational Analysis of 1-Chloro- and 1-Bromo-2-propanol

Karla M. S. Gonçalves,[†] Danielle R. Garcia,[‡] Teodorico C. Ramalho,[†] José D. Figueroa-Villar,[‡] and Matheus P. Freitas*,[†]

[†]Department of Chemistry, Federal University of Lavras, 37200-000 Lavras, MG, Brazil
[‡]Military Institute of Engineering—IME, 22290-270 Rio de Janeiro, RJ, Brazil

Ⓢ Supporting Information

ABSTRACT: The conformational isomerism of 1-chloro- (**1**) and 1-bromo-2-propanol (**2**) was theoretically and spectroscopically (NMR) analyzed. Conformers with the X—C—C—O (X = Cl and Br) fragment in the gauche orientation were found to be strongly prevalent both in the gas phase and solution, as analyzed by means of coupling constants in the diastereotopic methylene hydrogens. The gauche effect was calculated to be due to hyperconjugation rather than intramolecular X···HO hydrogen bond, indicating the rule of the stereochemical control in compounds with motifs (halohydrins) widely found in pharmaceutical and agrochemical products and intermediates.
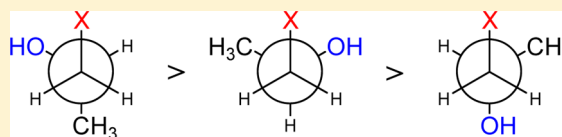
1. INTRODUCTION

Intermolecular interactions play a determinant role for biological activity (because of ligand—enzyme interactions) and molecular assembly, like in supramolecular systems. However, intramolecular interactions govern the conformations capable of performing or competing with the above intermolecular interactions. Despite the notable effect of steric, electrostatic, and many types of hyperconjugative interactions on conformational equilibria, the hydrogen bond is a major force responsible for structural stability. Halogens have been found to be proton acceptors is some halohydrins,[1,2] whereas organic fluorine hardly ever participates in hydrogen bonds.[2−4] The end applications of halohydrins, like 2-chloroethanol and enantiomerically pure halohydrins, include dye intermediates, pharmaceuticals, agrochemicals, pesticides, plasticizers, liquid crystals, and others.[5]

1,2-Difluoroethane[6−8] and 1,2-difluoropropane[9] experiences the gauche effect, i.e., the abnormal preference of gauche vicinal fluorine atoms instead of the less sterically/electrostatically hindered anti conformation in an ethane fragment. Replacement of a fluorine atom by the hydroxyl group to give 2-fluoroethanol maintains the gauche preference, which was found due to not being caused by an intramolecular hydrogen bond since the $n_F \rightarrow \sigma^*_{OH}$ interaction was not detected by natural bond orbital (NBO) analysis.[10] Nevertheless, the corresponding interaction in *trans*-2-bromocyclohexanol ($n_{Br} \rightarrow \sigma^*_{OH}$) was calculated to be ca. 1.1 kcal mol^{-1} in the diequatorial conformer.[11]

Unlike 1,2-difluoroethane, the dichloro and dibromo derivatives do not experience the gauche effect since the bulky groups repel each other, giving a repulsive contribution stronger than the attractive hyperconjugation $\sigma_{CH} \rightarrow \sigma^*_{CX}$ responsible for the gauche effect in 1,2-difluoroethane.[12] However, replacement of a single chlorine or bromine atom by the polar hydroxyl group in the 1,2-disubstituted ethane fragment gives the possibility of incorporating both the hyperconjugative nature of the gauche effect and hydrogen bond as driving forces of the conformational isomerism in these compounds. In line with this, the experimental study of 1-chloro- (**1**) and 1-bromo-2-propanol (**2**), together with theoretical calculations, can give important insights about the conformational preferences and intramolecular interactions in halohydrins. These compounds have diastereotopic hydrogens, and therefore, different chemical shifts and splitting patterns in NMR spectroscopy appear for the methylene hydrogens. A similar profile was found to be an important probe to search for the structural and conformational characterization of some haloesters[13] and other molecules.[14]

2. EXPERIMENTAL AND COMPUTATIONAL DETAILS

1-Chloro- (**1**) and 1-bromo-2-propanol (**2**) were purchased from Aldrich and used without further purification. The NMR spectra were acquired on a Varian Premium Compact spectrometer operating at 600 MHz for ^{1}H. The spectra were obtained from ca. 20 mg mL^{-1} in C_6D_6 and CD_3CN solutions in 5 mm NMR tubes.

Theoretical calculations were carried out using the Gaussian09 program.[15] The energy minima were located by scanning both the H—O—C—C and X—C—C—O (X = Cl and Br) dihedral angles at the B3LYP/6-31g(d,p) level,[16−18] in steps of 10°. Subsequent optimization (and frequency calculations to guarantee absence of imaginary frequencies for the optimized structures) at the B3LYP/aug-cc-pVDZ level[16,17,19] was performed for each minimum, as well as natural bond orbital (NBO) analysis,[20] including deletion of all Rydberg and antibonding orbitals using the NOSTAR keyword.

Table 1. Dihedral Angles (in Degrees), Conformational and Some Interaction Energies (in kcal mol^{-1} and Conformer Population in Parentheses), Chemical Shifts (in ppm, Relative to TMS), and Coupling Constants (in Hz) Calculated for 1 (X = Cl) and 2 (X = Br)

parameter	gg	ga	gg'	ag	aa	ag'	g'g	g'a	g'g'
1									
Cl–C–C–O	61.8	70.6	62.2	169.4	169.8	172.7	296.3	289.3	296.8
H–O–C–C	64.0	191.0	304.0	80.6	172.6	290.0	60.2	171.9	307.2
$E_{rel\,(gas)}$ (%)	3.17 (0)	2.73 (1)	0.00 (74)	1.87 (3)	1.98 (3)	1.75 (4)	0.99 (14)	2.97 (0)	3.13 (0)
$E_{rel\,(C6H6)}$ (%)	2.37 (1)	2.03 (2)	0.00 (68)	1.64 (4)	1.86 (3)	1.49 (5)	0.93 (14)	2.41 (1)	2.50 (1)
$E_{rel\,(CH3CN)}$ (%)	1.15 (7)	0.98 (9)	0.00 (49)	1.34 (5)	1.78 (2)	1.15 (7)	0.86 (11)	1.42 (4)	1.38 (5)
$E_{hyperc.\,(gas)}$	206.1	203.8	209.9	208.7	205.6	208.1	210.8	210.0	209.6
$n_{Cl} \rightarrow \sigma^*_{OH}$			1.59				1.45		
$\sigma_{CH} \rightarrow \sigma^*_{CO}$	4.26	4.42	4.29				4.32	4.56	4.37
$\sigma_{CH} \rightarrow \sigma^*_{CCl}$							4.76	7.33	4.77
$\sigma_{CC} \rightarrow \sigma^*_{CCl}$	3.55	3.40	3.54						
$\sigma_{CCl} \rightarrow \sigma^*_{CO}$				3.05	3.30	3.13			
$\sigma_{CO} \rightarrow \sigma^*_{CCl}$				2.16	1.98	2.14			
δ_{H1a}	2.12	2.62	2.48	3.12	3.05	2.71	2.74	3.61	2.79
δ_{H1b}	2.92	2.61	2.72	1.93	2.39	2.36	3.12	4.11	2.70
$^3J_{H2,H1a}$	8.6	8.8	9.1	6.1	6.1	6.1	1.6	2.7	1.4
$^3J_{H2,H1b}$	2.6	1.8	2.4	8.9	9.8	9.5	3.2	2.6	3.2
2									
Br–C–C–O	61.7	70.2	63.0	168.2	168.7	172.2	296.1	290.8	298.0
H–O–C–C	63.5	190.0	303.3	80.2	171.6	290.5	61.0	172.5	308.5
$E_{rel\,(gas)}$	3.11 (0)	2.68 (1)	0.00 (74)	1.81 (3)	2.07 (2)	1.69 (4)	0.98 (14)	2.94 (1)	3.04 (0)
$E_{rel\,(benzene)}$	2.31 (1)	1.99 (2)	0.00 (66)	1.57 (5)	1.94 (3)	1.42 (6)	0.91 (14)	2.35 (1)	2.41 (1)
$E_{rel\,(acetonitrile)}$	1.12 (7)	0.95 (9)	0.00 (47)	1.26 (6)	1.84 (2)	1.07 (8)	0.84 (11)	1.37 (5)	1.31 (5)
$E_{hyperc.\,(gas)}$	199.6	196.9	203.4	199.3	196.4	198.0	205.2	203.9	206.5
$n_{Br} \rightarrow \sigma^*_{OH}$			1.56				1.13		
$\sigma_{CH} \rightarrow \sigma^*_{CO}$	4.92	4.21	4.68				4.76	4.56	5.22
$\sigma_{CH} \rightarrow \sigma^*_{CBr}$							7.72	7.92	7.97
$\sigma_{CC} \rightarrow \sigma^*_{CBr}$	4.36	4.24	4.37						
$\sigma_{CBr} \rightarrow \sigma^*_{CO}$				3.62	3.42	3.66			
$\sigma_{CO} \rightarrow \sigma^*_{CBr}$				2.99	3.29	2.92			
δ_{H1a}	3.04	3.39	3.44	3.71	3.70	3.33	3.81	3.51	3.71
δ_{H1b}	3.62	3.38	3.70	2.92	3.13	3.20	4.08	4.01	3.63
$^3J_{H2,H1a}$	11.7	10.8	11.5	4.4	4.2	4.2	2.2	2.9	2.1
$^3J_{H2,H1b}$	2.7	2.0	2.5	12.2	11.5	11.8	4.0	3.2	3.7

Calculations were also performed using implicit solvents (benzene and acetonitrile) through the polarizable continuum model by Tomasi and co-workers (in its integral equation formalism[21]) and using a cavity built up with UFF (radii with spheres around each solute atom) at the same level of theory. The NMR calculations (^{1}H chemical shifts referenced to tetramethylsilane and spin−spin coupling constants) were carried out at the B3LYP/EPR-III level.[22,23] Geometries optimized at the dispersion corrected DFT WB97XD/aug-cc-pVTZ level were used for QTAIM calculations using the AIMAll program.[24]

3. RESULTS AND DISCUSSION

The conformational scanning for **1** and **2** in the gas phase gave 9 energy minima for each compound (see Supporting Information), which were subsequently optimized in the gas phase and using implicit solvent (benzene and acetonitrile) at the B3LYP/aug-cc-pVDZ level (Table 1). The energy results are consistent with further calculations performed at the MP2/6-311++g(d,p) level (see Supporting Information). The most stable forms in both compounds are similar, with X−C−C−O and H−O−C−C dihedral angles of 62.2° and 304.0° for **1**, respectively, and 63.0° and 303.3° for **2**. This indicates that, in the gas phase, the gauche conformer is prevalent, with the hydroxyl hydrogen directed toward the halogen, suggesting the appearance of the gauche effect (between the electronegative substituents) and hydrogen bond OH···X; X and CH$_3$ repel each other, because these groups are preferably antiperiplanar, i.e., *gg'* predominates over *g'g*, despite the latter being the second most stable conformation. Despite the decrease in population of the *gg'* conformer on going from the gas phase to solvents with increasing polarity (benzene and acetonitrile),

this form continues to be highly prevalent, while the conformations with *anti*-X−C−C−O dihedral angles (*ag*, *aa*, and *ag′*) are populated only by a few amounts in any medium. Halogen and oxygen with anti relationship prevents steric and electrostatic repulsion, but this orientation forces the gauche proximity between the halogen and the methyl group. Even though, the *g′g* conformer, which also exhibits such a X/CH₃ repulsive interaction, is calculated to be more stable than *ag*, *aa*, and *ag′* conformers in any medium.

The gauche preference along with the X−C−C−O fragment can be checked by analyzing the coupling constants of the diastereotopic methylene hydrogens H-1a and H-1b, which have distinct chemical shifts. According to the well-known Karplus curve, *gg*, *ga*, and *gg′* conformers are expected to exhibit large $^3J_{\text{H-1a,H-2}}$ and small $^3J_{\text{H-1b,H-2}}$ coupling constants, while *g′g*, *g′a*, and *g′g′* conformers should show small values for both couplings (Figure 1). For *ag*, *aa*, and *ag′* conformers, $^3J_{\text{H-1a,H-2}}$
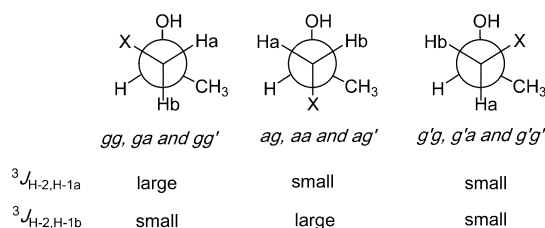

$^3J_{\text{H-2,H-1a}}$	large	small	small
$^3J_{\text{H-2,H-1b}}$	small	large	small

Figure 1. Conformations and coupling patterns expected for **1** (*X* = Cl) and **2** (*X* = Br).

should be small, and $^3J_{\text{H-1b,H-2}}$ is expected to be large. This trend is reproduced by spin−spin coupling constants calculations performed at the B3LYP/EPR-III level (Table 1). Experimentally, in benzene-*d₆* solution, H-1a (*δ* = 2.98 ppm for **1** and 2.84 ppm for **2**) shows $^3J_{\text{H-1a,H-2}}$ coupling constants of 6.4 Hz both for **1** and **2**, while the $^3J_{\text{H-1b,H-2}}$ values obtained from H-1b (*δ* = 3.00 ppm for **1** and 2.89 ppm for **2**) are 4.4 and 4.7 Hz, respectively. These findings indicate the preference for *g*(*g,a,g′*)-type conformations in benzene solution, which is extended to CD₃CN solution. In this polar solution, the $^3J_{\text{H-1a,H-2}}$ and $^3J_{\text{H-1b,H-2}}$ coupling constants were 5.8 and 4.7 Hz for **1** (H-1a at 3.46 ppm and H-1b at 3.52 ppm) and 5.9 and 4.6 Hz for **2** (H-1a at 3.37 ppm and H-1b at 3.42 ppm). It is worth mentioning that the decay in $^3J_{\text{H-1a,H-2}}$ on going from benzene to acetonitrile solution is consistent with calculations, in which the population of *gg′* was calculated to decrease from 68% (**1**) and 66% (**2**) in benzene solution to 49% (**1**) and 47% (**2**) in acetonitrile solution. In addition, H-1a is calculated to be more shielded than H-1b in the most stable conformers of **1** and **2** (Table 1), in agreement with the experiment. Thus, the gauche effect in **1** and **2** was confirmed by NMR since the X−C−C−O fragment is preferred to be in gauche arrangement rather than in the expected less sterically hindered anti conformation. The absence of self-association (intermolecular hydrogen bond) for **1** and **2** in the NMR solutions was probed using infrared spectroscopy (Supporting Information), in which the broad ν_{OH} in the neat liquid is quite different from the sharp signal at higher wavenumber obtained in cyclohexane solution at a concentration similar to that used in the NMR experiments, ca. 0.1 mol L⁻¹.

Despite the well-known gauche effect in some 2-substituted fluoroethanes (substituents = polar groups), the behavior found for **1** and **2** is surprising because chlorine and bromine atoms are bulkier than fluorine, and consequently, steric hindrance

would be expected to predominate over the gauche effect, like in 1,2-dichloro- and 1,2-dibromoethane.[12] NOESY experiments can give insights about the conformation and also about the relative distance between the halogen and the hydroxyl group, which is related to the steric hindrance between them, despite the already confirmed gauche effect. In addition, the NOESY confirms the correct assignment of H-1a (more shielded) and H-1b (less shielded). For **1** in CDCl₃, both signals in 3.99 (CH) and 1.27 ppm (CH₃) exhibit stronger dipolar interaction with the methylene hydrogen at 3.57 ppm than with the one at 3.45 ppm. Similar behavior is found for **2**, indicating the conformations of Figure 2, in which halogens and the hydroxyl
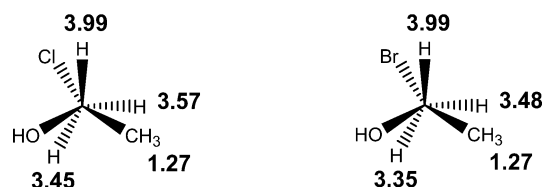

Figure 2. Qualitative orientations between hydrogens (chemical shifts are depicted in ppm, relative to TMS) obtained from NOESY experiments for **1** and **2**, in CDCl₃ solution.

group are apart from one another with a dihedral angle larger than 60° (which should be a perfect staggered arrangement), due to steric effect.

The overall energy of each conformer can be decomposed into Lewis (steric and electrostatic effects) and non-Lewis-type (hyperconjugation) interactions, according to the natural bond orbital (NBO) approach ($E_{\text{full}} = E_{\text{L}} + E_{\text{NL}}$). The most stable conformers *gg′* and especially *g′g* (in which X/CH₃ gauche repulsion takes place) are not expected to be favored by steric relief when compared to other conformers, particularly those with the X−C−C−O fragment in the anti orientation (in which the bulky O and X atoms are far from each other, despite X and CH₃ being gauche). However, *gg′* and *g′g* are substantially stabilized by hyperconjugation (Table 1), and therefore, electronic transfers from electron donors to empty orbitals are responsible for the gauche effect in **1** and **2**. Table 1 shows that important contributions for hyperconjugation are the antiperiplanar with σ_{CH} and σ_{CC} orbitals as good electron donors and σ^*_{CO} and $\sigma^*_{\text{C−Cl/Br}}$ as low-lying electron acceptor orbitals, favoring the *g*(*g,g′*,*a*)-type conformations. The $\sigma_{\text{C−Cl/Br}}$ orbital is known as a good electron donor in hyperconjugative interactions, but σ_{CO} is not, and therefore, the interactions mentioned above override those present in *a*(*g,g′*,*a*)-type conformations.

Conformations with X−C−C−O in gauche arrangement correspond to more than 80% in population, but only *gg′* and *g′g* are responsible for almost all of this amount. These conformations have the hydroxyl hydrogen directed toward the halogen, suggesting the presence of X···HO hydrogen bond, but also the oxygen and halogen electron lone pairs tend to apart from each other to avoid repulsion. In order to find out whether *gg′* and *g′g* are strongly prevalent because of the hydrogen bond or X/O electron lone pairs repulsion in the other gauche conformations, the quantum nature of the hydrogen bond ($n_{\text{X}} \rightarrow \sigma^*_{\text{OH}}$ interaction) was analyzed by NBO, and the electronic density along with the X···HO path was evaluated using QTAIM analysis. Intra- and intermolecular hydrogen bonds between X and OH have already been found in *trans*-2-halocyclohexanols;[2,11] the $n_{\text{X}} \rightarrow \sigma^*_{\text{OH}}$ interaction was

calculated to be 1.6 and 1.4 kcal mol^{-1} in **1**, and 1.6 and 1.1 kcal mol^{-1} in **2**. Despite this stabilizing electronic transfer, the σ_{OH} orbital is also directed toward the lone pairs in X, and therefore, the hydrogen bond (an attractive interaction) will be effective only if $n_X \rightarrow \sigma^*_{OH}$ overrides the four-electron/two-orbital n_X/σ_{OH} interaction.

In order to better search the presence of intramolecular hydrogen bond in **1** and **2**, QTAIM was used to analyze topological parameters along with the X···HO path. The QTAIM theory has shown to be useful in describing hydrogen bonds very accurately, using electronic density (ρ, that should fall within 0.002 atomic units (au) and 0.04 au) and its Laplacian ($\nabla^2\rho$, that should fall within 0.024 au and 0.139 au) to characterize bond paths between H-bound atoms.[25] According to QTAIM, the hydrogen bond in **1** and **2** could not be characterized in the gas phase, despite different conclusions obtained for chiral chloropropanols using microwave spectroscopy.[26] The bond path between X and H(O) was not found, while the Popelier's criteria[25] applied over the hydrogen atoms H(O) in the gg' and $g'g$ conformations, used to give insight about bond stability, did not significantly differentiate from the anti-type conformations (see Supporting Information). According to these criteria, the H atom involved in the H-bond should have loss of electronic charge [$q(H)$], increased atomic energy [$E(H)$], decreased first atomic dipole moment [$M_1(H)$], and decreased atomic volume [$V(H)$] in comparison to an H atom not involved in a hydrogen bond. In polar solution, any weak contribution from intramolecular hydrogen bond would be expected to disappear or, at least, be strongly reduced because of solvent influence.[27] Accordingly, the preferred orientation of the hydroxyl group in X–C–C–O gauche conformations can be attributed predominantly to lone pair repulsion in gg, ga, $g'g'$, and $g'a$ rather than the hydrogen bond in gg' and $g'g$.

4. CONCLUSIONS

1-Chloro- and 1-bromo-2-propanol experience the gauche effect, whose origin was found to be due to hyperconjugation rather than hydrogen bonding. Because the hydrogen bond has been involved in most biochemical processes and conformation plays a key role in ligand−enzyme interaction, these findings can be useful when designing performance analogues for use as pharmaceutical and/or agrochemical bioactives.

◼ ASSOCIATED CONTENT

Ⓢ Supporting Information
NMR spectra, QTAIM data, 3D potential energy surfaces, and three-dimensional conformer structures for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

◼ AUTHOR INFORMATION

Corresponding Author
*(M.P.F.) E-mail: matheus@dqi.ufla.br. Tel: +55 35 3829-1891. Fax: +55 35 3829-1271.

Notes
The authors declare no competing financial interest.

◼ ACKNOWLEDGMENTS

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