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Symmetry of hydrogen bonds in solution*

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Abstract: A classic question regarding hydrogen bonds (H-bonds) concerns their symmetry. Is the hydrogen centered or is it closer to one donor and jumping between them? These possibilities correspond to single- and double-well potentials, respectively.

The NMR method of isotopic perturbation can answer this question. It is illustrated with 3-hydroxy-2-phenylpropenal and then applied to dicarboxylate monoanions. The ^{18}O-induced ^{13}C NMR splittings signify that their intramolecular H-bonds are asymmetric and that each species is a pair of tautomers, not a single symmetric structure, even though maleate and phthalate are symmetric in crystals. The asymmetry is seen across a wide range of solvents and a wide variety of monoanions, including 2,3-di-*tert*-butylsuccinate and zwitterionic phthalates. Asymmetry is also seen in monoprotonated 1,8-bis(dimethylamino)-naphthalenediamines, *N*,*N*′-diaryl-6-aminofulvene-2-aldimines, and 6-hydroxy-2-formylfulvene. The asymmetry is attributed to the disorder of the local environment, establishing an equilibrium between solvatomers. The broader implications of these results regarding the role of solvation in breaking symmetry are discussed.

It was prudent to confirm a secondary deuterium isotope effect (IE) on amine basicity by NMR titration of a mixture of $PhCH_2NH_2$ and $PhCHDNH_2$. The IE is of stereoelectronic origin.

It is proposed that symmetric H-bonds can be observed in crystals but not in solution because a disordered environment induces asymmetry, whereas a crystal can guarantee a symmetric environment. The implications for the controversial role of low-barrier H-bonds in enzyme-catalyzed reactions are discussed.

Keywords: hydrogen bonds; isotope effects; nuclear magnetic resonance; molecular structure; solvation.

INTRODUCTION

Hydrogen bonds (H-bonds) are a key feature of molecular structure [1]. A classic question regarding the structure of H-bonds concerns their symmetry. If the two donor atoms, A and B, have the same proton affinity, is the hydrogen centered (A··H··B) or is it closer to one and jumping between them (A-H···B in rapid equilibrium with A···H-B)? These two possibilities correspond to single- and double-well potentials, respectively (Fig. 1). Representative examples of these are maleate (**1a**) and phthalate (**1b**) monoanions and enols of acetylacetone (**2**), respectively.

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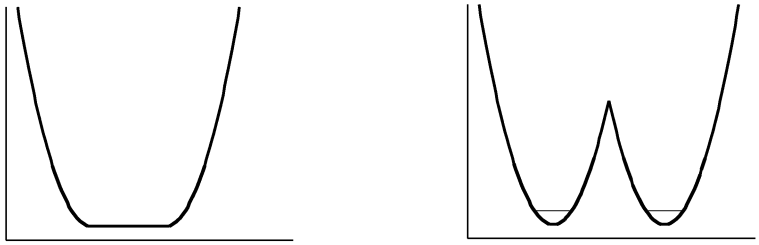
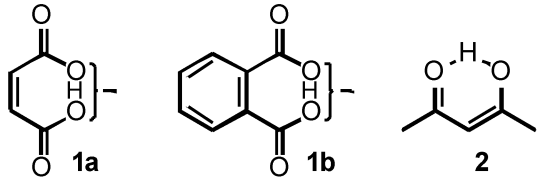


Fig. 1 Single- and double-well potentials for H motion.



The general understanding that has developed is that single-well potentials require an OO distance below 2.4 or 2.5 Å [2]. This makes sense, insofar as the barrier between the energy wells must diminish as the wells approach each other. In **2** the OO distance is just too long to lower the barrier enough to produce a single-well potential [3]. Although double-well potentials are associated with strong H-bonds, single-well potential H-bonds are among the strongest, especially in FHF^-. The origin of that strength is often attributed to resonance stabilization. All H-bonds can be described as resonance hybrids, which reach their maximum stabilization when the two resonance forms have identical energy, as with a single-well potential.

A greater strength must be attributed to symmetric H-bonds, in order to allow their OH distances to expand from their normal 1.0 Å to the 1.2 Å that is half the 2.4-Å OO distance. It should be noted that this expansion is not a minor perturbation, but requires ~60 kJ mol^{-1}, as inferred from O–H stretching frequencies. Furthermore, because of the strength of these short, low-barrier H-bonds, they have been proposed to stabilize intermediates and transitions states in enzyme-catalyzed reactions, independent of whether the barrier drops to zero [4], although this is a matter of some controversy [5]. The strength of an H-bond is ambiguous, because it depends on the choice of reference. We have therefore focused on the structural question of the symmetry of the H-bond, and this article is a personal summary of our 20-year search for symmetric intramolecular H-bonds, drawn from a plenary lecture presented at the 19th IUPAC Conference on Physical Organic Chemistry, and updating an earlier review [6]. It is entirely different from the plenary lecture presented at the 12th conference in 1994 [7].

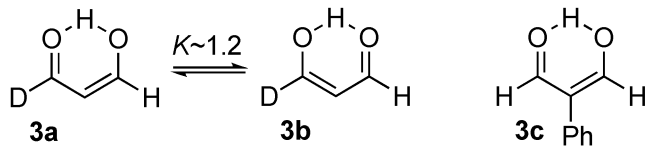
METHODOLOGY

Our approach is to use the method of isotopic perturbation, which was developed by Martin Saunders to address the question of symmetry in carbocations [8]. It is an NMR method that succeeds even if signals are coalesced owing to rapid exchange. It depends on measuring the isotope shift (isotope effect, IE, on chemical shift) due to an isotope *n* atoms distant from the reporter nucleus (eq. 1) [9]. Because heavy isotopes generally lead to an upfield shift, ${}^n\Delta$ is usually negative. There are two contributions to the observed isotope shift, namely, an intrinsic shift, Δ_o, owing to the mere presence of an isotope, and a shift induced by perturbation of an equilibrium, Δ_{eq} (eq. 2).

$${}^n\Delta = \delta_{heavy} - \delta_{light} \quad (1)$$

$$\Delta_{obs} = \Delta_o + \Delta_{eq} \quad (2)$$

This latter term, Δ_{eq}, is conveniently illustrated with 3-hydroxypropenal-*d* (**3a**,**3b**) [10], the enol of malonaldehyde, similar to **2**. According to model compounds, the enolic C–H stretching frequency of **3a** is near 3020 cm^{-1}, but the aldehydic C–H of **3b** is near 2770 cm^{-1}. The C–D frequencies are in the opposite order, but lower. Consequently, **3a** has a higher net zero-point energy, corresponding to an equilibrium constant [**3b**]/[**3a**] of ~1.2 at 25 °C. Moreover, in the ^{13}C NMR an enolic CH carbon, as in **3a**, appears at 173 ppm, whereas an aldehydic CH carbon, as in **3b**, appears at 196 ppm. Because of rapid tautomerization, separate signals are not seen at 173 and 196 ppm. Instead, an average signal is seen, but at a chemical shift that is the weighted average of 173 and 196 ppm. Because of the position of the equilibrium, that average, for the CH, is closer to 196 ppm, whereas the average for the CD is closer to 173. From all these values, the separation between CH and CD is estimated to be ~2 ppm.

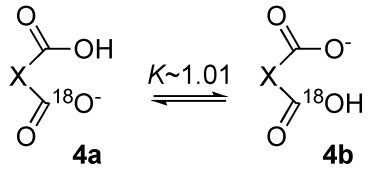


In practice, it is easier to work with 3-hydroxy-2-phenylpropenal (**3c**), synthesized as a mixture of d_0, d_1, and d_2 isotopologues. The ^{13}C NMR shows a separation of 0.26 ppm between d_0 and d_2 signals, which is a measure of Δ_o. The informative separation is between **3c**-d_0 and the CH of **3c**-d_1, which is a measure of Δ_{eq}, arising from perturbation of an equilibrium between the two tautomers of **3c**-d_1. The observed separation is 0.76 ppm at 25 °C. A larger separation is seen at lower temperature, where the equilibrium becomes more imbalanced, and the same phenomenon of a Δ_{eq} is seen in the ^1H NMR spectrum. Thus, **3c** is confirmed to exist as a mixture of two asymmetric tautomers.

It might be thought that the asymmetry is due to the introduction of isotopes. However, the Born–Oppenheimer approximation guarantees that the potential-energy surface governing nuclear motion is independent of nuclear mass [11]. Moreover, the method of isotopic perturbation has succeeded in showing that various metal chelates of **3c** [12], as well as 1,6-dioxa-6aλ^4-thiapentalene and 1,6,6aλ^4-trithiapentalene [13], are symmetric.

DICARBOXYLATE MONOANIONS

We next consider the monoanions of dicarboxylic acids and investigate how mono-^{18}O substitution can perturb a hypothetical equilibrium between tautomers (**4a**,**4b**, plus an additional tautomer that is protonated on the ^{16}O of the ^{18}O-labeled carboxyl, which merely halves the overall IE) [14]. Again, owing to vibrational frequencies and zero-point energies, an ^{18}O-labeled carboxyl group is ~1 % less acidic than an ordinary carboxyl [15]. Consequently, the equilibrium between **4a** and **4b** is shifted slightly toward **4b**. Moreover, in the ^{13}C NMR a carboxyl group appears near 170 ppm, whereas a carboxylate appears near 176 ppm, and these chemical shifts can be measured in the diacid and the dianion. Separate signals for carboxylic acid and carboxylate groups are not seen in the monoanion, but only an average. That average is a weighted average, perturbed by the equilibrium, so that the carbon attached to ^{18}O is shifted upfield by ~0.02 ppm. This is in addition to an upfield Δ_o of 0.026 ppm, which can be measured in the diacid or dianion. The signature of a tautomeric mixture is thus an additional isotope shift in the monoanion, greater than in the diacid or dianion, and this is indeed seen in succinic acid (**4**, X = CH_2CH_2), whose monoanion does not have an intramolecular H-bond and thus must be a mixture of tautomers [16].

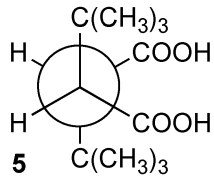


For the monoanions of maleic acid (**1a**, or **4**, X = *cis*-CHCH) and phthalic acid (**1b**), which are single, symmetric species in crystals, there ought to be no tautomeric equilibrium for the isotope to perturb. Therefore, we expected only an intrinsic upfield Δ_o of 0.026 ppm, for ^{18}O-labeled diacid, dianion, and monoanion, independent of the state of protonation. Nevertheless, much to our surprise, we observed an additional isotope shift in these monoanions, greater than in the diacid or dianion. This is the signature of a tautomeric mixture, which was confirmed by many control experiments [14].

These studies were facilitated by the ease with which mono-^{18}O-labeled dicarboxylic acids can be synthesized. All that is necessary is to hydrolyze the corresponding anhydride in $H_2{}^{18}O$. However, it might be noted that the one synthetic triumph from my laboratory was the preparation and characterization of four-membered-ring malonic anhydrides [17], which had been sought unsuccessfully for 80 years. Studies were thus extended to a wide range of dicarboxylic acids, in a search for monoanions with symmetric H-bonds, rather than as a mixture of two tautomers. The wide range permitted wide variation of the OO distance. Nevertheless, all of them showed an additional ^{18}O-induced isotope shift in their monoanions, greater than in their diacid or dianion [18]. These perturbation isotope shifts were detectable at carboxyl carbons and conspicuously at ipso carbons.

Initially, it was thought that the asymmetry was a consequence of the polarity of water, which stabilizes the localized charge of an asymmetrically H-bonded monoanion, as is indicated by computations [19]. Nevertheless, further studies revealed that the dicarboxylate monoanions show perturbation isotope shifts across a wide range of solvents, not only in water and dimethyl sulfoxide (DMSO) but also in such nonpolar solvents as tetrahydrofuran (THF), dichloromethane, and chloroform [18].

The difference, ΔpK, between first and second acidity constants of a dicarboxylic acid is often taken as a measure of the strength of the intramolecular H-bond in its monoanion [20]. By this criterion, the strongest H-bond is in the monoanion of (±)-α,α'-di-*tert*-butylsuccinic acid (**5**), for which ΔpK is 9.54 in 50 % aqueous ethanol [21]. Nevertheless, in methanol, acetone, and THF this too shows an ^{18}O-induced isotope shift that is larger than in the diacid [22]. Besides, the X-ray crystal structures of several of its salts show that its H-bond is asymmetric, even though the OO distance is a short 2.41 Å.



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RATIONALE

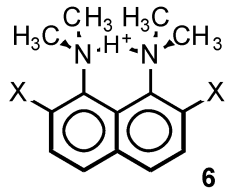
How can we account for the observation that all of these dicarboxylate monoanions exist in solution as a pair of asymmetric tautomers? This is in strong contrast with crystals, where many studies have found that these are symmetric. In some cases, sufficient data are provided to distinguish that the H is indeed centered between the two oxygens, rather than disordered, either statically or dynamically, between two equivalent positions [23]. Similarly, the enol of dibenzoylacetone is a mixture of tautomers in solution

but symmetric in the crystal [24]. These are exceedingly simple counterexamples to the hope that an X-ray crystal structure reflects the structure in solution.

The asymmetry persists in nonpolar solvents. Therefore, it is not simply a consequence of the polarity of water, which stabilizes the localized charge of the asymmetric H-bond. Besides, a crystal too is a polar environment, with counterions and strong electric fields. What distinguishes a crystal is that it is an organized medium that can guarantee that both carboxyl groups are in identical environments. In contrast, it would require considerable negative entropy to organize the solution so that both carboxyls are solvated identically. Instead, the inherent disorder of the local environment solvates one of the carboxyls better than the other, stabilizing the tautomer with H on the other carboxyl. Thus, the H-bond is instantaneously asymmetric. Computer simulations on phthalate monoanion, including dynamic disorder of the position of the counterion or of the solvent molecules, support this influence of the local environment [25].

TETRAMETHYLNAPHTHALENEDIAMINES

The negative charge of a carboxylate is exposed to solvent, so that it is very sensitive to the disorder of solvation. Might a buried charge, as in protonated tetramethylnaphthalenediamines (**6**), be less sensitive? These too have strong H-bonds, as evidenced by their acidity, which is reduced by as much as 12 pK units (for X = OCH_3) relative to model amines.



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Are these H-bonds symmetric, single-well-potential H-bonds? This too can be tested with the method of isotopic perturbation. If the H-bond is asymmetric, deuteration of a methyl group increases the basicity of its nitrogen and shifts the equilibrium toward tautomers with protonated NCD_3 and unprotonated NCH_3. This shift can be detected via the deuterium-induced ^{13}C NMR isotope shifts (eq. 1) at the various carbons around the rings. In contrast, if the H-bond is symmetric, only intrinsic isotope shifts will be detected.

Successful application of the method of isotopic perturbation to **6** requires that α-deuteration increase the basicity of NCD_3 relative to NCH_3. The evidence for such a secondary IE was the greater basicity of $PhCD_2NH_2$, compared to $PhCH_2NH_2$ [26]. However, the measured ΔpK varied with the sample of $PhCD_2NH_2$, suggesting a systematic error due to an impurity. Besides, the IE was attributed to an inductive effect, which seems too insignificant to contribute. Before embarking on the multistep synthesis of isotopically labeled **6** (X = OCH_3), it was deemed prudent to confirm a secondary deuterium IE on amine basicity.

DIGRESSION: SECONDARY DEUTERIUM ISOTOPE EFFECTS ON AMINE BASICITY

A primary IE is one where a bond to the isotope is being made or broken. A secondary IE is one where the bond to the isotope remains intact. Many secondary deuterium IEs have been observed in solvolyses, where a change of CH hybridization from sp^3 to sp^2 leads to a change of zero-point energy and an obvious origin for the IE. With amines there is no change of hybridization, neither at C nor at N, and no obvious origin for the IE.

To test the IE on amine basicity, we used an NMR titration method that had been developed for a totally different project [27]. It involves the addition of small aliquots of acid to a mixture of two bases, and the measurement of NMR chemical shifts after each addition, which are averaged according to the extent of protonation of each base. It is readily shown that the chemical shifts obey eq. 3, where δ^0 or δ^+ is for the deprotonated or protonated form, respectively, as measured at the beginning or end of the titration. Therefore. a plot of the quantity on the left vs. $(\delta_H - \delta_H{}^0)(\delta_D{}^+ - \delta_D)$ should be linear with zero intercept and with a slope equal to the ratio of acidity constants for protium- and deuterium-carrying ammonium ions.

$$(\delta_D - \delta_D{}^0)(\delta_H{}^+ - \delta_H) = (K_a{}^H/K_a{}^D)(\delta_H - \delta_H{}^0)(\delta_D{}^+ - \delta_D) \quad (3)$$

This method is capable of exquisite precision, because it is based only on chemical-shift measurements, not on pH or volume or molarity as in the usual pH titrations. It is very sensitive, so that minute differences in basicities can be detected. Moreover, because the titration is performed on a mixture of the two bases, under conditions guaranteed identical for both, it avoids systematic error due to an impurity that might affect the measurement of one of the acidity constants alone. A further advantage is that it can be applied in any solvent, even where a pH electrode would be inoperative.

Figure 2 shows a plot from an NMR titration of a mixture of $PhCH_2NH_2$ and $PhCHDNH_2$, analyzed according to eq. 3. The slope corresponds to $K_a{}^H/K_a{}^D = 1.0420 \pm 0.0009$, or a ΔpK of 0.0179 ± 0.0004 [28]. Similar values were observed for a number of additional amines. This confirms the previous claim of a secondary deuterium IE on amine basicity. However, an inductive explanation still seems unlikely.

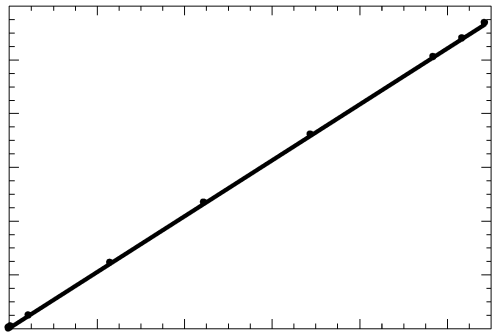


Fig. 2 NMR titration of a mixture of $PhCH_2NH_2$ and $PhCHDNH_2$, analyzed according to eq. 3. Reprinted with permission from ref. [28]. Copyright © 2003 American Chemical Society.

Instead, we must seek an explanation that recognizes that there is no change of hybridization and no obvious origin for the IE. Of course, what is obvious depends on one's knowledge. I confess that I was too ignorant to see an origin for the IE. However, amines are known to show Bohlmann bands in their IR spectra, at 2700–2800 cm^{-1}, lower than the 2900 cm^{-1} of a typical C–H stretch. Upon *N*-protonation, these revert to the typical frequencies. Therefore, the zero-point energy increases on protonation, but the increase is less for C–D than for C–H.

The reduction of frequency is attributed to negative hyperconjugation, or delocalization of the lone pair into the σ^*_{CH} orbital, which is most effective when it is antiperiplanar to the C^{-1}–H bond (Fig. 3). Such an origin for the IE can be tested with **7**. This amine was synthesized as a mixture of two isotopomers (stereoisomers that differ only in the position of the isotope). By NMR titration it was found that the isotopomer with deuterium axial, and therefore antiperiplanar to the nitrogen lone pair, is indeed the more basic, with $K_a{}^{eq}/K_a{}^{ax} = 1.060 \pm 0.006$. Therefore, this IE is of stereoelectronic origin, and it is not necessary to invoke an inductive effect.

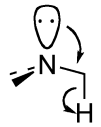
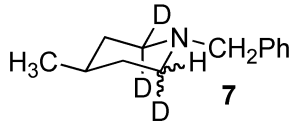


Fig. 3 Delocalization of nitrogen lone pair into antiperiplanar σ^*_{CH}.



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NONADDITIVITY OF ISOTOPE EFFECTS ON BASICITY

The stereoelectronic origin of the secondary IE on amine basicity leads to an interesting prediction regarding the nonadditivity of IEs. Such a nonadditivity would be a violation of the widely assumed Rule of the Geometric Mean.

This nonadditivity was investigated with the isotopologues $(CH_nD_{3-n})_3N$ of trimethylamine [29]. Because of the reduction of zero-point energy, there is a preference for conformations with C–H antiperiplanar to a lone pair, and D gauche. A further consequence is that those conformations are less basic. The first H on a methyl will take this position and decrease the basicity of CHD_2N over CD_3N. An additional H, as on a CH_2D, must compete for that position, so that the further decrease in basicity will be less, and also less for CH_3. Thus, the IE per H will decrease as the number of H increases. Equivalently, the IE per D will increase as the number of D increases. This represents a nonadditivity of IEs that we have been able to investigate experimentally by a series of pairwise NMR titrations of trimethylamine isotopologues. The nonadditivity is such a small effect that its detection requires exquisite accuracy.

The IEs measured in D_2O are reported in Table 1. The numbers in parentheses are the errors in the last decimal place. As with the amines discussed previously, deuterium decreases basicity, and all K_a^H/K_a^D are >1. The noteworthy feature with trimethylamine is that the decrease in basicity, per deuterium, increases with the number of deuteriums.

Table 1 IEs of $(CH_nD_{3-n})_3$ on trimethylamine basicities.

	CH_3/CH_2D	CH_2D/CHD_2	CH_3/CHD_2	CH_3/CHD_2[a]	d_0/d_8	d_6/d_8
K_a^H/K_a^D	1.15736(3)	1.1623(7)	1.3487(22)	1.3452(9)	1.4934(7)	1.1073(19)
ΔpK_a	0.06347(1)	0.0653(3)	0.1299(7)	0.1288(3)	0.1742(2)	0.0443(7)
ΔpK_a per D	0.02116(0)	0.02178(9)	0.02165(12)	0.02147(5)	0.02177(2)	0.0221(4)

[a]Product of CH_3/CH_2D and CH_2D/CHD_2.

The values themselves are so similar that they are difficult to compare. Figure 4 displays ΔpK_a per D, as pairwise comparisons of CH_3, CH_2D, and CHD_2 from left to right, against CH_3, CH_2D, CHD_2, and CD_3 from front to back. To exaggerate the nonlinearity, 0.021 has been subtracted from every value. As an indication of how tiny the variations are, it may be noted that the section drawn corresponds to the 21st floor of a building, above columns that reach to the ground 20 floors below.

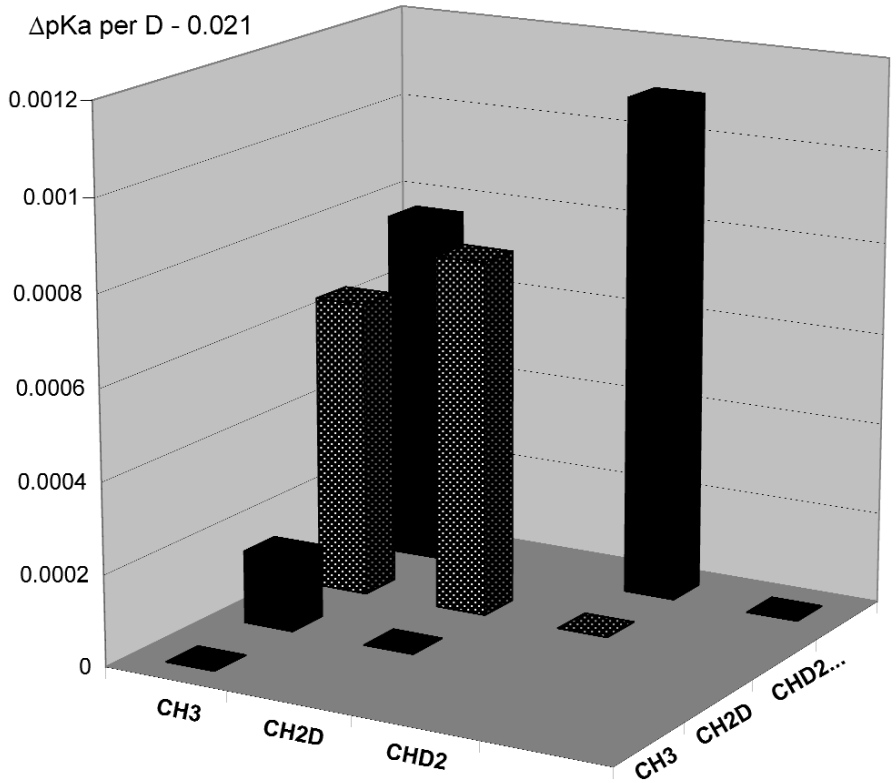


Fig. 4 Nonlinearity of IEs on trimethylamine basicities in D_2O, comparing $(CH_nD_{3-n})_3$ (n = 3,2,1) to $(CH_nD_{3-n})_3$ (n = 2,1,0), displayed as ΔpK_a per D – 0.021. Reprinted with permission from ref. [29]. Copyright © 2008 American Chemical Society.

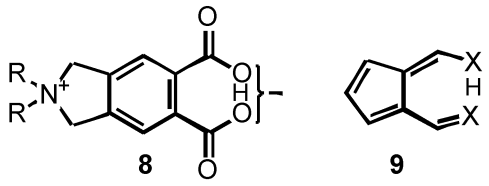
TETRAMETHYLNAPHTHALENEDIAMINES

With the assurance that α-deuteration increases the basicity of NCD_3 relative to NCH_3 we undertook the application of the method of isotopic perturbation to **6**, in order to distinguish whether its H-bond is symmetric or asymmetric [30]. In practice, the method was applied to a statistical mixture of $d_{0,3,6,9,and12}$ isotopologues of **6** (X = H and OCH_3) in methanol-d_4, $CDCl_3$, and DMSO-d_6. The ^{13}C NMR splittings and intensities at the various ring carbons of both ions are consistent with perturbation isotope shifts, intrinsic shifts, or a combination of both. These two kinds of shift can be distinguished because the perturbation shifts are equal in magnitude and of opposite sign at the two sides of the molecule. The observation of perturbation shifts at some carbons means that the proton resides in a double-minimum potential and that each ion is a pair of rapidly interconverting tautomers. Therefore, burying the charge under four methyls does not diminish the role of solvation sufficiently to permit a symmetric H-bond.

ZWITTERIONS AND NEUTRALS

To further probe the influence of solvation on the symmetry of H-bonds, we studied zwitterions **8** (R = butyl, octyl) and neutrals **9** (X = O, NAr) [31]. If the disorder of solvation is created by a dynamic disorder of the position of the counterion, then fixing the positive charge symmetrically with respect to the two carboxyl groups, as in **8**, will remove that source of disorder. Alternatively, if the exposed negative

charge of a carboxylate is sensitive to the disorder of solvation, perhaps a neutral, such as **9**, will be less sensitive.



8 **9**

As with other phthalates, isotopic perturbation in **8** was provided by mono-^{18}O carboxyls. The zwitterions showed larger isotope shifts at carboxyl and ipso carbons, in CD_3OD and CD_2Cl_2 [32]. The symmetry of the H-bonds in neutrals 6-hydroxy-2-formylfulvene **9** (X = O) and *N*,*N*′-diaryl-6-amino-fulvene-2-aldimine **9** (X = NHPh and NH-3,5-Xyl) was probed with perturbation by CDX [33], as in **3**. Observed ^{13}C NMR isotope shifts at several positions can be attributed to a combination of an intrinsic shift and the perturbation of a tautomeric equilibrium.

Thus, even a zwitterion like **8**, where the positive charge is located symmetrically with respect to the phthalate carboxyls, does not show a symmetric H-bond. Nor does a neutral, such as **9** (X = O, NHAr), although it may be that this remains sensitive to the disorder of solvation because a partial positive charge is delocalized by resonance to the OH and NH. In methanol, that charge can be solvated by H-bonding, but in CD_2Cl_2 solvent dipoles stabilize the charge. Those solvent molecules are continuously rearranging their dipole moments, so that the instantaneous stabilization varies with time and with location.

ORIGIN OF H-BOND'S APPARENT STRENGTH

Our continued inability to detect symmetric H-bonds casts doubt on their special stabilization. Because H-bonds can be described as resonance hybrids, it has long been expected that they reach their maximum stabilization when the two resonance forms have identical energy, as with a single-well potential. Indeed, some H-bonds have been classified as resonance-assisted H-bonds [34], or sometimes as H-bonds with covalent character. Yet if there were extra stabilization associated with symmetry, symmetric H-bonds ought to be more common and more readily detectable.

We therefore conclude that there is no great stabilization associated with symmetric H-bonds. Of course there is a reduction of zero-point energy when a double-well potential is converted to single, but this could contribute only 17 kJ mol^{-1} (if the 2800 cm^{-1} of a H-bonded OH or NH drops to zero frequency). Why then are symmetric H-bonds seen in some crystals? It may be that they are not due to any special stabilization, but to crystal-packing forces that overcome overly long 1.2-Å OH distances.

Why are symmetric H-bonds thought to be so stable? In part, this is because there is a excellent correlation between H-bond strength and heavy-atom distance [35]. The correlation is not linear, but shows a distinct jump between solution and gas phase. The correlation arises simply because the weak H-bonds are all neutrals, and the strong ones are gas-phase ions (with one dubious exception). We interpret this dichotomy as arising because the energy of forming an H-bond involving an ion is greatly increased by ion–dipole attraction. Likewise, the heavy-atom distance is shortened by ionic contraction. Therefore, the correlation between H-bond length and strength is tenuous. If short, low-barrier H-bonds with great strengths are a feature only of gas-phase ions, then it is essential to account for solvation.

If **6** is not symmetric, its H-bond is not stabilized by resonance involving two identical resonance forms. Then why is it so weakly acidic? We suggest that the H-bonds are not strong in themselves. Instead, we return to the proposal that the enhanced basicity of tetramethylnaphthalenediamines arises from relief of strain, primarily steric and lone-pair repulsion, upon protonation [36]. Indeed, the normal

basicity of 1,8-diaminonaphthalene shows that the H-bond itself cannot be responsible for the enhanced basicity of the more strained derivatives. Similarly, the large ΔpK in **5** is due primarily to protonation-induced relief of the carboxylate repulsions in its dianion, as enforced by steric repulsions of its *tert*-butyl groups. The large ΔpK is not due to an enhanced strength of a symmetric H-bond in its mono-anion, whose H-bond is not symmetric.

Furthermore, in accounting for the role of short, strong, or low-barrier H-bonds in some enzymatic catalysis, there may be no need to invoke any extra stabilization due to the H-bond itself. Instead, relief of strain can stabilize the transition state and increase k_{cat}. If a basic group, B^-, in aqueous medium H-bonds to HA, the energy would be lowered. This is the reference. However, if B^- is destabilized in an enzyme active site, then H-bonding to HA will lower the energy to an even greater extent. The greater energy lowering is not due to any unusual strength of the H-bond itself but to relief of destabilization. This feature of destabilization and its influence on H-bond strength have also been noted in connection with the greater variability of pK_a in DMSO [37]. However, it is not a new idea that enzymes may reduce activation energies not only by stabilizing the transition state but also by introducing strain into the enzyme-substrate complex [38]. A similar, but not entirely equivalent, interpretation focuses on how solvation and electrostatic complementarity affect (apparent) H-bond strength [39].

BREAKING OF SYMMETRY BY SOLVATION

All our experimental results, across a wide range of solvents and across a variety of H-bonded species, have found that these are present as a mixture of asymmetric tautomers. We have failed to detect a symmetric species, although it is possible that these are a low-temperature phenomenon [40]. The experimental results therefore suggest that asymmetry is inherent to all solutions, at least near room temperature. The asymmetry is attributed to the inherent disorder of the local environment, which solvates one of the basic sites better than the other, stabilizing one tautomer over the other. This is true regardless of whether that solvation is by H-bonding by hydroxylic solvent to carboxylates, by proximity of the counterion to one of the charged donor atoms, or by the orientation of solvent dipoles. 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 necessarily 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 Fig. 5. (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, meaning isomers (or stereoisomers or

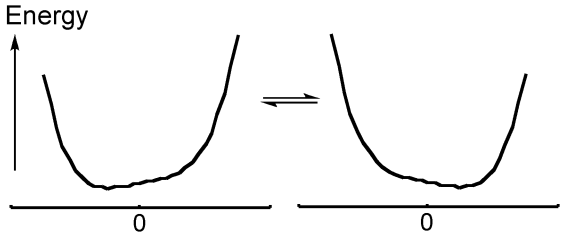


Fig. 5 Equilibrating H-bond solvatomers, each with a single-well potential describing energy vs. bond-distance difference *d*(AH)-*d*(HB).

tautomers) that differ in solvation. This is a more proper use of the term than an earlier classification of species that are not isomeric [41].

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 ground-state system in order to achieve a symmetric configuration that allows the electron or proton to transfer [42]. A classic example is NH_3 [43], 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 well, it would rapidly tunnel to the other. However, in an interacting solvent the nitrogen is pyramidal, and the inversion barrier in substituted derivatives can be measured [44].

Other examples are those where the selection rules for IR and Raman intensities break down in species whose symmetry is reduced by the local solvation environment. Examples include HF_2^-, CS_2, I_3^-, NO_3^-, and aqueous thiourea [45]. 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 [46], 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 to elucidate the role of solvation in breaking symmetry.

SUMMARY AND CONCLUSIONS

The H-bonds in 3-hydroxy-2-phenylpropenal (**3c**), in the monoanions of a wide range of dicarboxylic acids (**4a**,**4b**), in protonated tetramethylnaphthalenediamines (**6**), in phthalate zwitterions **8**, and in neutrals **9** (X = O, NHAr) are all asymmetric. Acccording to the method of isotopic perturbation, each of these species is present in solution as a mixture of two equilibrating tautomers. This contrasts with crystals, where some of these species are symmetric, with a centered H.

A digression concerned secondary deuterium IEs on amine basicity. These were confirmed with highly accurate NMR titrations and shown to be of stereoelectronic origin. It was also possible to demonstrate a nonadditivity of IEs on the basicities of the isotopologues of trimethylamine.

The contrast between crystalline phases and solution is attributed to the disorder of the solvation environment, regardless of whether that solvation is by H-bonding by hydroxylic solvent, by proximity to the counterion, or by the orientation of solvent dipoles. Symmetry-breaking by solvation is proposed to be a general phenomenon, beyond the question of H-bonds. The further implication of these results for the controversial role of low-barrier H-bonds in enzyme-catalyzed reactions is discussed, and it is proposed that acceleration arises from relief of strain, rather than from any special strength of the H-bond.

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