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Hydrogen-Bond Symmetry in Zwitterionic Phthalate Anions: Symmetry Breaking by Solvation

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Abstract: The cationic nitrogen of zwitterion **1** is located symmetrically with respect to its intramolecular OHO hydrogen bond. Incorporation of one ^{18}O allows investigation of the H-bond symmetry by the NMR method of isotopic perturbation. In both CD_3OD and CD_2Cl_2 equilibrium isotope shifts are detected at the carboxyl and *ipso* carbons. Therefore, **1** exists as a pair of interconverting tautomers, not as a single symmetric structure with its hydrogen centered between the two oxygens. The H-bond is instantaneously asymmetric, and there is an equilibrium between solvatomers (isomers or stereoisomers that differ in solvation). The broader implications of this result regarding the role of the local environment ("solvation") in breaking symmetry are discussed.

Introduction

A hydrogen bond (H-bond) is a stabilizing interaction between a proton donor A−H and a proton acceptor B.[1] The strength of an H-bond increases as the basicities of the two donor atoms approach each other and as the distance between A and B decreases.[2] For OHO H-bonds, as the O−O distance approaches 2.4 Å, the O−H and H···O distances both approach 1.2 Å. This then becomes a symmetric structure, with the hydrogen centered between the two heavy atoms.[3] The hydrogen motion is described by a potential well with a single minimum, instead of two minima corresponding to individual A−H···B and A···H−B.[4] Neutron-diffraction studies of various dicarboxylate monoanion crystals such as maleate and phthalate, as well as some protonated 1,8-bis(dimethylamino)naphthalenes, indicate a short O−O or N−N distance and a centrally localized hydrogen.[5] Besides, according to high-level ab initio calculations, the barrier to proton transfer in maleate monoanion lies below the zero-point energy, so this is effectively a single-well potential in the gas phase.[6]

Those studies were in crystals or the gas phase, and an H-bond in solution does not necessarily have the same properties. NMR studies showed that the monoanions of many dicarboxylic acids exist as a pair of tautomers in aqueous solution.[7] Initial results had suggested that they become symmetric in organic solvents,[8] but further studies showed that they are a pair of tautomers in all solvents.[9] Similar behavior was observed for two protonated 1,8-bis(dimethylamino)naphthalenes,[10] and also for some 6-aminofulvene-2-aldimines,[11] implying unequal N−H distances. The symmetry of H-bonds is of renewed interest because of a proposal that low-barrier H-bonds play a special role in enzymatic catalysis,[12] although this is somewhat controversial.[13]

Our method for distinguishing between symmetric and asymmetric structures in solution is the method of isotopic perturbation of equilibrium. It requires an isotopic substitution. If there are two equivalent tautomers, their equivalence is lifted by the isotope. Such behavior is then revealed in the isotope shift, the difference in NMR chemical shifts between reporter nuclei X in molecules with heavy and light isotopes (eq 1). This method succeeds even when rapid chemical exchange coalesces NMR signals, as in its first application, to carbocations.[14] Its rationale is readily understood in 2-phenyl-3-hydroxypropenal in chloroform, benzene, or pyridine, where deuterium substitution confirmed that its intramolecular H-bond is asymmetric,[15] even though it is considered a strong one, owing to resonance assistance.[16]

$$\Delta = \delta X_{heavy} - \delta X_{light} \quad (1)$$

This method was used to determine the symmetry of the intramolecular H-bonds in monoanions of mono-^{18}O-labeled

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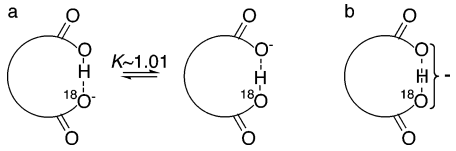


Figure 1. (a) Equilibrating pair of tautomers with asymmetric H-bonds. (b) Single, symmetric species.

dicarboxylic acids. If the monoanion is present as an equilibrating mixture (Figure 1a), greater COOH character is favored for the labeled carboxyl and greater CO_2^- character for the unlabeled. These correspond to upfield and downfield NMR shifts, respectively. The observed isotope shift is given by eq 2, where Δ_0 is an intrinsic shift due to the isotope, K is the ratio of acidity constants of ^{16}O and ^{18}O acids,[17] and D is the difference between static chemical shifts of COOH and CO_2^- groups. The intrinsic isotope shift Δ_0 can be measured in the diacid and can be assumed to be the same in the monoanion, and D can be approximated as the difference between the chemical shifts of the diacid and the dianion. The intrinsic isotope shift is the only term if the monoanion exists as a single, symmetric species (Figure 1b). The result that distinguishes an equilibrating pair of tautomers is thus an isotope shift detectably greater than the intrinsic shift.

$$\Delta = \Delta_0 + \frac{K-1}{K+1} D \qquad (2)$$

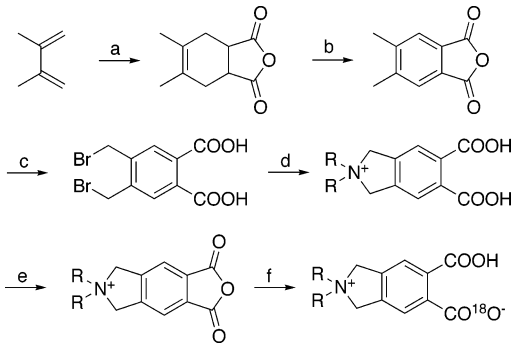
Previous work examined a wide range of dicarboxylic acid monoanions, including maleate and phthalate. An observed isotope shift greater than the intrinsic shift was detected in every monoanion studied, and in all solvents. Therefore, each of these is an equilibrium mixture of two tautomers, each with an asymmetric H-bond.

The asymmetry of these H-bonds in solution contrasts with the symmetry that is calculated in the gas phase and observed in some crystals. It was therefore proposed that the asymmetry is due to the disorder of the local environment, which prevents identical solvent or counterion interactions with both carboxyl groups. For example, identical H-bonding by water or other protic solvent to both carboxyls is unlikely, because this would require a network of H-bonds organized through the solvent. Likewise, in less polar solvents an associated counterion cannot be localized symmetrically with respect to the two carboxyls. This lack of symmetry is in contrast to the organized environment found in crystals.

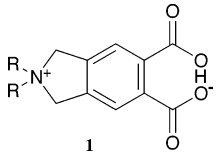
Computer simulations on phthalate monoanion support this role of the local environment.[18] Three aspects favoring asymmetry were distinguished: (1) A polar solvent, modeled simply as a continuum dielectric, stabilizes an asymmetric structure relative to the symmetric one. (2) Interaction with discrete solvent molecules or with a counterion further stabilizes asymmetric structures. (3) Dynamic disorder of the solvent molecules or of the location of the counterion makes the asymmetric H-bond still more likely.

The role of the counterion in disrupting the symmetry of the H-bond in phthalate monoanion may be addressed with zwitterion **1**. The two oxygens have identical basicity, and they are forced close to each other, and thus, a symmetric H-bond is possible. The cationic nitrogen is fixed equidistant from the two carboxyl groups and eliminates the dynamic disorder of its location relative to the negative charge. It is readily synthesized from 4,5-bis(bromomethyl)phthalic acid. Introduction of one ^{18}O then allows the nature of its H-bond to be probed by the method of isotopic perturbation.

Scheme 1[a]



[a] Reagents and conditions: (a) maleic anhydride, THF (tetrahydrofuran), 25 °C; (b) S_8, propylene carbonate, 215 °C; (c) aqueous NaOH, heat; HCl; *N*-bromosuccinimide, benzoyl peroxide, benzene, reflux; (d) excess R_2NH (R = butyl, octyl), THF; HCl; (e) CH_3COCl; (f) $H_2{}^{18}O$, THF; CH_3CO_2K, CH_3OH.



1

Experimental Section

The synthesis of **1**-^{18}O is outlined in Scheme 1. Cycloaddition of 2,3-dimethylbutadiene and maleic anhydride, followed by aromatization, produced 4,5-dimethylphthalic anhydride,[19] which was hydrolyzed to the diacid,[20] and dibrominated. Double nucleophilic substitution with dibutylamine or dioctylamine and workup with HCl yielded the chloride salt of the quaternary ammonium diacid. Conversion to the anhydride, facile hydrolysis with $H_2{}^{18}O$ (Sigma-Aldrich, 97% ^{18}O), and neutralization produced the zwitterion. NMR samples of **1**-^{18}O were prepared using syringe and vacuum-line techniques for transfer to NMR tubes fitted with J. Young valves. NMR spectra were obtained on a Varian Unity-500 spectrometer operating at a ^{13}C frequency of 125.823 MHz and with a narrow sweep width and a four-fold augmentation of data points, to improve digital resolution. Experimental procedures and spectroscopic characterization are in Supporting Information, and further details of procedures will be available.[21]

Results

In CD_2Cl_2 the ^1H NMR spectrum of **1** (R = octyl) shows a signal far downfield, at δ 20.08, characteristic of a low-barrier H-bond. ^{18}O-Induced ^{13}C isotope shifts of zwitterion **1** (R = butyl, octyl) and its cationic diacid are collected in Table 1. Just as with phthalic acid,[8,9] an intrinsic isotope shift of 25−26 parts per billion (ppb) was observed for the carboxylic acid carbons of the cations in both CD_3OD and CD_2Cl_2, but the intrinsic isotope shift could barely be resolved for the ipso

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Table 1. ^{18}O-Induced ^{13}C Isotope Shifts (ppb) of Zwitterion **1**

R	solvent	carbon	$-\Delta_{obs}$	$-\Delta_0$[a]	$-\Delta_{eq}$
butyl	CD_3OD	carboxyl	40	25	15
		ipso	35	4	31
octyl	CD_3OD	carboxyl	40	25	15
		ipso	39	2	37
octyl	CD_2Cl_2	carboxyl	28	26[b]	2
		ipso	12	<5[b]	>7

[a] From cationic diacid. [b] Assumed to be same as in CD_3OD (diacid is insoluble in CD_2Cl_2).

carbons. The dibutyl analogue is insufficiently soluble in CD_2Cl_2, both as cationic diacid and zwitterion.

The magnitude of the equilibrium isotope shift Δ_{eq} was obtained by subtracting the intrinsic isotope shift observed in the cationic diacid from the observed shift in the zwitterionic monoanion. An equilibrium isotope shift of 15 ppb is found for the carboxyl carbons of both **1**-^{18}O (R = butyl) and **1**-^{18}O (R = octyl) in CD_3OD. An even larger equilibrium shift is found at the ipso carbons. In CD_2Cl_2 the equilibrium isotope shift of 2 ppb at the carboxyl carbon of **1**-^{18}O (R = octyl) is small, hardly above the resolution. Whereas the equilibrium isotope shift at the ipso carbon is only 7 ppb, smaller than in CD_3OD, it is again large enough that it cannot be confused with an intrinsic isotope shift.

Although all these isotope shifts are small, in the parts-per-billion range, isotope effects due to ^{18}O are always expected to be small. With proper attention to spectral resolution, they can be measured with reasonable accuracy. Therefore, we assert that the values are reliable.

Discussion

The observed isotope shifts of **1**-^{18}O in both CD_3OD and CD_2Cl_2 are significantly larger than the intrinsic isotope shifts observed in the cationic diacids. The increase in the observed isotope shift, exceeding the intrinsic isotope shift, represents an equilibrium isotope shift, as listed in Table 1. Therefore, these zwitterions exist as a pair of equilibrating tautomers, each corresponding to an asymmetric H-bond. The isotope shifts, clearly larger than the intrinsic, are evidence for a tautomeric equilibrium in both of these solvents, protic or aprotic.

The observed equilibrium isotope shifts of **1**-^{18}O (R = butyl, octyl) in both CD_3OD and CD_2Cl_2 agree with those observed for phthalate monoanion in a variety of solvents.[10b] Although small, the observed isotope shifts in the zwitterion show an increase from the intrinsic isotope shifts seen in the cationic diacid, evidence of an equilibrium isotope shift resulting from the isotopic perturbation of a tautomeric equilibrium. Were there no such equilibrium, there would be no additional isotope shift in the zwitterion. Therefore, each of these zwitterions is definitely not present as a single symmetric species. Instead, there are (at least) two species, each with asymmetric H-bonds.

To test for artifacts, several control experiments were carried out on related dicarboxylate monoanions.[8] Among the results obtained were the observations of an inverse dependence of isotope shifts on temperature, a twofold effect with di-^{18}O-substitution at one carboxyl, an increase of isotope shifts on going from H_2O to D_2O (owing to a predictable isotope effect on an isotope effect), and substantial isotope shifts at the ipso, ortho, and meta carbons of phthalate monoanion (even though these carbons are too distant from the site of isotopic substitution to show any resolvable intrinsic isotope shift). All of these observations are consistent with an equilibrium between two tautomers that is perturbed by the isotope.

Is **1** suitable for probing H-bond symmetry? It does qualify as a low-barrier H-bond, according to the neutron-diffraction data on LiHphthalate·CH_3OH, which show a centered hydrogen.[5] It does not have an unusually strong H-bond, though, as judged from acidity constants in water.[22] Besides, those acidity constants parallel those for succinic acid, whose monoanion in methanol does not favor conformations with an internal H-bond.[23] Therefore, it is not surprising that **1** has an asymmetric H-bond in methanol. Of course, the same asymmetry was seen with phthalate in water, where it was attributed to the disorder of H-bonding of the carboxyls to solvent.[7] However, the strengths of H-bonds increase in aprotic solvents.[24] Thus. the H-bond of **1** is a strong intramolecular one in CD_2Cl_2, as judged from its downfield OH signal at δ 20.08, and it, too, is found to be asymmetric.

The isotope shifts are smaller in CD_2Cl_2 than in methanol. We doubt that this is because the H-bond is "more symmetric" in CD_2Cl_2. Symmetry is a yes/no property, and the definite answer here is that **1** in either methanol or CD_2Cl_2 is a mixture of two tautomers, each of which is asymmetric. We would then attribute the lower isotope shifts in CD_2Cl_2 to a lower sensitivity of the reporter nuclei to their state of protonation.[9]

Does the isotopic substitution itself induce a separation into two tautomers? It might be thought that the method of isotopic perturbation is doomed to require every structure to appear asymmetric, simply because the isotopic substitution creates an asymmetry. Here two substitutions are needed, both ^{18}O and ^{13}C, one for the perturbation, the other as a rare isotope for the NMR detection. Only without these would the zwitterion be truly symmetric. Nevertheless, it follows from the Born−Oppenheimer Approximation that the potential-energy surface governing nuclear motion is independent of nuclear mass,[25] even though the isotope can affect acid strength via zero-point energies. Moreover, the power of the method to distinguish symmetric from asymmetric structures is supported by experimental results on some metal chelates of 2-phenyl-3-oxidopropenal,[26] and on dioxathiapentalene and trithiapentalene,[27] all of which are found to be symmetric.

The asymmetry of the H-bonds of these zwitterions in solution contrasts with the symmetry that is observed in some crystals of hydrogen maleate and similar monoanions. It is not a misinterpretation of the crystal structure, because the neutron-diffraction data from potassium hydrogen chloromaleate are better fit with a centered hydrogen than with half hydrogens at each oxygen, in static or dynamic disorder.[28] The contrast between crystals and solution had been attributed to solvent polarity, inasmuch as a polarizable medium or a neighboring

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ion is calculated to stabilize an asymmetric structure.[29] However, the asymmetry is general, even in nonpolar solvents, such as the CD_2Cl_2 here. Besides, a crystal is also a polarizable medium with strong electric fields. We therefore had proposed that the disorder of neighboring ions, especially in nonpolar solvents, is what creates the asymmetry. Zwitterion **1** allows this proposal to be rejected.

In summary, the observed isotope shifts of **1**-^{18}O (R = butyl, octyl) demonstrate that these zwitterions exist as a pair of equilibrating tautomers, in both protic and aprotic solvents. This is the same result as in many of our other studies of H-bonds. It seems to be a general phenomenon that H-bonds are not symmetric in solution, although we cannot exclude the possibility that symmetric H-bonds are a low-temperature phenomenon.[30] Nevertheless, the asymmetry of the H-bonding in **1** shows that the previous cases of asymmetry cannot be attributed merely to the varying location of a counterion. Instead the asymmetry seems to be a general feature of H-bonds in solution.

Comments Regarding Solvatomers. Computer simulations had suggested that interaction with an asymmetrically located counterion can be responsible for stabilizing the asymmetric H-bond, especially in nonpolar solvents.[18] This interaction cannot desymmetrize zwitterion **1**, where the quaternary nitrogen is on a symmetry axis. The experimental results therefore suggest that asymmetry is inherent to all solutions, not through the counterion, but through the disorder of interactions with individual solvent molecules. In principle, the conformational disorder of the alkyl chains might also contribute, but their interactions are much weaker than those of the solvent molecules that are closer to the carboxyls. Those solvent molecules are continuously rearranging their dipole moments, so that the instantaneous stabilization varies with time and with location. Even a nonpolar solvent molecule, with no net dipole moment, has local dipoles that reorient, or a polarizability that is modulated, as the molecule tumbles around an H-bond. This is in contrast to the organized environment found in crystals. The disorder of solvation is a fundamental feature of solutions. It is obvious, but has hardly been explored.

Although these results require a mixture of two tautomers, rather than a single symmetric species, we cannot conclude that the H-bond is described by a double-well potential. This may be so, with the instantaneous solvation stabilizing one well more than the other. The alternative is a single-well potential where the solvation stabilizes an asymmetric structure, as in Figure 2. (Another possibility, a double-well potential where the zero-point energy lies above the barrier, is equivalent to a single-well potential for this discussion.) As the solvation changes, the hydrogen moves across the H-bond. In each of these structures the H-bond is asymmetric, and the equilibrium between them can be perturbed by isotopic substitution. These structures can be called solvatomers, signifying isomers or stereoisomers or (as here) tautomers that differ in solvation. This is a more proper use of the term than an earlier designation

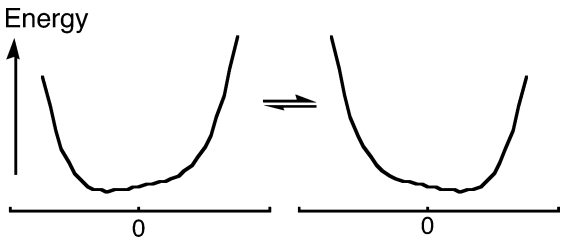

Figure 2. Equilibrating H-bond solvatomers, each with a single-well potential describing energy vs bond-distance difference $d(AH) - d(HB)$.

that was applied to species that differ in the type of solvent molecules and thus are not isomeric.[31]

Comments Regarding the Role of Low-Barrier H-Bonds in Enzymatic Reactions. We cannot exclude the possibility that the active site of an enzyme is like a crystal, with an ordered environment that permits a symmetric H-bond. Yet if the energy of solvation is sufficient to prevent a symmetric structure, then there is no special stabilization associated with them.

Although the strongest of H-bonds are symmetric, these two characteristics do not necessarily parallel each other. One way to lower the barrier to proton transfer and approach a symmetric H-bond is to constrain the heavy atoms to proximity. Yet, it must be recognized that this constraint does not strengthen the H-bond but weakens it. If the constraint were relaxed, the species would become more stable. Therefore, a symmetric or low-barrier H-bond does not exhibit unusually high stability. Indeed, we have suggested that enzymatic acceleration by low-barrier H-bonds is due to relief of a destabilization, as had been suggested by Jencks,[32] rather than to any stabilization from the H-bond itself.[33]

Implications Regarding the Generality of Solvation for Breaking of Symmetry. A wide variety of situations have been encountered where the local environment reduces symmetry. One of the most familiar is in the theory of electron or proton transfer, where reorganization energy must be provided to an asymmetric system in order to achieve a symmetric configuration that allows the electron or proton to transfer.[34] A classic example is NH_3,[35] where nitrogen inversion is subject to a double-well potential. In the gas phase the nitrogen is delocalized between the two wells. If it could be localized in one, it would rapidly tunnel to the other. However, in any interacting solvent the nitrogen is pyramidal, and the inversion barrier in substituted derivatives can be measured.[36]

Another familiar set of examples depends on the selection rules for IR and Raman intensities in centrosymmetric molecules. The paradigm of a symmetric H-bond is HF_2^-, but in crystalline toluidinium HF_2^- the forbidden in-phase stretch acquires IR intensity owing to a loss of centrosymmetry.[37] Similarly, the bending mode and the antisymmetric stretch of CS_2, which are Raman inactive in isolation, become allowed in the liquid.[38] The Raman spectra of I_3^- solutions show transitions

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that are forbidden in the isolated D_{3h} ion, and the intensity increases from acetonitrile to ethyl acetate to ethanol.[39] Even nonlinear molecules can show intensities that signal a lower symmetry. Raman and resonance-Raman spectra of NO_3^- in water, ethylene glycol, methanol, and acetonitrile show transitions that are forbidden in D_{3h} symmetry,[40] Likewise, Raman spectra of aqueous thiourea show bands that would be forbidden by a symmetry plane through the C═S.[41]

A more subtle effect is the effect of solvent on the intensity ratios in the vibronic fine structure of pyrene fluorescence. This correlates with solvent polarity,[42] but it is also consistent with the ability of the solvent to disrupt the local symmetry of the molecule and allow otherwise weak transitions. All of these phenomena are worthy of further study, by a wide variety of experimental and computational techniques, to elucidate the role of solvation in breaking symmetry.

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Conclusions

NMR spectra show equilibrium isotope shifts at carboxyl and ipso carbons of the zwitterions **1** (R = butyl, octyl). Therefore, these exist as pairs of interconverting tautomers and not as single symmetric species. This result shows that the asymmetry of the H-bonds of the monoanions of various dicarboxylic acids is not due to an asymmetrically positioned counterion, as had been proposed. This asymmetry is inherent to solutions, and the disorder of solvation is a fundamental feature of solutions with wide-ranging implications.

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Supporting Information Available: Synthetic procedures and spectroscopic characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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