

Acidities in Cyclohexanediols Enhanced by Intramolecular Hydrogen Bonds

Xin Chen, David A. Walthall, and John I. Brauman*

Contribution from the Department of Chemistry, Stanford University,
Stanford, California 94305-5080

Received January 13, 2004; E-mail: brauman@stanford.edu

Abstract: Equilibrium gas-phase acidities of the six isomeric cyclohexanediols were measured in a Fourier transform ion cyclotron resonance mass spectrometer. Although all six cyclohexanediols have the same functional groups and similar structures, the acidities vary over 11 kcal/mol. This large difference is due mostly to the balance between hydrogen bonding and geometric strain. To understand the origins of the acidity differences in more detail, the conformations and energetics of the cyclohexanediols were studied using density functional theory, which gave good agreement with the experimental acidities. Finally, methanol–methoxide and methanol–methanol interactions were used as a model for the hydrogen bonding.

Introduction

Interactions between functional groups are often classified as dipole–dipole interactions, dipole–induced dipole interactions, van der Waals interactions, and hydrogen bonding. Although these interactions are usually weaker than classical chemical bonds, they play an important and often dominant role in chemical and physical properties in both intramolecular and intermolecular interactions. For example, hydrogen bonds between water molecules result in the unusually high boiling point and viscosity of liquid water. Protein folding can also be regarded as a result of intramolecular and intermolecular interactions.

The simplest model to study intramolecular interactions between two functional groups is difunctional compounds. In solution, direct interactions are often masked by interactions between functional groups and solvent molecules, which often have functional groups as well. For this reason, the gas phase is a good environment to study the interactions, since solvent effects are eliminated. Many difunctional compounds have been studied in the gas phase, including diamines,¹ diethers,² diketones,² dithiols,³ alkanediols,⁴ and dicarboxylic acids.⁵ Most of them were α,ω -difunctionalized alkanes, which have a flexible carbon chain between two ending functional groups. As the chain increases in length, the distance and relative orientation between the functional groups changes, which changes the interactions. Since the backbone is flexible, the conformations or conformational distributions of the compounds are ruled largely by the interactions between the two end groups. For

example, in doubly protonated diammonium ions, the only stable conformation is believed to be fully extended. This conformation minimizes the Coulombic repulsion. By contrast, in monocationic diamines and anionic alkanediols, the strong hydrogen bonds force ring structures. These large conformational changes often cause large changes in the entropy, which can make interpretation of the measured acidities more difficult. Houriet and co-workers adopted another strategy.⁶ Seven conformationally stable β -amino alcohols were synthesized. In each of these molecules, the N–C–O dihedral angle was fixed using multiple ring systems. The range of dihedral angles in these molecules was from 0° to 180°. The gas-phase basicity measurements revealed the angular dependence of the interaction between the amino group and the hydroxyl group on vicinal carbons.

It is also possible to place the difunctional groups onto a ring of fixed size. Both the constitutional and geometric positions of the functional groups on the ring will change the interactions of these groups, which can lead to interesting differences among these molecules. Another advantage of this method is that the polarizabilities are nearly the same for all of the species. For many systems, gas-phase energetic properties, including acidities, basicities, and electron affinities, correlate strongly with the polarizability, or size, of the molecule. This makes comparisons between systems of different sizes much more difficult. Difunctionalized ring structure compounds which differ only in the positions of the functional groups, such as the six cyclohexanediols, have exactly same chemical formulas and functional groups. They also have the same polarizabilities, as estimated by group additivity.⁷ For the α,ω -difunctionalized alkanes, the polarizability increases each time a methylene unit is added, and similar problems can make the analysis of multiple ring systems difficult.

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Cyclohexane is a good choice for the fixed-size ring system. Because it is well studied and relatively unstrained, the effects of substituents on the thermochemistry of the species can be easily assessed. Many of the monofunctionalized cyclohexanes and difunctionalized alkanes have been systematically studied, which makes comparison to difunctionalized cyclohexanes easier. In addition, the cyclohexane skeleton can distort, which can lead to competition between intramolecular hydrogen bonding and the strain of distorting the skeleton. Cyclohexanediol is one of the simplest examples of a difunctionalized cyclohexane. This system of molecules is interesting in part because of the stereochemistry involved. The geometric orientation of hydroxyl groups, either axial or equatorial, will result in different chemical properties. Their relative positions on the ring, and whether they are *cis* or *trans*, will change the ability of the molecules to form intramolecular hydrogen bonds. In addition, hydroxyl groups on a six-membered rings are common structures in nature, such as sugars, and have been subjects of many studies. For example, Abraham studied the conformation of *cis*-1,3-cyclohexanediol in various solutions as a model for glucose and galactose.⁸

In this work, we have measured the gas-phase acidities of the cyclohexanediols in a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer. This system is especially informative because of the large difference in acidity and hydrogen bonding between compounds that appear so similar. We also used density functional theory calculations to study the hydrogen bonding and other factors contributing to their acidities. These results were compared to those obtained with linear diols and methylcyclohexanols. The hydrogen bonds formed were modeled using free methanol–methoxide and methanol–methanol interactions.

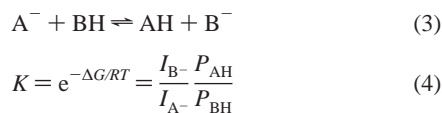
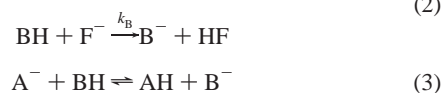
Experimental Section

Instrumentation and Reagents. All experiments were carried out in a Fourier transform ion cyclotron resonance mass spectrometer consisting of an inlet system, a vacuum system, and a 2.54 cm cubic trapped-ion analyzer cell placed between the poles of an electromagnet operated at 0.60 T. The duty cycle and the data collection were controlled by IonSpec FTMS software and electronics. Unwanted ions were ejected from the cell by excitation at the ion's natural ICR frequency. Rough pressures were measured with a Duniway T-100-K vacuum ion gauge. The background pressure was roughly 2×10^{-9} Torr, and during experiments the total pressure was about 6×10^{-7} Torr. The technique to obtain accurate pressure measurement of the neutral reagents is described in detail later.

Nitrogen trifluoride (NF₃) was purchased from Ozark-Mahoning. *cis*-1,2-Cyclohexanediol and *trans*-1,2-cyclohexanediol were purchased individually from Aldrich, with purities of 99% and 98%, respectively. Both 1,3-cyclohexanediol and 1,4-cyclohexanediol were purchased as a mixture of *cis* and *trans*, with purities of 98% and 99%, respectively. The diols were separated using a slight modification of the literature procedure.^{9,10} The purity of the diols was determined by NMR to be >99% for the three of the species, and 95% for the *trans*-1,4-

cyclohexanediol species, which contained about 5% of *cis*-1,4-cyclohexanediol. All reagents used in the ICR machine were purified by multiple freeze–pump–thaw cycles.

Equilibrium Experiments. The gas-phase acidities were measured by the ion equilibrium method. Fluoride anions (F[−]) were generated by dissociative electron capture by NF₃ (eq 1), and then were allowed to deprotonate both the diol and the reference acid (eq 2). An equilibrium was established between the anions when their ratio remained constant (eq 3). The equilibrium constant was calculated using eq 4, where *P* is the pressure of the neutral gas and *I* is the ion intensity. To ensure that equilibrium had been reached, one of the anions was ejected and the system allowed to re-equilibrate. The values obtained for the anion ratio after ejection of either anion were essentially the same as the original ratio, so we are confident that the steady-state ratio that we measured is the true equilibrium ratio. The experiments were repeated on multiple days, each day using multiple pressures, and the equilibrium constants obtained were within 10% of each other.



$$K = e^{-\Delta G/RT} = \frac{I_{\text{B}^-} P_{\text{AH}}}{I_{\text{A}^-} P_{\text{BH}}} \quad (4)$$

The presence of the more acidic *cis*-1,4-cyclohexanediol in *trans*-1,4-cyclohexanediol introduces some additional uncertainty into the acidity measurement of *trans*-1,4-cyclohexanediol. The value that we measured for the acidity of *trans*-1,4-cyclohexanediol is formally a lower limit to the value of $\Delta G^\circ_{\text{acid}}$. Thus, *trans*-1,4-cyclohexanediol is at least 0.3 kcal/mol less acidic than benzyl alcohol. Although the uncertainty in this acidity is larger than for those of the other diols, changes to the acidity of this compound would not alter any of our arguments since it is the least acidic of the cyclohexanediols.

However, we believe that we have measured the actual acidity of *trans*-1,4-cyclohexanediol for several reasons. As long as the vapor pressure of *cis*-1,4-cyclohexanediol is relatively low compared to the pressure of *trans*-1,4-cyclohexanediol and the time of the experiment is short, kinetic simulations indicate that the value that we measured for the ratio of ion intensities will be close to the equilibrium value. The fact that we were able to obtain nearly the same value for the ratio of ion intensities, independent of which anion was ejected, indicates that the ratio which we measured was very close to the equilibrium ratio. We believe that the relative vapor pressures of the *cis* and *trans* diols in the sample are proportional to their concentrations. Finally, the measured acidity of *trans*-1,4-cyclohexanediol is close to the acidity of *trans*-1,3-cyclohexanediol and about 3 kcal/mol more acidic than that of methylcyclohexanols, both of which are consistent with our expectations. The measured acidity of *trans*-4-methylcyclohexanol of 366.2 kcal/mol¹¹ provides a reasonable upper limit to the value of $\Delta G^\circ_{\text{acid}}$ for *trans*-1,4-cyclohexanediol.

We measured the acidities of each of the cyclohexanediols against various reference acids, rather than in a direct comparison, which would have required labeled compounds. This had the additional advantage of giving equilibrium constants closer to unity, thus increasing the precision of the measurements. The reference acids used were chosen to have acidities similar to those of the diols and fast proton transfer to ensure a rapid establishment of the equilibrium. The diol anions tend to form complexes with the neutral diols, even at the lowest pressure of diols that we used. This process is pressure dependent, and

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(10) The 1,3-cyclohexanediol mixture was dibenzoated and separated on a silica gel column with a pentane and ether mixture used as the eluent. The benzyl groups were cleaved using a K₂CO₃/MeOH mixture. The resulting diols were purified on a silica gel column. The 1,4-cyclohexanediol mixture was diacetated and separated on a silica gel column using a pentane and ether mixture as the eluent. The resulting diacetated species were treated with K₂CO₃/MeOH to cleave the acetates and purified on a silica gel column.

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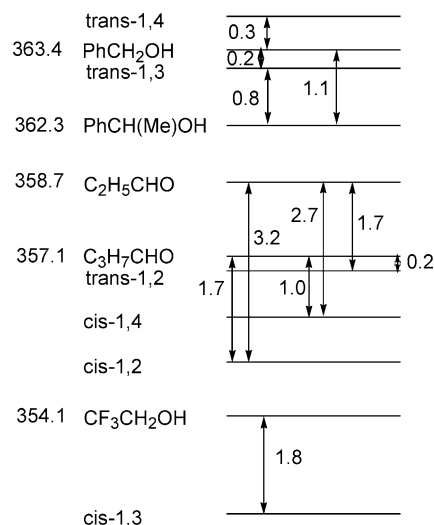


Figure 1. Acidity ladder for the cyclohexanediols. Values are given in kcal/mol.

we were able to adjust the pressure so that the dimer accounted for less than 20% of the total anion intensity. Because the reaction forming the dimer was slow compared to the reactions between the diol and the reference acid, the ratio of ion intensities measured is close to the equilibrium value for the ratio, and no correction was necessary. This introduces an error of up to 0.15 kcal/mol. Whenever possible, the relative acidities of the reference acids were checked against each other. Unfortunately, the proton-transfer reaction between butyraldehyde and propionaldehyde was too slow to allow an equilibrium to be established.¹² The acidities of all of the reference acids were originally measured in a single work^{13,14} except for butyraldehyde and 1-phenylethanol. To maintain the internal consistency of the acidity ladder, we were required to assign a value to butyraldehyde that is 0.5 kcal/mol more acidic than the value reported by a previous study done in this laboratory,¹⁵ and was determined by anchoring it to propionaldehyde. Similarly, the acidity measured for 1-phenylethanol in this work is 1.1 kcal/mol more acidic than the literature value,¹⁶ and was determined by anchoring it to benzyl alcohol. The previous value for 1-phenylethanol was measured by a kinetic method. Using several reference acids, we were able to make an acidity ladder (Figure 1) comparing the diols' acidities. The internal consistency of the measurements was quite good; there was less than 0.2 kcal/mol relative error. The three parts of the acidity ladder are tied together in the work by Bartmess, Scott, and McIver.¹³ Although there is some additional uncertainty in comparing diols that are in different sections of the acidity ladder, they are far enough apart that the relative order and analysis would not change.

The ion equilibrium method requires accurate relative pressure measurements to obtain accurate relative acidities. In our laboratory, the absolute neutral pressures are usually measured by an ion gauge and calibrated against a Baratron at higher pressures. Unfortunately, cyclohexanediols did not have sufficient vapor pressure to allow us to use the Baratron. Instead, we used a kinetic method to estimate the relative ratio of the neutral pressures. In a typical experiment, F^- was allowed to react with two different acids, AH and BH, which were either a cyclohexanediol and a reference acid, or two reference acids

(eq 2). The relative ratios of the anions formed were proportional to the ratio of the pressures (eq 5). At short times, the contribution from

$$\frac{[A^-]}{[B^-]} = \frac{k_A [AH]}{k_B [BH]} \quad (5)$$

eq 3 is not significant compared to the contribution from eq 2, so the ratio between the two ions is just the ratio in eq 5. From this expression, the relative neutral pressures can be obtained if we know k_A and k_B . We assumed that the reaction efficiencies were very close to each other for the diols and the reference acids. Because the reactions are highly exothermic, we estimated the reaction efficiencies to be unity. Therefore, k_A and k_B are just the collision rates, which can be estimated by the Su-Chesnavich model.¹⁷ This model requires the dipole moments of the diols, which are not experimentally available, so the dipole moments were calculated by DFT. Because the dipole moments of the cyclohexanediols are slightly different for the different conformations, the Su-Chesnavich collision rate will also change. We believe that the absolute error in the pressures measured in this way is less than 30%, and since two pressure measurements are needed for one equilibrium constant, the error can be as large as 0.5 kcal/mol. However, the relative error in the pressure measurements between the diols and the reference acids should be smaller, and the relative error between two cyclohexanediols should be even smaller. We therefore estimate the uncertainty from the pressure measurements to be 0.3 kcal/mol.

Computation. All calculations were performed using Gaussian 98.¹⁸ Optimized geometries, and the energies given in Tables 1 and 2, were calculated at the B3LYP/6-311+G(d,p) level of theory. Tests showed that this is the minimal basis set to converge the acidities of alcohols and diols. The agreement between experimental and calculated acidities does not improve with more diffuse or polarized functions. Differences in acidities between alcohols (or/and diols) are almost independent of basis set. Zero-point energy and thermal corrections were calculated at the 6-31+G(d,p) level, and vibrational frequencies were unscaled.

Results

By establishing an equilibrium between the anions and neutrals for both a cyclohexanediol and a reference acid, the relative acidity was established. Combining these relative acidities allowed us to create an acidity ladder (Figure 1). Experimental acidities of the cyclohexanediols were extracted from this ladder using a least-squares fitting algorithm, and are given in Table 1.

Most calculations were performed using Gaussian 98 at the B3LYP/6-311+G(d,p) level of theory.¹⁸ Computation results are given in Table 1. The hydroxyl groups in the cyclohexanediols can be either axial or equatorial. The conformation of the whole molecule was the chair conformation, except for *cis*-1,4-cyclohexanediol anion, which was a twist-boat. The most stable conformations of each species are listed in the table. The different rotational isomers of the hydroxyl groups gave slightly different energies and dipoles, but only the properties of the most stable rotational conformation are listed. The calculated

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Table 1. Cyclohexanediol Acidities^a

cyclohexanediol		$\Delta H^{\circ}_{\text{calc}}{}^{b,c}$		$\Delta G^{\circ}_{\text{acid,calc}}{}^b$	$\Delta\Delta G^{\circ}_{\text{acid,calc}}{}^{b,c}$	$\Delta G^{\circ}_{\text{acid,exp}}$	$\Delta\Delta G^{\circ}_{\text{acid,exp}}{}^c$
		neutral	anion				
<i>trans</i> -1,2	ee	-1.7	3.0	355.5	3.8	357.0	4.7
<i>cis</i> -1,2	ea	-0.8	2.3 ^d	354.0	2.3	355.5	3.2
			2.8 ^e				
<i>trans</i> -1,3	ea	1.5	12.0 ^d	360.0	8.3	363.2	10.9
			10.9 ^e				
<i>cis</i> -1,3	aa	-0.8	0	351.7	0	352.3	0
	ee		11.1				
<i>trans</i> -1,4	aa	0.5	11.7	362.5	10.8	363.7	11.4
	ee		12.3				
<i>cis</i> -1,4	twist-boat	4.5	4.3	355.0	3.3	356.1	3.8
	chair		12.0				

^a All ΔH° and ΔG° values are in kcal/mol. All calculations were done at the B3LYP/6-311+G(d,p) level. ^b After ZPE and thermal correction with unscaled frequencies. Only the most stable conformations were considered. For example, $\Delta G^{\circ}_{\text{acid,calc}}$ for *cis*-1,4-cyclohexanediol is the energy difference between neutral chair and anion boat. ^c Values are relative to *cis*-1,3-cyclohexanediol. ^d The deprotonated alcohol is axial. ^e The deprotonated alcohol is equatorial.

Table 2. Methanol–Methoxide Model Calculations^a

model geometry ^b	$\Delta E_{\text{acid}}{}^c$	$\Delta\Delta E_{\text{acid}}{}^d$	$\Delta E_{\text{complex,mm}}{}^e$	$\Delta E_{\text{complex,mm}}{}^f$	$\Delta\Delta E_{\text{complex}}{}^g$	group
<i>trans</i> -1,2 ee	370.7	-17.8	-1.2	-17.8	-16.6	II
<i>cis</i> -1,2 ea	369.2	-19.3	-2.3	-18.4	-16.1	II
<i>trans</i> -1,3 ea	376.6	-11.9	-0.9	-6.9	-6.0	III
<i>cis</i> -1,3 aa	367.2	-21.3	-4.9	-24.9	-20.0	I
<i>trans</i> -1,4 aa	377.8	-10.7	-0.3	-8.1	-7.8	III
<i>trans</i> -1,4 ee	378.9	-9.6	-0.2	-4.1	-3.8	III
<i>cis</i> -1,4 twist-boat	366.6	-21.9	-4.9	-25.7	-20.8	I
<i>cis</i> -1,4 chair	377.8	-10.7	-0.4	-6.6	-6.2	III
1,2-ethanediol	372.0	-16.5	-1.9	-19.0	-17.1	II
1,3-propanediol	368.6	-19.8	-4.7	-24.9	-20.2	I
1,4-butanediol	365.0	-23.5	-5.2	-26.8	-21.6	I
1,5-pentanediol	365.4	-23.1	-5.4	-26.3	-20.9	I
methanol dimer	367.4	-21.1	-5.8	-26.9	-21.1	I

^a All values are in kcal/mol, and are calculated by B3LYP/6-311+G(d,p) without ZPE correction. ^b This model geometry is the functional site geometry, as discussed in the text. ^c These acidities are calculated with the same equatorial/axial configuration for the neutral and anion species. ^d Calculated acidities relative to methanol (388.5 kcal/mol, calculated using same method). ^e Complexation energy of the model methanol–methanol complex. See text for details. The values given are relative to two separated methanols. ^f Complexation energy model methanol–methoxide complex. See text for details. The values given are relative to a separated methanol and methoxide. ^g Difference between $\Delta E_{\text{complex,mm}}$ and $\Delta E_{\text{complex,mm}}$.

acidities¹⁹ were taken as the difference between the most stable conformations of the neutral and the anion. B3LYP/6-311+G(d,p) slightly overestimates the acidities of simple alcohols. The same is true for diols, as can be seen in Table 1. However, good agreement was achieved between relative experimental acidities and the relative values from calculation. The relative differences between the calculated and experimental acidities are less than 1 kcal/mol for five of the six diols, and 2.6 kcal/mol for *trans*-1,3-cyclohexanediol.

Both the anions of the diols and the anions of the reference compounds form very stable complexes with the neutral diols. The attempt to experimentally measure the complexation energy ($\Delta H_{\text{complex}}$) failed because the complex is favored even under the lowest diol pressure that we could use. Therefore, only the lower limit of the complexation energies can be estimated. $\Delta H_{\text{complex}}$ must be larger than 30 kcal/mol to compensate for the entropy loss upon formation. This is greater than the methanol–methoxide complexation energy of about 27 kcal/

mol.^{20–24} A DFT calculation performed on the *trans*-1,2-cyclohexanediol dimer anion shows that it adopts a chelate geometry and predicts 33 kcal/mol of the complexation energy.

Discussion

Unlike in solution, the acidities in the gas phase correlate strongly with the polarizabilities. Under some circumstances, the polarizability, or size, of the system can be even more important than the detailed structure. For example, larger simple alcohols have significantly higher acidities than smaller ones, while small differences are observed among alcohols with same sizes but different structures. Introducing a second functional group often emphasizes the importance of structure. The interactions between the two functional groups usually dominate over the polarizability. One of the common types of interactions is hydrogen bonding. It is well known that hydrogen bonding can significantly affect acidities and basicities. Crowder and Bartmess have studied α,ω -alkane diols of varying lengths.⁴ The diols are more acidic than the corresponding 1-alkanol with a similar mass. Mautner analyzed the thermochemistry of

(19) The entropies used in calculating ΔG° were used without any corrections. In general, the entropies calculated for each species were very similar. The neutral entropies are slightly larger than the entropies of the anion. The species that have intramolecular hydrogen bonds have only slightly lower entropies because they lose a hydroxyl group rotation. Some of the species have multiple populated conformations, such as diaxial and diequatorial *trans*-1,3-cyclohexanediol. This will contribute to the acidity by increasing the entropy ($1 + \exp(\Delta\Delta G_{\text{acid}}/RT)$). However, all of these corrections should be small, and we believe that the entropies do not contribute significantly to the relative acidities of the cyclohexanediols.

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intramolecular hydrogen bonds in several protonated difunctional groups in terms of bond-weakening factors, entropy changes, and thermal stabilities.²⁵ The bond-weakening factor that Mautner used to describe the molecules is a measure of how much the molecular structure stretches and bends the hydrogen bond. Houriet suggested that the hydrogen bonding is essential in ion–dipole and ion–induced dipole interactions for the β -amino alcohols he studied.⁶ Strong interactions between difunctional groups not only directly change the acidities, but also affect the polarizability dependence of the acidities. For α,ω -alkanediols, the acidity is almost constant when the number of methylenes between the hydroxyl groups is larger than two. This is a deviation from the general trend that increased mass gives rise to increased acidity because of the larger polarizability. 1,5-Pentanediol was even found to be slightly less acidic than 1,4-butanediol. This may be because the eight-membered ring required to form an intramolecular hydrogen bond for pentanediol has measurably more strain. DFT calculations also support this, as shown in Table 2. It appears that the polarizability effect of a substituent on acidity is stronger for a free anion than for a hydrogen-bonded anion, and that the hydrogen-bonding and polarizability effects are not additive.

To analyze the acidities of the cyclohexanediols, we need to first understand the acidities of axial and equatorial hydroxyl groups. Cooks and co-workers, in a study of the acidities of methylcyclohexanols, observed that axial hydroxyl groups are more acidic than equatorial hydroxyl groups.¹¹ Both *cis*-2- and *cis*-4-methylcyclohexanols are each about 1 kcal/mol more acidic than their corresponding *trans* configurations. In both cases, the *cis* configuration has an axial hydroxyl group while the *trans* configuration has an equatorial one. Our DFT calculations on cyclohexanols support their conclusion. Neutral equatorial cyclohexanol is calculated to be about 1.6 kcal/mol more stable than axial cyclohexanol. For the anions, the energy difference is only about 0.1 kcal/mol, with equatorial more stable. This gives an acidity difference of 1.5 kcal/mol, which agrees well with both experiments.

Polarizabilities for all six cyclohexanediols are essentially same, so the structural differences are what cause the large acidity differences. From Table 1, we can see that the dominant factor in determining the acidity is whether the two alcohols are *cis* versus *trans* rather than their position on the ring. The balance between hydrogen bonding and geometric strain is major subject of this work. Depending on the strength of the hydrogen bonding and geometric strain, the cyclohexanediols are categorized into four groups and discussed below.

***cis*-1,2-Cyclohexanediol and *trans*-1,2-Cyclohexanediol.** Unlike butane, 1,2-ethanediol (ethylene glycol) favors a *gauche* conformation instead of an *anti* conformation because only the *gauche* conformation allows hydrogen bonding between the two vicinal hydroxyl groups. Both *cis*- and *trans*-1,2-cyclohexanediols are structurally similar to 1,2-ethanediol, ignoring the four carbons not directly bonded to hydroxyl groups, and they both adopt *gauche* conformations. For *cis*-1,2-cyclohexanediol (Figure 2), the *anti* conformation is impossible because of the ring structure. In *trans*-1,2-cyclohexanediol (Figure 3), the *anti* conformation is physically possible, but would require the hydroxyl groups to be diaxial, which is less stable than diequatorial. Both the anion and neutral of the two cyclohex-

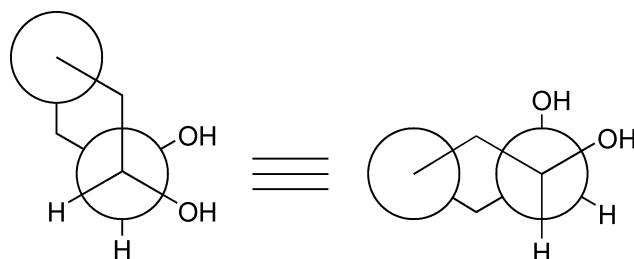


Figure 2. Conformation of neutral *cis*-1,2-cyclohexanediol.

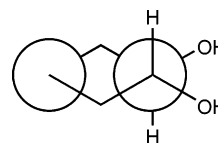


Figure 3. Conformation of neutral *trans*-1,2-cyclohexanediol.

anediols have hydrogen bonds, and this is energetically more important for the anion.

Both *cis*- and *trans*-1,2-cyclohexanediols are more acidic than 1,2-ethanediol because of the increased polarizability of the cyclohexanediols. Table 1 shows that *cis*-1,2-cyclohexanediol is more acidic than *trans*-1,2-cyclohexanediol by about 1.5 kcal/mol. *cis*-1,2-Cyclohexanediol has one hydroxyl group axial and the other equatorial (Figure 2), while the stable conformation of *trans*-1,2-cyclohexanediol has both alcohols diequatorial (Figure 3). DFT calculations also show that, for the diol, the *cis* anion has the negatively charged oxygen axial while the equatorial hydroxyl group remains protonated. The *cis* equatorial anion is about 0.5 kcal/mol less stable than the *cis* axial anion. In the *trans* anion species, both the protonated and the deprotonated hydroxyl groups are equatorial. Just like *cis*- and *trans*-2-methylcyclohexanol, the *cis* isomer is more acidic than the *trans* isomer in *cis*- and *trans*-1,2-cyclohexanediol.

***trans*-1,3-Cyclohexanediol and *trans*-1,4-Cyclohexanediol.** For the anion and neutral of *trans*-1,3- and *trans*-1,4-cyclohexanediol, it is impossible to form an intramolecular hydrogen bond. However, both neutrals are more acidic than the methylcyclohexanols. The second hydroxyl group in the diols increases the acidity by ion–dipole interactions. In addition, *trans*-1,3-cyclohexanediol is more acidic than *trans*-1,4-cyclohexanediol by about 0.5 kcal/mol, possibly because the dipole is closer to the anion. According to DFT calculations, the diequatorial conformation of the *trans*-1,4-cyclohexanediol is more stable than the diaxial conformation. In the anion, the ordering is reversed, with the diaxial more stable by about 0.6 kcal/mol. This result contradicts the observation that substituents are more stable when they are equatorial rather than axial. However, ion–dipole interactions are stronger when they are closer, and the ion–dipole stabilization in the diaxial conformation is larger than the destabilization from steric repulsions. Other disubstituted cyclohexanes show a similar preference for the diaxial conformation. Wiberg and co-workers studied *trans*-1,4-dichloro-, *trans*-1,4-dibromo-, *trans*-1,2-dichloro-, and *trans*-1,2-dibromocyclohexanes theoretically and experimentally.^{26,27} For all of these species, the diaxial conformation is favored over the diequatorial conformation. Their findings suggested that the stabilization of the diaxial conformation is electrostatic. A

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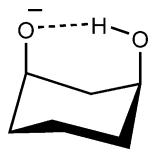


Figure 4. Conformation of *cis*-1,3-cyclohexanediol anion.

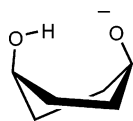


Figure 5. Structure of *cis*-1,4-cyclohexanediol anion.

similar argument can be used to explain the fact that the calculations show that *trans*-1,3-cyclohexanediol anion has the alkoxide group equatorial rather than axial. In this case, the local dipole of the OH group has a stabilizing interaction with the alkoxide anion. Unfortunately, we cannot experimentally determine the conformations of the cyclohexanediols in the gas phase, so our result is purely calculational. The ordering is expected to be reversed in solvents with high dielectric constants.

***cis*-1,3-Cyclohexanediol.** *cis*-1,3-Cyclohexanediol is 10.9 kcal/mol more acidic than *trans*-1,3-cyclohexanediol. To give this result, the anion of the species must be forming a hydrogen bond (Figure 4). To form this intramolecular hydrogen bond, the anion must have both hydroxyl groups diaxial. This means that the hydrogen bond in *cis*-1,3-cyclohexanediol anion is at least strong enough to overcome the strain energy required to put both hydroxyl groups axial. The diaxial and diequatorial conformations in the neutral species are relatively close in energy, so it is not immediately clear which conformation is dominant. A solution NMR study of this molecule showed that the diequatorial conformation is more stable.⁸ The energy difference between diequatorial and diaxial ranges between 0.1 and 2.7 kcal/mol in favor of diequatorial, depending on the solvent used. Extrapolation to the gas phase gives an energy difference of 0–0.7 kcal/mol in favor of diaxial, depending on the solvation model used. In addition, DFT calculations predict that diaxial is more stable by about 0.8 kcal/mol, which agrees with the calculations done by Guler.²⁸ We believe that, in the gas phase, the diaxial conformation is more stable for the neutral *cis*-1,3-cyclohexanediol, although the diequatorial conformation may also contribute.

***cis*-1,4-Cyclohexanediol.** *cis*-1,4-Cyclohexanediol is 7.6 kcal/mol more acidic than the *trans* isomer. Analogous to the *cis*-1,3-cyclohexanediol case, this can only be the result of an intramolecular hydrogen bond in the anion species. However, to form an intramolecular hydrogen bond, the cyclohexane skeleton must be in the boat or twist-boat conformation, and our calculations show that it is a twist-boat conformation (Figure 5). For unsubstituted cyclohexane, the twist-boat conformation is less stable than the chair conformation by 5.5 kcal/mol. Strain energy calculations were performed by comparing the energy difference between the cyclohexane skeleton of *cis*-1,4-cyclohexanediol and the most stable conformation of cyclohexane. These calculations show that the cyclohexane skeleton of the *cis*-1,4-cyclohexanediol anion has about 7 kcal/mol of strain energy, which the hydrogen bonding in this anion overcomes. In the case of the neutral species, the intramolecular hydrogen

bond that could be formed in the twist-boat conformation is much less stabilizing. Our DFT calculations show that the chair is more stable by 4.1 kcal/mol.

Houriet et al. used the proton-bound dimer kinetic method to study the acidity of *cis*- and *trans*-1,4-cyclohexanediols.²⁹ They found only a 1.2 kcal/mol difference, whereas we find a 7.6 kcal/mol difference. In this case, the kinetic acidities are significantly different from the thermodynamic acidities. Crowder and Bartmess noticed a similar result when they compared their equilibrium acidities of alkanediols to the kinetic acidities.⁴ They proposed that the proton-bound complex involving the diol probably did not reflect the thermodynamic conformation of the isolated diol anion. Our calculations on the *trans*-1,2-cyclohexanediol dimer anion, which adopts a chelate geometry, support this analysis. In the proton-bound complex, the *cis*-1,4-cyclohexanediol lacked an intramolecular hydrogen bond, had a different hydrogen bond conformation than the anion, or was a mixture of these species.

Methanol–Methoxide Model. To better understand the hydrogen-bonding and ion–dipole interactions in the diols, methanol–methoxide and methanol–methanol interactions were calculated. Methanol–methoxide complexes were optimized by fixing the coordinates of the two oxygen atoms and the bridging hydrogen atom to the same positions in the diols anions. This is equivalent to fixing the two O–H distances and the O–H–O hydrogen bond angle. Similarly, the methanol–methanol complexes were optimized. In this case, four atoms were fixed, including the three atoms participating in the hydrogen bond and the additional dangling hydrogen from the hydroxyl group. In this way, the cyclohexanediols and alkanediols are artificially divided into two parts. The atoms that were fixed were called the functional site, and the rest we called the skeleton. The functional site is simply a methanol–methanol complex, or a methanol–methoxide complex with a given conformation. By evaluating the complexation energy, we can determine how much the distortion of the hydrogen bond affects the energetics. The results of these calculations on the diols and their functional sites are given in Table 2. For comparison, free methanol–methoxide and methanol–methanol interactions were also calculated where none of the atoms were frozen. These are listed in Table 2 as methanol dimer. They are assumed to be undistorted anionic and neutral hydrogen bonds, respectively. The free methanol–methoxide complexation energy is the only value that can be compared directly to experiment, and good agreement is achieved. The average $\Delta E_{\text{complex}}$ for six experimental studies was -26.4 kcal/mol, ranging from -18.4 to -28.8 kcal/mol. We calculated -26.9 kcal/mol.

The diols in Table 2 can be categorized into three groups. Group I consists of those molecules that have hydrogen bonds that strongly contribute to acidity, and are the most acidic diols in the table. These include diaxial *cis*-1,3, *cis*-1,4 boat, and all linear α,ω -diols except 1,2-ethanediol. The hydrogen bond in the neutral complexes accounts for about 4.7–5.4 kcal/mol, which is close to the value of 5.8 kcal/mol calculated for the free methanol dimer. In the anions the interaction accounts for about 24.9–26.8 kcal/mol, which is close to the value of 26.9 kcal/mol calculated for the free methanol–methoxide interaction. This makes the total contribution to acidity by the

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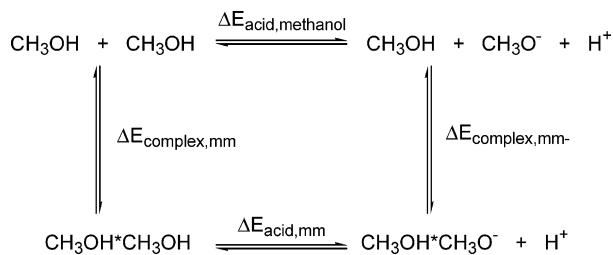


Figure 6. Thermochemical cycle used in methanol model calculations.

intramolecular hydrogen bond 20–22 kcal/mol. These species have only very slightly distorted hydrogen bonds, and their model calculations are only different by about 1 kcal/mol from the free methanol complex model. Group II consists of the vicinal diols: *cis*-1,2-cyclohexanediol, *trans*-1,2-cyclohexanediol, and 1,2-ethanediol. The members of group II have significantly distorted hydrogen bonds. This is reflected in their neutral interaction energies, which have intermediate values between the values of groups I and III, and account for 1–2 kcal/mol of complexation energy. Similarly, the interaction energy for the anions in group II is significantly more stabilizing than for those that have no hydrogen bond, but lower than the value for those that have strong hydrogen bonds. Group III is composed of those diols with no hydrogen bonding, such as *trans*-1,3-, chair *cis*-1,4-, and *trans*-1,4-cyclohexanediol, and are the least acidic diols in the table. These have almost no neutral complexation energies and are energetically very close to two infinitely separated methanols. They do not have any hydrogen bonding, so the largest contribution to the energies in the methanol–methoxide interactions for these species is the ion–dipole interaction, which accounts for 4–8 kcal/mol of stabilization in the anions.

From the thermochemical cycle (Figure 6) and eqs 6–8, one can see that $\Delta\Delta E_{\text{complex}}$ is equal to $\Delta\Delta E_{\text{acid}}$, the enhancement of the acidity by the hydrogen bonding.

$$\Delta E_{\text{complex, mm}} + \Delta E_{\text{acid, mm}} = \Delta E_{\text{acid, methanol}} + \Delta E_{\text{complex, mm-}} \quad (6)$$

$$\Delta E_{\text{acid, mm}} - \Delta E_{\text{acid, methanol}} = \Delta E_{\text{complex, mm-}} - \Delta E_{\text{complex, mm}} \quad (7)$$

$$\Delta\Delta E_{\text{acid}} = \Delta\Delta E_{\text{complex}} \quad (8)$$

However, this is only true for the methanol dimer. For the diols,

because the skeleton also contributes to the acidity, the two values calculated using the methanol dimer approximation are not equal. From the difference between these two values, one can estimate the contribution to acidity by the skeleton, which helps to increase the acidity. One can see from Table 2 that $\Delta\Delta E_{\text{acid}}$ is more negative than $\Delta\Delta E_{\text{complex}}$. Because the skeleton contains only methylene groups, the only important contribution from it is the polarizability. For 1,2-ethanediol and 1,3-propanediol there is little or no additional skeleton, and the difference between $\Delta\Delta E_{\text{acid}}$ and $\Delta\Delta E_{\text{complex}}$ is small for those compounds.

The contribution to acidity from the skeleton of the cyclohexanediols is in the order of group III > group II > group I. The ion–induced dipole interactions depend not only on the polarizability, but also on the charge. For strongly hydrogen-bonded species, the charge is more dispersed than in the non-hydrogen-bonded species. This makes the polarizability contribution from the skeleton smaller than that for weakly hydrogen-bonded species, which have a more concentrated charge. Thus, while hydrogen bonds do increase the acidities of the diols, they cause the stabilizing effects from the polarizability to be smaller.

Summary and Conclusion

Acidities of the six cyclohexanediols were measured using equilibrium studies in an FT-ICR. Despite having the same functional groups and similar structures, the six cyclohexanediols have significantly different acidities. Hydrogen bonding, ion–dipole interactions, polarizability, and stereochemistry determine the acidity of these diols. We have found for our system that as the strength of the hydrogen bonding increases, the contribution from polarizability decreases. The balance between hydrogen bonding and geometric strain is critical in this system. These interactions are significantly different in different diols and in the anions and neutrals. By combining experiments and calculations, we have determined that the neutrals and anions can adopt similar or different conformations, and can follow or violate the rule that substituents prefer equatorial positions over axial ones. The presence of a hydrogen bond can significantly change the conformations or the distribution among conformers, as in the case of *cis*-1,3-cyclohexanediol. It can even distort the carbon skeleton, as in case of *cis*-1,4-cyclohexanediol.

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