ACCOUNTS
of chemical research

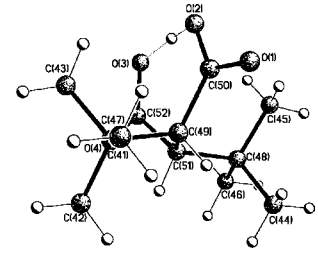
Are Short, Low-Barrier Hydrogen Bonds Unusually Strong?

CHARLES L. PERRIN*

Department of Chemistry & Biochemistry, University of California—San Diego, La Jolla, California 92093-0358, United States

RECEIVED ON JULY 8, 2010

CONSPECTUS



In a symmetric hydrogen bond (H-bond), the hydrogen atom is perfectly centered between the two donor atoms. The energy diagram for hydrogen motion is thus a single-well potential, rather than the double-well potential of a more typical H-bond, in which the hydrogen is covalently bonded to one atom and H-bonded to the other. Examples of symmetric H-bonds are often found in crystal structures, and they exhibit the distinctive feature of unusually short length: for example, the O—O distance in symmetric OHO H-bonds is found to be less than 2.5 Å. In comparison, the O—O distance in a typical asymmetric H-bond, such as $ROH\cdots OR_2$, ranges from about 2.7 to 3.0 Å.

In this Account, we briefly review and update our use of the method of isotopic perturbation to search for a symmetric, centered, or single-well-potential H-bond in solution. Such low-barrier H-bonds are thought to be unusually strong, owing perhaps to the resonance stabilization of two identical resonance forms [A—H···B ↔ A···H—B]. This presumptive bond strength has been invoked to explain some enzyme-catalyzed reactions. Yet in solution, a wide variety of OHO, OHN, and NHN H-bonds have all been found to be asymmetric, in double-well potentials. Examples include the monoanion of (±)-2,3-di-*tert*-butylsuccinic acid and a protonated tetramethylnaphthalenediamine, even though these two ions are often considered prototypes of species with strong H-bonds. In fact, all of the purported examples of strong, symmetric H-bonds have been found to exist in solution as pairs of asymmetric tautomers, in contrast to their symmetry in some crystals. The asymmetry can be attributed to the disorder of the local solvation environment, which leads to an equilibrium among solvatomers (that is, isomers that differ in solvation).

If the disorder of the local environment is sufficient to break symmetry, then symmetry itself is not sufficient to stabilize the H-bond, and symmetric H-bonds do not have an enhanced stability or an unusual strength. Nor are short H-bonds unusually strong. We discuss previous evidence for "short, strong, low-barrier" H-bonds and show it to be based on ambiguous comparisons. The role of such H-bonds in enzyme-catalyzed reactions is then ascribed not to any unusual strength of the H-bond itself but to relief of "strain."

Introduction: Symmetric (Short, Strong, Low-Barrier) Hydrogen Bonds

Hydrogen bonding (H-bonding) is one of the most widely studied aspects of molecular structure,[1] with nearly 150 000 entries in Chemical Abstracts, plus innumerable others where the topic appears in the article but not in the abstract. Our interest in recent years has been in symmetric H-bonds, where the hydrogen is centered between the two donor atoms (**1**), in a single-well potential (Figure 1a). These are contrasted with the more usual case of a double-well potential (Figure 1b), where the hydrogen is bonded to one of the donor atoms and H-bonded to the other. In the special case that the two structures (**2a**, **2b**) are of nearly equal energy (Figure 1c), the hydrogen may jump from one donor to the other. We have reviewed this topic previously,[2] and this Account is a summary and update of what we have learned. In particular, we question the premise that symmetric or short H-bonds are unusually strong.

A···H···B [A–H···B ⇌ A···H–B]
1 **2a** **2b**

Published on the Web 10/12/2010 www.pubs.acs.org/acr
10.1021/ar100097j

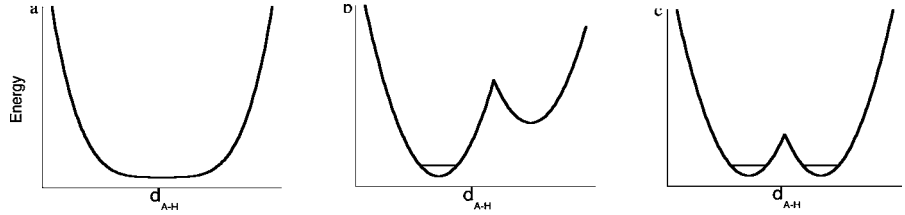


FIGURE 1. Potentials for H motion: (a) Single-well, (b) double-well, and (c) isoenergetic double-well.

Symmetric H-bonds are quite unusual. They are associated with a short distance between the two donor atoms, less than 2.5 Å for OHO H-bonds. This is consistent with the transformation of the potential-energy diagram from that of Figure 1c to that of Figure 1a as the wells approach each other. Because that transformation leads to a diminution of the barrier between the two wells, such "short" H-bonds are also designated as "low-barrier". Moreover, they seem to show extra stability or strength. The designation "short", "strong", or "low-barrier" thus depends on the criterion used for characterization. Other distinctive features, such as a high-frequency (downfield) ^{1}H NMR signal, primary isotope shifts, an unusual H/D fractionation factor, and intense continuous IR absorption, accompany those criteria.[3] These short, strong, low-barrier H-bonds have attracted great interest recently for their possible role in stabilizing intermediates or transition states in enzyme-catalyzed reactions.[4]

The term "symmetric" should be clarified. We are concerned with H-bonds where the hydrogen is shared between the two donor atoms. These would be symmetric if the two donors are identical, but a shared hydrogen can also result if the two donors have the same basicity, as in chloromaleate monoanion or the complex between 4-methylpyridine and pentachlorophenol.[5] This prerequisite for a strong H-bond is often called the principle of pK_a equalization.[6] Another potentially confusing usage of the term "symmetric" is with regard to Figure 1c, which is a symmetric potential but does not embody a symmetric H-bond, with a shared hydrogen.

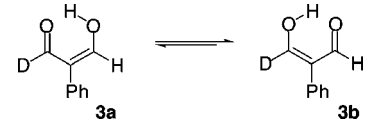
Methodology

Asymmetric H-bonds can be distinguished experimentally from symmetric ones by the NMR method of isotopic perturbation. This was originally applied to carbocations,[7] and it succeeds even if signals are coalesced by rapid exchange. The method depends on measuring the isotope shift (isotope effect on chemical shift) $^n\Delta$, due to a heavier isotope *n* atoms away from the reporter nucleus (eq 1).[8] There are two contributions to the observed Δ (eq 2): an intrinsic shift, Δ_o, owing to the mere presence of an isotope, and a shift induced by perturbation of an equilibrium, Δ_{eq}, arising from differences in zero-point energies between the two participants in the equilibrium.

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

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

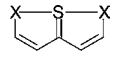
The method can be illustrated nicely with 2-phenyl-3-hydroxypropenal-*d*, where the innocuous phenyl is merely for synthetic convenience.[9] This is known from microwave spectroscopy of the parent hydroxypropenal to be a mixture of two asymmetric tautomers (**3a**⇄**3b**). According to model enols and aldehydes, the C−H stretching frequency of **3a** is near 3020 cm^{-1}, whereas the aldehydic C−H of **3b** is near 2770 cm^{-1}. The C−D frequencies of **3a** and **3b** are in the opposite order, but their zero-point energies are lower and of less influence. 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 spectrum, the chemical shift of an enolic CH, as in models for **3a**, appears at δ 173, whereas that of an aldehydic CH, as in models for **3b**, appears at δ 196. Owing to rapid tautomerization, separate signals at δ 173 and 196 are not seen. Instead only an average signal is seen, but weighted by the populations. Because the equilibrium favors **3b**, that average for the CH is closer to δ 196, whereas the average for the CD is closer to δ 173. From all these values, the separation between CH and CD is estimated to be ∼2 ppm.



Because the ^{13}C signal of a CD is indistinct, it is easier to measure the separation between the CH signals of 2-phenyl-3-hydroxypropenal and 2-phenyl-3-hydroxypropenal-*d*. This separation was found to be 0.76 ppm at room temperature, and greater at lower temperature, where the equilibrium is more unbalanced. The same behavior is seen in the ^{1}H NMR spectrum, because again aldehyde CH═O is at higher chemical shift than enolic CH−O. Therefore, 2-phenyl-3-hydroxypropenal-*d* is confirmed to be an equilibrating mixture of two tautomers, **3a** and **3b**, with an asymmetric H-bond.

Lest it be thought that the asymmetry is due to the isotopic substitution itself, the potential-energy surface (subject to

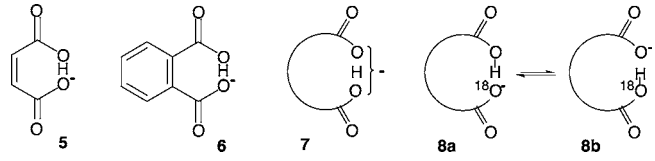
the Born−Oppenheimer approximation) is determined only by the electrons, independently of nuclear masses. Then even 2-phenyl-3-hydroxypropenal, without D, must be an equilibrating mixture of two tautomers, with an asymmetric H-bond. In contrast, deuterium-substituted 1,6-dioxa-6aλ^4-thiapentalene (**4**, X = O) and 1,6,6aλ^4-trithiapentalene (**4**, X = S) are symmetric,[10] as well as various metal chelates of **3**.[11]



4

Search for Symmetric H-Bonds

The canonical examples of symmetric H-bonds are in monoanions of some dicarboxylic acids, such as maleate (**5**) and phthalate (**6**). According to neutron-diffraction studies on their crystals, the H is truly centered between the two oxygens,[5] as suggested in **7**. We have carried out extensive ^{13}C NMR studies on their symmetry in solution, with mono-^{18}O-labeling to perturb a putative equilibrium between two tautomers (**8a** ⇄ **8b**).[12] The intrinsic isotope shift Δ_o (eq 2) can be measured in the diacid or dianion. In all cases, across a wide range of dicarboxylic acids and thus a wide range of O−O distances, a small but significant Δ_{eq} is measurable in the monoanion, corresponding to a mixture of tautomers. It was difficult to publish those initial results, despite convincing control experiments,[13] because they contradicted well-established evidence for symmetry (or centered hydrogens) in crystals. To reconcile this contradiction (and to achieve publication without offending the crystallography community), we proposed that this asymmetry is a consequence of the polarity of aqueous solution, which stabilizes the localized negative charge of **8a** or **8b** more than the delocalized one of **7**.[14] Computer simulations support this interpretation[15] However, further studies in nonpolar organic solvents continued to show Δ_{eq}.[12] We therefore concluded that the difference between a crystal and a solution is that a crystal is organized. Consequently, the environments around the two carboxyl groups in a crystal can be guaranteed to be identical, whereas a solution is disorganized, with one of the carboxyls instantaneously solvated better than the other. Thus the H-bond is asymmetric. Computer simulations support this interpretation too.[16]



5 **6** **7** **8a** **8b**

In further pursuit of a relationship between strength of H-bonds and symmetry, we investigated the "strongest"

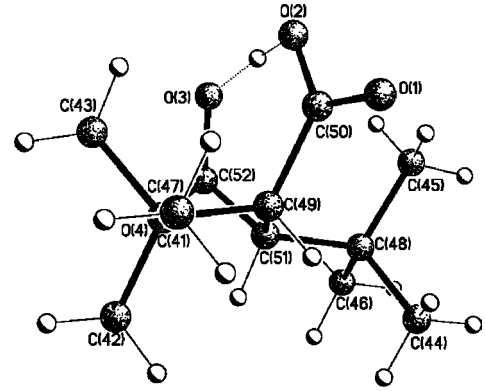
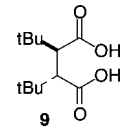


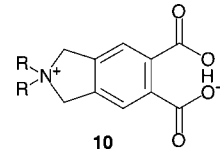
FIGURE 2. Crystal structure of hydrogen (*R*,*R*)-α,α′-di-*tert*-butylsuccinate.[19]

H-bond among dicarboxylate monoanions. A common and convenient measure of H-bond strength is ΔpK_a, the difference between first and second acid-dissociation constants. According to this measure, (±)-α,α′-di-*tert*-butylsuccinic acid (**9**), with a ΔpK_a of 9.54, has the strongest H-bond.[17] It is stronger even than the H-bond of aqueous FHF^-, which is symmetric but whose $\Delta G°$ and $\Delta H°$ for formation from HF + F^- are only −0.54 kcal/mol and +1.5 kcal/mol (endothermic!), respectively.[18] Nevertheless, ^{18}O-induced ^{13}C NMR isotope shifts in solution show that the monoanion of **9** is asymmetric, consistent with X-ray crystal structures of five of its monoanion salts, despite a remarkably short O−O distance of 2.41−2.45 Å.[19] The anion of the tetrapropylammonium salt is shown in Figure 2. Its O(2)−O(3) distance is 2.416 Å, and its O−H distances are 1.06 and 1.36 Å.



9

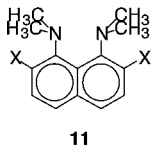
We then designed a modification that might show a symmetric H-bond. Zwitterion **10** seemed like a good candidate, because its positive charge is located symmetrically with respect to its two carboxyls and to its intramolecular OHO H-bond. Nevertheless, **10** too is a mixture of tautomers, with an asymmetric H-bond.[20]



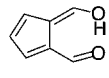
10

An informative example is the H-bond in protonated 1,8-bis(dimethylamino)naphthalenes (**11**, X = H, OCH_3), which show enhanced basicity that is often attributed to the strength of their H-bonds. Nevertheless, isotopic perturbation by CD_3

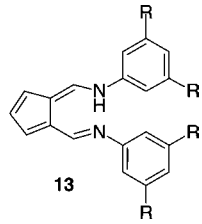
groups, which increase the basicity of a nitrogen to which they are attached,[21] shows that the H-bonds are not symmetric.[22] The same conclusion was reached based on NMR coupling constants, although the H-bond becomes more symmetric with a noncoordinating counterion and at low temperature.[23] Various other OHO and NHN H-bonds, as in 6-hydroxy-2-formylfulvene (**12**) and two *N*,*N*′-diaryl-6-aminofulvene-2-aldimines (**13**, R = H, CH_3), might be symmetric because their seven-membered rings allow more flexibility. Besides, they are neutrals, so ionic solvation is less important. Yet according to D-induced ^{13}C isotope shifts, analogous to those in **3**, these too are asymmetric.[24]



11

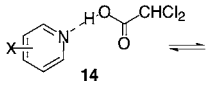


12

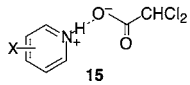


13

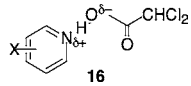
Finally, to explore the possibility that the disorder of solvation might be less important at low temperature, where entropy has a lesser effect, we investigated 1:1 complexes (**14**) between substituted pyridines and dichloroacetic acid. These too are neutral species, in tautomeric equilibrium with the pyridinium−dichloroacetate ion pair (**15**), and they have the further advantage of being intermolecular, allowing the geometry to adjust to an optimum that would permit a single-well potential, as in $[(CF_3COO)_2H]^-$.[25] Nevertheless, ^{18}O-induced isotope shifts in the ^{13}C NMR spectra of complexes of $Cl_2CHC^{18}O_2H$ with substituted pyridines in CD_2Cl_2 at low temperature show no drop to Δ_o when the acidities of the H-bond donors become matched.[26] Such a drop would have indicated a single-well H-bond (**16**). Instead, the isotope shifts reach a maximum, consistent with a mixture of tautomers.



14



15



16

Solvatomers

Our view of the role of solvation has evolved as we continued to find asymmetric H-bonds in a widening variety of circumstances. Initially, we had proposed that the asymmetry is a consequence of the polarity of aqueous solution.[14] Then further studies in nonpolar organic solvents continued to show asymmetric H-bonds.[12] We therefore attributed the asymmetry to the disorder of the local environment, whether because of H-bonding in protic solvents or because of the interaction with an asymmetrically positioned counterion in nonpolar solvents. Yet in zwitterion **10**, the quaternary nitrogen of the internal counterion is on a symmetry axis and cannot desymmetrize the local environment. Nevertheless, its H-bond too is asymmetric. Therefore, we concluded that an asymmetric environment is inherent to all solutions, not necessarily through H-bonding or positioning of counterion, but even through interactions with individual solvent molecules. Those solvent molecules are continually reorienting, so that the instantaneous solvation varies, quite unlike the organized environment found in crystals. The disorder of instantaneous solvation is a fundamental feature of solutions. It is obvious, but it has only occasionally been explored.

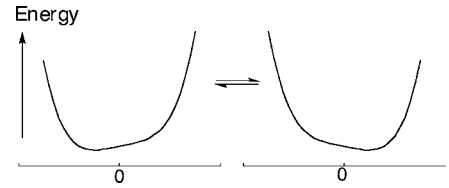


FIGURE 3. Equilibrating H-bond solvatomers, each with a single-well potential for H motion.

Although all our results demonstrate a mixture of tautomers, rather than a single symmetric species, the H-bond is not necessarily described by a double-well potential. The alternative is a single-well potential, but with an additional potential-energy contribution due to the instantaneous solvation. (A third possibility is a double-well potential where the zero-point energy lies above the barrier, but this is equivalent to a single-well potential in this context.) As changes in solvation shift the relative energies of the various structures, the hydrogen moves across the H-bond. Except for the rare occasion when the solvation happens to be symmetric, an asymmetric structure is stabilized, as suggested in Figure 3. Depending on the magnitude of the instantaneous stabilization relative to *kT*, the hydrogen is more or less distributed across the O−O distance. The multitude of different structures that result are properly called solvatomers, meaning isomers or stereoisomers or (as here) tautomers that differ in solvation.

A multiplicity of solvatomers in a single-well potential like that of Figure 3 can tentatively be rejected in favor of mixture of two tautomers in a double-well potential. Although the observation of a perturbation isotope shift Δ_{eq} is consistent with either potential, we maintain that the magnitude of the observed shift suggests a double-well potential. If the hydrogen were distributed across the O−O distance, with a zero-point energy difference that varies linearly with distance, then it is readily shown (Supporting Information) that the observed Δ_{eq} would be reduced to one-third of the Δ_{eq} for a two-site H-bond. That Δ_{eq} value can be evaluated in succinate monoanion, which lacks an intramolecular H-bond and must

be two-site. Yet the observed Δ_{eq} values of aqueous dicarboxylate monoanions with an intramolecular H-bond are nearly the same as that in succinate and are not reduced threefold. Therefore, it is likely that the hydrogen in an intramolecular H-bond of a dicarboxylate monoanion is on one carboxylate or the other and is not distributed across the O−O distance.

Is There a Relationship between Symmetry and Shortness of H-Bonds?

There is undoubtedly a relationship between symmetry and shortness. Decreasing the distance between donor atoms must eventually decrease the barrier to hydrogen motion below the zero-point energy, so that a double-well potential becomes a single-well one. An example of this transformation occurs when ice is compressed to ice X, with an O−O distance of 2.27 Å and a single-well potential.[27] However, observations of short H-bonds are usually not accompanied by evidence for their symmetry.[28]

Is There a Relationship between Symmetry and Strength of H-Bonds?

Why might symmetry be associated not only with shortness but also with strength? One source of stabilization is the decrease of zero-point energy when a double-well potential is converted to single. However, the maximum contribution is only 4 kcal/mol (for a 2800-cm^{-1} vibration).

Insofar as H-bonds can be described as resonance hybrids,[29] they ought to attain maximum stabilization when the two resonance forms (**2a** ↔ **2b**) have identical energy. This is the basis for expecting symmetric H-bonds to be strong. This feature should not be confused with the classification of some H-bonds as resonance-assisted.[30] Among these are enols of β-dicarbonyl compounds, such as **3**. However, their resonance resides in their π systems, whereas the H-bond is σ. The significance of that resonance for H-bonding is that it equalizes the basicity of the two oxygens and thereby strengthens the H-bond. Even so, **3** does not have a symmetric H-bond, according to deuterium-induced ^{13}C NMR shifts.[9]

Our continued inability to find symmetric H-bonds in solution suggests that they have no special stability. If they were so stable, they ought to be more widespread and we ought to have found some. Moreover, if they were so stable, solvation should not be capable of disrupting their symmetry. Yet all the H-bonds that we have investigated are asymmetric, so that the two resonance forms (**2a**, **2b**) cannot be identical, and the stabilization is less than maximum. Therefore it is doubtful that resonance ever provides much stabilization to H-bonds. The presumed maximum stabilization associated with two identical resonance forms is not sufficient to constrain the H-bond to be symmetric. We therefore conclude that there is no exceptional stabilization associated with symmetric H-bonds.

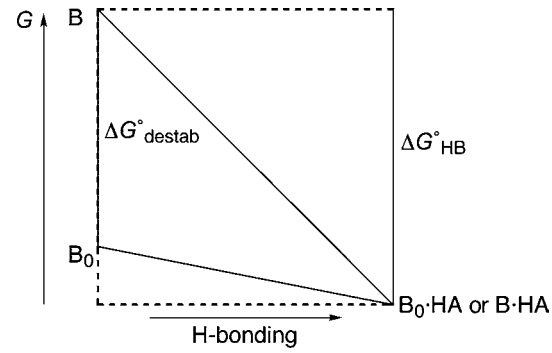


FIGURE 4. Energy diagram showing apparent H-bond stabilization, $\Delta G°_{HB}$, due to relief of strain $\Delta G°_{destab}$ in base B or due to relief of destabilization $\Delta G°_{destab}$ of anionic B in an aprotic environment (relative to unstrained or aqueous B_0) on forming a H-bond.

How then can we account for p*K* enhancements that are attributed to H-bond strength in the monoanion of **9** and in protonated **11**? The enhancements cannot be attributed to H-bonds that are strong owing to symmetry, because they are not symmetric. Might the enhancements be attributed to H-bonds that are strong, albeit asymmetric? We reject this possibility, because it is merely an unsupported hypothesis. There is no independent evidence for a strong H-bond in solution in the absence of the resonance stabilization associated with symmetry.

Are the p*K* enhancements due to some sort of strain? The *tert*-butyl groups in **9** would seem to be a clue to steric strain. However, the *tert*-butyls are anti and far from each other, and the X-ray structures of monoanion salts of **9** show no unusual distortions, except that the carboxyls are forced into proximity, compressing the O−O distance.[19] The origin of the strain is revealed by the X-ray structure of the dianion of **9**, which shows severe electrostatic repulsion between the two carboxylates.[31] To reduce that repulsion, the carboxylates are twisted nearly perpendicular to the central C−C bond. Nevertheless, destabilization remains in the dianion, and it is relieved in the monoanion by inserting a proton between the carboxylates. A similar relief of strain was proposed to account for the high basicity of 1,8-bis(dimethylamino)naphthalenes (**11**).[32] Indeed, the near-normal basicity of the parent 1,8-diaminonaphthalene shows that the H-bond itself cannot be responsible for the enhanced basicity of its strained derivatives. The p*K* enhancements can thus be attributed to a relief of strain (generalized beyond steric strain to distortions of distances and angles), rather than to any unusual H-bond strength. Fig-

ure 4 illustrates how the stabilization due to relief of strain upon H-bonding is not due to H-bond strength.

There is a further destabilization of symmetric H-bonds. An O−O distance of 2.4−2.5 Å implies an O−H distance of 1.2−1.25 Å, longer than the normal 1.0 Å. Stretching the O−H distance by even 0.2 Å, against the force constant corresponding to a 2800-cm^{-1} vibration, requires nearly 15 kcal/mol. This represents a considerable destabilization,[29] which the presumed resonance stabilization of symmetric H-bonds cannot overcome. The destabilization may be the reason that we do not detect them.

If symmetric H-bonds are destabilized, then why are they found in some crystals? The default explanation is that crystal-packing forces are somehow responsible for tolerating the long O−H distance. Compression of the heavy-atom distance converts a double-well potential into a single-well one, but we deny that there is any stabilization associated with this.

Is There a Relationship between Shortness and Strength of H-Bonds?

Although H-bonds do not derive any unusual strength from symmetry, can the shortness of some H-bonds be taken as evidence that they are strong? The counterpart of resonance stabilization of symmetric H-bonds is covalent character in short H-bonds. This can be recognized by a negative Laplacian of the electron density.[33] Covalent character would appear to represent stabilization of short H-bonds. For example, bihalide anions XHX^- compressed within fullerenes are claimed to be strengthened,[34] but the strength is not necessarily that of the H-bond itself.

The reason that short H-bonds are believed to be unusually strong is largely an influential graph relating H-bond strength to heavy-atom distance.[3] The graph does not show a linear correlation but rather a distinct jump, almost a discontinuity, between short, strong bonds in the gas phase and long, weak ones in solution. The apparent relation arises simply because all the weak H-bonds are neutrals and all the strong ones (with one dubious exception) are gas-phase ions, whose H-bonds are classified as charge-assisted.[6] We attribute the dichotomy to ion-dipole attraction, which stabilizes ionic adducts and also shortens distances by ionic contraction. Thus H-bonds of gas-phase ions are strong, but a relation between heavy-atom distance and H-bond strength in solution is tenuous. Indeed, the data above for FHF^- show that the formation of its H-bond in water is nearly thermoneutral, even though its gas-phase H-bond strength is a champion 38.6 kcal/mol.[35] Likewise, the stabilization of XHX^- within fullerenes, associated with covalent character,[34] is not due to H-bonding but to ion-dipole attraction. More compelling is a compilation of data for dicarboxylic acid monoanions (in the Supporting Information of ref 19), which denies a correlation between O−O distance and ΔpK_a, as a measure of H-bond strength. The correlation coefficient is a puny 0.39, and it corresponds to distances that increase with ΔpK_a, rather than decrease.

Despite such counterevidence, a relationship between shortness and strength has become a common supposition in recent years. In support of this assertion, a search using SciFinder reveals numerous claims for strong H-bonds when the only evidence is a short heavy-atom distance. *We maintain that this designation is a misnomer, and we deplore its use*.

What then causes short H-bonds? A short H-bond would be a consequence of the transformation from a double well (Figure 1c) to a single well (Figure 1a), but we have found no examples of single-well H-bonds in solution. The H-bonds that we have studied are instead short because of compression that forces the donor atoms together. In the conjugate bases (**11**, dianion of **9**), that compression induces much strain, which is relieved, but only in part, by inserting a proton between the heavy atoms. The strain that remains cannot strengthen the H-bond, but must weaken it. If the compression could be relaxed, the H-bonded species would become even more stable. Therefore, the shortness of the H-bond must destabilize it.

If short H-bonds are destabilized, why are they seen so often? Again the default explanation is that crystal-packing forces compress the heavy atoms and shorten the H-bond. It may be that other heavy atoms have stronger van der Waals repulsions, whereas H-bonding represents an attraction that reduces its repulsion. If so, H-bonds can be said to be facultative (capable of functioning under various environmental conditions), or permissive of short distances.

H-Bonds in Enzyme Catalysis

Finally, we join other critics of the claims that short, strong, or low-barrier H-bonds contribute to enzymatic catalysis.[36] Although there are distinguishing characteristics associated with such bonds, there is no evidence for extra stabilization due to the H-bond itself. It is certainly well established that there is no unusual stabilization when the condition of pK_a equalization is met.[37] The claim that H-bond strengths can increase on going to the transition state comes from the sensitivity of H-bond strength to ΔpK_a, which is greater in an aprotic medium.[38] However, the effect is exaggerated by plotting H-bond strengths in dimethyl sulfoxide (DMSO) versus ΔpK_a in H_2O, rather than ΔpK_a in DMSO.

Short H-bonds are quite common in proteins. One survey of crystal structures found 7860 short H-bonds among 948 proteins, not only in side chains but also in backbones.[39] They are short because of compression. Their ubiquity, beyond enzyme active sites, shows that there is no need to suggest increased strength or catalytic power from being short. Instead, H-bonds are simply permissive of short distances.

Figure 4 also shows how destabilization of an anion in an aprotic medium can be relieved by H-bond formation. Relief of "strain" of an anion in an aprotic enzyme active site can thus stabilize the transition state, relative to the enzyme–substrate complex, and thereby increase k_{cat}.[40] This figure is equivalent to Figure 3 of ref 38, expressing the greater sensitivity of H-bond strength to ΔpK_a in aprotic media, but Figure 4 shows how the stabilization is not due to any unusual strength of the H-bond itself but instead to relief of "strain".

Summary and Conclusions

According to isotope shifts, the H-bonds in 3-hydroxy-2-phenylpropenal (**3**), in the monoanions of a wide range of dicarboxylic acids, including (±)-α,α′-di-*tert*-butylsuccinic (**9**), in zwitterions **10**, in protonated tetramethylnaphthalenediamines (**11**), in neutrals **12** and **13**, and in pyridine–dichloroacetic acid complexes (**14**, **15**) are all asymmetric. This asymmetry contrasts with the observation of a centered H in some crystals. The contrast can be attributed to solvation, which creates an instantaneous local environment that is disordered.

Because all the H-bonds that we have investigated are asymmetric in solution, we conclude that there is no H-bond that is stabilized by symmetry *per se*, nor any special stabilization associated with symmetric, short, or low-barrier H-bonds. The p*K* enhancements that are taken as evidence for a strong H-bond can instead be attributed to relief of strain. If symmetric or low-barrier H-bonds were so stable, they ought to be more common and we ought to have found some. Besides, if they were so stable, the local solvation environment should not be capable of disrupting their symmetry.

Moreover, we deny any relationship between shortness of H-bonds and strength. Instead, it is proposed that H-bonds are simply permissive of short distances. The further implication of these results for the proposed role of short, strong, or low-barrier H-bonds in enzymatic reactions is discussed briefly, and it is proposed that the observed acceleration arises from relief of strain, rather than from any enhanced strength of the H-bond itself.

This research was supported by continuous NSF Grants, including the most recent, CHE07-42801. I am grateful to my co-workers, cited in the references, for their excellent skills.

Supporting Information Available. Derivation that the observed Δ_{eq} for a hydrogen distributed across the O–O distance is 1/3 of the Δ_{eq} for a two-site H-bond. Comparison of experimental Δ_{eq} values of dicarboxylate monoanions. This material is available free of charge via the Internet at http://pubs.acs.org.

BIOGRAPHICAL INFORMATION

Charles L. Perrin was born in Pittsburgh in 1938. He graduated from Harvard College in 1959 and received his Ph.D. in 1963 from Harvard University, under the direction of the late F. H. Westheimer. Following an NSF Postdoctoral Fellowship at UC Berkeley, he joined the founders of the new campus at UC San Diego, where he is now Distinguished Professor of Chemistry (not emeritus). He has held visiting professorships in Göteborg, Paris, Padua, and Copenhagen, and he has won numerous UCSD teaching prizes. His research spans a broad range of structural and mechanistic chemistry, including anomeric effects, stereoelectronic control, isotope effects, dynamic NMR, solvation, and hydrogen bonding. This is his third Account.

FOOTNOTES

*E-mail: cperrin@ucsd.edu.

REFERENCES

1 Pimentel, G. C.; McClellan, A. L. *The Hydrogen Bond*; W. H. Freeman, San Francisco, 1960. Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: Oxford, 1997. Scheiner, S. *Hydrogen Bonding: A Theoretical Perspective*, Oxford University Press, New York, 1997.

2 Perrin, C. L.; Nielson, J. B. "Strong" Hydrogen Bonds in Chemistry and Biology. *Annu. Rev. Phys. Chem.* **1997**, *48*, 511–544. Lau, J. S.; Perrin, C. L. Isotope Effects and Symmetry of Hydrogen Bonds in Solution: Single and Double-Well Potentials. In *Isotope Effects in Chemistry and Biology*; Kohen, A., Limbach, H. H., Eds.; CRC Press: Boca Raton, FL, 2005; Chapter 8. Perrin, C. L. Symmetry of Hydrogen Bonds in Solution. *Pure Appl. Chem.* **2009**, *81*, 571–583.

3 Hibbert, F.; Emsley, J. Hydrogen Bonding and Chemical Reactivity. *Adv. Phys. Org. Chem.* **1990**, *26*, 255–379.

4 Cleland, W. W. The Low-Barrier Hydrogen Bond in Enzymic Catalysis. *Adv. Phys. Org. Chem.* **2010**, *44*, 1–17.

5 Ellison, R. D.; Levy, H. A. A Centered Hydrogen Bond in Potassium Hydrogen Chloromaleate. A Neutron Diffraction Structure Determination. *Acta Crystallogr.* **1965**, *19*, 260–268. Steiner, T.; Majerz, I.; Wilson, C. C. First O-H-N Hydrogen Bond with a Centered Proton Obtained by Thermally Induced Proton Migration. *Angew. Chem., Int. Ed.* **2001**, *40*, 2651–2654.

6 Gilli, P.; Pretto, L.; Bertolasi, V.; Gilli, G. Predicting Hydrogen-Bond Strengths from Acid-Base Molecular Properties. The pK_a Slide Rule: Toward the Solution of a Long-Lasting Problem. *Acc. Chem. Res.* **2009**, *42*, 33–44.

7 Saunders, M.; Telkowski, L.; Kates, M. Isotopic Perturbation of Degeneracy. Carbon-13 NMR Spectra of Dimethylcyclopentyl and Dimethylnorbornyl Cations. *J. Am. Chem. Soc.* **1977**, *99*, 8070–8072. Siehl, H.-U. Isotope Effects on NMR Spectra of Equlibrating Systems. *Adv. Phys. Org. Chem.* **1987**, *23*, 63–162.

8 Hansen, P. E. Isotope Effect on Chemical Shifts in Hydrogen-Bonded Systems. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 967–981.

9 Perrin, C. L.; Nielson, J. B.; Kim, Y.-J. Symmetry of Hydrogen Bonds in Solution, an Overview. *Ber. Bunsen-Ges.* **1998**, *102*, 403–409. Perrin, C. L.; Kim, Y.-J. Symmetry of the Hydrogen Bond in Malonaldehyde Enol in Solution. *J. Am. Chem. Soc.* **1998**, *120*, 12641–12645.

10 Perrin, C. L.; Kim, Y.-J.; Kuperman, J. Structures of 1,6-Dioxa-6aλ4-thiapentalene and of 1,6,6aλ4-Trithiapentalene C_s or C_{2v} Symmetry? *J. Phys. Chem. A* **2001**, *105*, 11383–11387.

11 Perrin, C. L.; Kim, Y.-J. Symmetry of Metal Chelates. *Inorg. Chem.* **2000**, *39*, 3902–3910.

12 Perrin, C. L.; Nielson, J. B. Asymmetry of Hydrogen Bonds in Solutions of Monoanions of Dicarboxylic Acids. *J. Am. Chem. Soc.* **1997**, *119*, 12734.

13 Perrin, C. L.; Thoburn, J. D. Evidence for a Double-Minimum Potential for Intramolecular Hydrogen Bonds of Aqueous Hydrogen Maleate and Hydrogen Phthalate Anions. *J. Am. Chem. Soc.* **1989**, *111*, 8010–8012. Perrin, C. L.; Thoburn, J. D. Symmetries of Hydrogen Bonds in Monoanions of Dicarboxylic Acids. *J. Am. Chem. Soc.* **1992**, *114*, 8559–8565.

14 Perrin, C. L. Symmetries of Hydrogen Bonds in Solution. *Science* **1994**, *266*, 1665–1668.

15 Mavri, J.; Hodoek, M.; Hadi, D. Ab initio SCF and Møller-Plesset Calculations on the Hydrogen Bond in Hydrogen Malonate. Effects of Neighbor Ions and Polarizable Medium. *J. Mol. Struct.* **1990**, *209* (THEOCHEM 68), 421–431.

16 Garcia-Viloca, M.; González-Lafont, À.; Lluch, J. M. Asymmetry of the Hydrogen Bond of Hydrogen Phthalate Anion in Solution. A QM/MM Study. *J. Am. Chem. Soc.* **1999**, *121*, 9198–9207.

17 Eberson, L.; Wadsö, I. Intramolecular Hydrogen Bonding as a Factor in Determining the K_1/K_2 Ratios of Dicarboxylic Acids. *Acta Chem. Scand.* **1963**, *17*, 1552–1562.

18 Salomon, M.; Stevenson, B. K. Studies on Aqueous HF System. *J. Chem. Eng. Data* **1974**, *19*, 42–44.

19 Perrin, C. L.; Lau, J. S.; Kim, Y.-J.; Karri, P.; Moore, C.; Rheingold, A. L. Asymmetry of the "Strongest" OHO Hydrogen Bond, in the Monoanion of (±)-α,α′-Di-*tert*-butylsuccinate. *J. Am. Chem. Soc.* **2009**, *131*, 13548–13554.

20 Perrin, C. L.; Lau, J. S. Hydrogen-Bond Symmetry in Zwitterionic Phthalate Anions: Symmetry Breaking by Solvation. *J. Am. Chem. Soc.* **2006**, *128*, 11820–11824.

21 Perrin, C. L.; Ohta, B. K.; Kuperman, J. β-Deuterium Isotope Effects on Amine Basicity, "Inductive" and Stereochemical. *J. Am. Chem. Soc.* **2003**, *125*, 15008–15009. Perrin, C. L.; Ohta, B. K.; Kuperman, J.; Liberman, J.; Erdélyi, M. Stereochemistry of β-Deuterium Isotope Effects on Amine Basicity. *J. Am. Chem. Soc.* **2005**, *127*, 9641–9647.

22 Perrin, C. L.; Ohta, B. K. Symmetry of N-H-N Hydrogen Bonds in 1,8-Bis(dimethylamino)naphthalene·H^+ and 2,7-Dimethoxy-1,8-bis(dimethylamino)naphthalene·H^+. *J. Am. Chem. Soc.* **2001**, *123*, 6520–6526.

23 Pietrzak, M.; Wehling, J. P.; Kong, S.; Tolstoy, P. M.; Shenderovich, I. G.; Lopez, C.; Claramunt, R. M.; Elguero, J.; Denisov, G. S.; Limbach, H. H. Symmetrization of Cationic Hydrogen Bridges of Protonated Sponges Induced by Solvent and Counteranion Interactions as Revealed by NMR Spectroscopy. *Chem.—Eur. J.* **2010**, *16*, 1679–1690.

24 Perrin, C. L.; Ohta, B. K. Symmetry of O-H-O and N-H-N Hydrogen Bonds in 6-Hydroxy-2-formylfulvene and 6-Aminofulvene-2-aldimines. *Bioorg. Chem.* **2002**, *30*, 3–15.

25 Fillaux, F.; Cousson, A.; Archilla, J. F. R.; Tomkinson, J. A. Neutron Scattering Study of Strong-Symmetric Hydrogen Bonds in Potassium and Cesium Hydrogen Bistrifluoroacetates: Determination of the Crystal Structures and of the Single-Well Potentials for Protons. *J. Chem. Phys.* **2008**, *128*, 204502/1–11.

26 Perrin, C. L.; Karri, P. Reappraisal of Single-Well Hydrogen Bonds in Pyridine-Dichloroacetic Acid Complexes. *Chem. Commun.* **2010**, *46*, 481–483.

27 Sugimura, E.; Iitaka, T.; Hirose, K.; Kawamura, K.; Sata, N.; Ohishi, Y. Compression of H_2O Ice to 126 GPa and Implications for Hydrogen-Bond Symmetrization: Synchrotron X-Ray Diffraction Measurements and Density-Functional Calculations. *Phys. Rev. B* **2008**, *77*, 214103/1–6.

28 Day, V. W.; Hossain, M. A.; Kang, S. O.; Powell, D.; Lushington, G.; Bowman-James, K. Encircled Proton. *J. Am. Chem. Soc.* **2007**, *129*, 8692–8693. Sørensen, J.; Clausen, H. F.; Poulsen, R. D.; Overgaard, J.; Schiøtt, B. Short Strong Hydrogen Bonds in 2-Acetyl-1,8-dihydroxy-3,6-dimethylnaphthalene: An Outlier to Current Hydrogen Bonding Theory. *J. Phys. Chem. A* **2007**, *111*, 345–351.

29 Coulson, C. A. The Hydrogen Bond—A Review of the Present Position. *Research (London)* **1957**, *10*, 149–159.

30 Gilli, G.; Bellucci, F.; Ferretti, V.; Bertolasi, V. Evidence for Resonance-Assisted Hydrogen Bonding from Crystal-Structure Correlations on the Enol Form of the β-Diketone Fragment. *J. Am. Chem. Soc.* **1989**, *111*, 1023–1028.

31 Perrin, C. L.; Lau, J. S.; Kim, Y.-J.; Karri, P.; Moore, C.; Rheingold, A. L. Addition and Correction to Asymmetry of the "Strongest" OHO Hydrogen bond, in the Monoanion of (±)-α,α′-Di-*tert*-butylsuccinate. *J. Am. Chem. Soc.* **2010**, *132*, 2099–2100.

32 Alder, R. W. Strain Effects on Amine Basicities. *Chem. Rev.* **1989**, *89*, 1215–1223. Staab, H. A.; Saupe, T. Proton Sponges and the Geometry of Hydrogen Bonds. Aromatic Nitrogen Bases with Exceptional Basicities. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 865–879.

33 Flensburg, C.; Larsen, S.; Stewart, R. F. Experimental Charge Density Study of Methylammonium Hydrogen Succinate Monohydrate. A Salt with a Very Short O-H-O Hydrogen Bond. *J. Phys. Chem.* **1995**, *99*, 10130–10141. Schmidtmann, S.; Farrugia, L. J.; Middlemiss, D. S.; Gutmann, M. J.; McIntyre, G. J.; Wilson, C. C. Experimental and Theoretical Charge Density Study of Polymorphic Isonicotinamide-Oxalic Acid Molecular Complexes with Strong O···H···N Hydrogen Bonds. *J. Phys. Chem. A* **2009**, *113*, 13985–13997. Tian, S. X.; Li, H.-B. A Theoretical Study of the Photodetachment and Intramolecular Hydrogen-Bonding Energies of Hydrogen Maleate Anions. *J. Phys. Chem. A* **2007**, *111*, 4404–4410.

34 Miño, G.; Contreras, R. Non-electrostatic Components of Short and Strong Hydrogen Bonds Induced by Compression inside Fullerenes. *Chem. Phys. Lett.* **2010**, *486*, 119–122.

35 Larson, J. W.; McMahon, T. B. Gas-Phase Bihalide and Pseudobihalide Ions. An Ion-Cyclotron Resonance Determination of Hydrogen-Bond Energies in XHY^- Species (X, Y = F, Cl, Br, CN). *Inorg. Chem.* **1984**, *23*, 2029–2033.

36 Schutz, C. N.; Warshel, A. The Low Barrier Hydrogen Bond (LBHB) Proposal Revisited: The Case of the Asp···His Pair in Serine Proteases. *Proteins: Struct., Funct., Bioinf.* **2004**, *55*, 711–723. Guthrie, J. P. Short Strong Hydrogen Bonds: Can They Explain Enzymic Catalysis. *Chem. Biol.* **1996**, *3*, 163–170. Kraut, D. A.; Sigala, P. A.; Pybus, B.; Liu, C. W.; Ringe, D.; Petsko, G. A.; Herschlag, D. Testing Electrostatic Complementarity in Enzyme Catalysis: Hydrogen Bonding in the Ketosteroid Isomerase Oxyanion Hole. *PLoS Biol.* **2006**, *4*, 501–519. Fuhrmann, C. N.; Daugherty, M. D.; Agard, D. A. Subangstrom Crystallography Reveals that Short Ionic Hydrogen Bonds, and not a His-Asp Low-Barrier Hydrogen Bond, Stabilize the Transition State in Serine Protease Catalysis. *J. Am. Chem. Soc.* **2006**, *128*, 9086–9102.

37 Shan, S.-O.; Loh, S.; Herschlag, D. The Energetics of Hydrogen Bonds in Model Systems: Implications for Enzymatic Catalysis. *Science* **1996**, *272*, 97–101.

38 Shan, S.-O.; Herschlag, D. The Change in Hydrogen Bond Strength Accompanying Charge Rearrangement: Implications for Enzymatic Catalysis. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 14474–14479.

39 Rajagopal, S.; Vishveshwara, S. Short Hydrogen Bonds in Proteins. *FEBS J.* **2005**, *272*, 1819–1832.

40 Perrin, C. L.; Ohta, B. K. Symmetry of NHN Hydrogen Bonds in Solution. *J. Mol. Struct.* **2003**, *644*, 1–12.