# Theoretical Studies of Proton Transfers

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Transfer of a proton from one atom to another has been called "the most general and important reaction in chemistry".[1] This elementary reaction plays a crucial role in a myriad of processes including acid–base neutralization, electrophilic addition, and a score of enzymatic reactions.[2] Since most of the vast literature that has accumulated over the years[1-3] concerns proton transfers in solution, it has been difficult to separate intrinsic characteristics from solvent effects. For example, early solution work explained the decreasing acidity of alcohols arising from larger alkyl substituents by "electron release" which reduces the stability of the anion relative to the neutral species. However, later determination of a *reverse* order of acidity in the gas phase[4] demonstrated that the trend in solution is dominated by solvent effects and that the alkyl groups *stabilize* the negative charge of the anionic species via their polarizabilities.

The reactions typically studied by the gas-phase work may be characterized as

$$AH^+ + B \xrightarrow[\text{association}]{} (AH\text{–}B)^+ \xrightarrow[\text{proton transfer}]{} (A\text{–}HB)^+ \xrightarrow[\text{dissociation}]{} A + BH^+ \quad (1)$$

Because of the large energies involved in the association and dissociation steps, there is generally little information available about the proton-transfer step. Experimental limitations have prevented the elucidation of much structural data concerning the $(AH\text{–}B)^+$ or $(A\text{–}HB)^+$ complexes or the transition state that separates them. Ab initio molecular orbital methods[5] are capable of providing information that complements experimental data and that circumvents solvent effects. Structures and energies of any species along the proton–transfer coordinate may be obtained by geometry optimizations; additional insights may be gleaned from the electronic wave functions.

We focus our attention here on proton transfers taking place along preexisting H bonds, particularly those bonds present in organic systems or in biomolecules such as proteins. Since the large number of structural constraints in these molecules leads to a wide variation in observed geometrical characteristics of H bonds,[6] it is necessary to study proton transfers over a similar range of geometries. Whereas theoretical methods are well adapted to such a task, their chief limitation is related to the size of system that may be studied. It is therefore necessary to make a judicious choice of small prototype molecules that adequately represent the real systems of interest. As a first approximation to the hydroxyl and amine groups that participate in H bonds, we choose the hydrides $H_2O$ and $NH_3$, thereby assuming that non-hydrogen atoms, e.g., alkyl groups, that are directly bonded to the O and N atoms lead to only minor differences (an approximation tested below). $SH_2$ has been studied as well, principally for comparison between first- and second-row atoms. With regard to specific theoretical procedure, our strategy involves identification of a method that is both moderate in terms of computer requirements and accurate in its quantitative treatment of the proton-transfer process. The latter criterion is tested by comparison with results of more sophisticated theoretical procedures and/or any available experimental data.

What sort of information may we expect to obtain from the calculations? Figure 1 illustrates the features of a potential energy curve for the transfer of a proton between groups A and B (also referred to herein as "subunits"). The difference in energy between the left (AH–B) and right (A–HB) wells is designated as $\Delta E$, which provides an estimate of the equilibrium populations of the two configurations. The kinetics of the transfer step are extremely sensitive to the height of the energy barrier $E^\dagger$ involving the transition state (A–H–B). Since we are generally interested in a particular geometry of the H bond, a number of constraints are typically imposed upon the structure. For example, the length of the H bond, $R$(AB), may be frozen at a given value; angular restrictions may also be included.

Many chemists have found it useful to analyze reactions using a theory developed by Marcus,[7] which relates the reaction rate via a $\Delta F^*$ term to the overall exothermicity $\Delta F^{\circ\prime}$. The quantities in Figure 1 are

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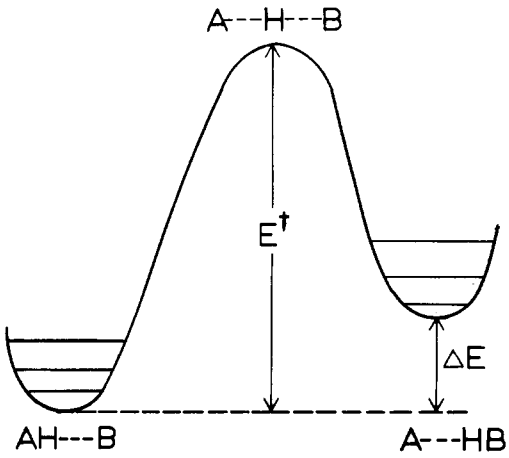


**Figure 1.** Schematic potential energy curve for proton transfer between subunits A and B. The horizontal lines in each well represent vibrational levels.

concerned with the reaction subsequent to complex formation. Hence, our $\Delta E$ is the energy analog of Marcus's $\Delta F_R°'$. $E^\dagger$ is related to $\lambda$, the "intrinsic contribution to the barrier".[7] It may be possible to evaluate $\lambda$ quantum mechanically for a number of "exchange reactions" (where groups A and B are identical) and "cross-reactions" (A $\neq$ B). The validity of the commonly used additivity assumption that $\lambda_{AB} = {}^1/_2(\lambda_{AA} + \lambda_{BB})$ could also be tested in this manner.

This Account is a summary of the calculations carried out in this laboratory over the last several years.[8-20] In addition to obtaining reliable data, a major emphasis has been placed on identification of fundamental concepts capable of explaining a number of diverse trends in as simple a manner as possible and, thereby, providing a framework for predictions in larger systems where calculations of the required accuracy are not feasible.

## Dependence upon Length of H Bond

We begin by constructing systems where the two molecules $XH_n$ and $YH_m$ are held together by a H bond containing the proton to be transferred, viz., $(H_nX\text{-}H\text{-}YH_m)^+$. For each system, proton-transfer potentials were then calculated[8-10] for a series of H-bond lengths $R(XY)$. The transfer barriers $E^\dagger$ are illustrated as a function of $R(XY)$ in Figure 2 where the barrier for transfer from X to Y in the $(H_nX\text{-}H\text{-}YH_m)^+$ system is denoted as XH → Y. It may be first noted that the energy barrier to proton transfer increases quickly as

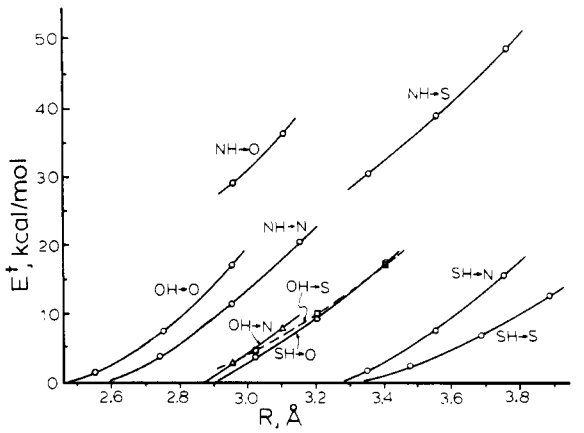


**Figure 2.** Energy barriers to proton transfer as a function of the H-bond length $R$. Label on each curve represents the atoms directly involved in the transfer. Systems examined are $(H_nX\text{-}H\text{-}YH_m)^+$ where $XH_n$ and $YH_m$ = $OH_2$, $NH_3$, and $SH_2$. As an example, the transfer barrier from amine ($NH_3$) to hydroxyl ($OH_2$) is labeled NH → O.

**Table I**
**Energy Barriers to Proton Transfer**

| system | $R$, Å | basis set | $E^\dagger$, kcal/mol SCF | $E^\dagger$, kcal/mol MP3 |
|---|---|---|---|---|
| $(H_2O\text{-}H\text{-}OH_2)^+$ | 2.74 | 4-31G | 7.3 | 5.1 |
| | | 6-311G*(*) | 10.3 | 7.7 |
| $(HO\text{-}H\text{-}OH)^-$ | 2.74 | 4-31G | 7.1 | 3.8 |
| | | 6-311G*(*) | 11.8 | 7.7 |
| | 2.646 | 4-31G | 3.9 | 1.6 |
| | | 6-311G*(*) | 6.9 | 4.3 |
| $(H_3N\text{-}H\text{-}NH_3)^+$ | 2.731 | 4-31G | 3.8 | 2.0 |
| | | 6-311G*(*) | 5.2 | 2.7 |
| $(H_2S\text{-}H\text{-}SH_2)^+$ | 3.482 | 4-31G | 1.6 | 0.6 |
| | | [641/31/2] | 5.7 | 3.2 |

the bond is elongated, suggesting that small stretches of the bond lead to dramatic reductions in the rate of proton transfer. An enzyme might thus control the transfer between two residues at a particular stage of its catalytic mechanism via small conformational changes that affect the interresidue distance.

For a given H-bond length, the energy barrier for transfer between two hydroxyl groups (OH → O) is somewhat higher than for internitrogen transfer. Thus, the former transfer can be considered significantly less facile for equivalent geometries. The intersulfur transfer barrier rises noticeably less quickly than the OH → O and NH → N curves and is hence less dependent upon the H-bond length. Since the NH → O curve is much higher than OH → N, a NH–O bond could function much like a one-way valve that allows the proton to shift from O to N but not in the reverse direction. A similar observation applies to the amine and sulfhydryl groups or to any other pair with markedly different basicities, e.g., CH–O. On the other hand, the OH → S and SH → O curves are nearly coincident so transfers in either direction in a S–H–O bond should be equally facile. At the point where the various curves intercept the horizontal axis, the barrier vanishes and the potential collapses into a single-well function. It is hence no longer valid to speak in terms of a proton transfer between two minima.

**Accuracy of Calculations.** Most of the data presented in Figure 2 were calculated at the SCF level with use of a split-valence 4-31G basis set that excludes polarization functions and electron correlation. Should

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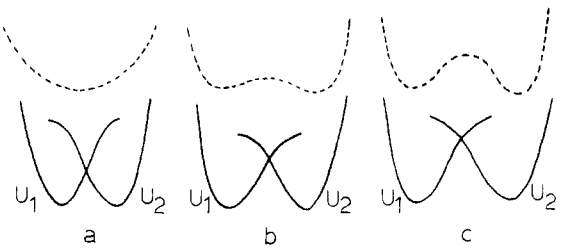


**Figure 3.** Superposition of proton dissociation potentials $U_1$ and $U_2$. Each dashed curve corresponds to the sum of the potentials below it. Cases a–c represent progressively longer H bonds.

such a procedure furnish accurate results? In general, the answer is a qualified no. That is, correct results would arise only if (a) both correlation and larger basis sets had negligible effects or if (b) these two effects were opposite in sign and cancelled one another. In the case of proton transfers between hydride molecules, case b holds to a fair extent.

The penultimate column of Table I contains transfer barriers calculated at the SCF level for a number of systems[14] while electron correlation is included via a third-order many-body perturbation treatment (MP3) in the last column. Considering $(H_2O–H–OH_2)^+$ as an example, inclusion of electron correlation lowers the transfer barrier (from 7.3 to 5.1 kcal/mol) whereas a substantial enlargement of the basis set to one denoted[14] 6-311G*(*) has the opposite effect of raising the barrier to 10.3. These two trends approximately cancel one another and the MP3/6-311G*(*) barrier of 7.7 is in good agreement with the SCF/4-31G value of 7.3. Similar trends are noted in the other systems although the cancellation is less complete in the case of sulfur. We conclude that while SCF/4-31G calculations are not as intrinsically reliable as more complete treatments, this approach does provide a satisfactory treatment of the proton-transfer process for these systems.[21]

When one is studying a proton transfer between two different molecules, it is essential that the theoretical approach accurately reproduce the relative proton affinities of the two subunits. While the SCF/4-31G method overestimates the proton affinities of $NH_3$ and $OH_2$ by some 15 kcal/mol in comparison with experimental values, the *difference* in proton affinity of 36 kcal/mol is reproduced quite accurately.[10] On the other hand, SCF/4-31G reverses the experimentally observed proton affinities of $OH_2$ and $SH_2$.[19] Since enlargement of the basis set to 4-31G* leads to correct relative proton affinities,[19] the proton transfers involving $SH_2$ and $OH_2$ (or $NH_3$) were studied with this basis.[10] The accuracy of the transfer barriers in these asymmetric systems were confirmed by comparison with correlated data.[10,15]

**Underlying Principles.** It is instructive to decompose the proton transfer between A and B into two separable but simultaneous processes: the dissociation of the proton from A (represented by curve $U_1$ in Figure 3) and its association with B ($U_2$).[11] To a first approximation, we treat the total energy of the system as the sum of the $U_1$ and $U_2$ potentials, represented by the dashed curves. A short H bond corresponds to the situation depicted in Figure 3a where the minima in the $U_1$ and $U_2$ curves are close to one another. Their sum contains a single symmetric minimum in which the proton lies equidistant between the A and B groups. When the two groups are somewhat further apart, the intersection between the two curves occurs above their points of inflection and the resulting sum contains a central maximum (Figure 3b). Hence, there are two wells present in the potential with a small barrier separating them. Further elongation of the H bond (case 3c) results in a higher barrier. These principles explain the rapid increase in the proton-transfer barrier observed with longer H bonds in Figure 2, as well as its disappearance as the two subunits approach one another. Use of proton dissociation curves computed for each of the subunits by ab initio methods rather than assuming an idealized shape confirmed this behavior (although these "composite" barriers are uniformly lower than those in Figure 2).[11]

These principles are capable also of explaining quantitative differences between the various systems.[11] For example, the NH → N curve in Figure 2 closely resembles that for OH → O with the exception of a horizontal displacement of approximately 0.1 Å. The equilibrium N–H bond length in isolated $(H_3N–H)^+$ was calculated to be 0.05 Å longer than is $r$(O–H) in $(H_2O–H)^+$. Since the two proton dissociation curves have similar shapes, the longer N–H bond is equivalent to translation of the $U_1$ and $U_2$ curves toward one another (see Figure 3), each by this amount, resulting in the observed displacement toward smaller barriers. In a like manner, the slightly higher barriers found for transfer of a proton between methanol molecules than between waters[11] can be traced to the shorter O–H bond length in $CH_3OH_2^+$. The less dramatic rise in barrier height with increase of $R$(SS) is a direct result of the less steep nature of the proton-dissociation curve of $(H_2S–H)^+$, caused in turn by the more diffuse nature of the electron cloud of the second-row atom.[10]

We now allow differentiation between A and B in order to extend our discussion to asymmetric systems. Let us perturb the initially symmetric system by allowing A to become more basic. Since A has a higher proton affinity than that of B, the system will be progressively stabilized as the proton moves from B toward A. That is, the energy of A–HB is slightly decreased, A–H–B more so, and AH–B most of all. We thus expect a positive value of $\Delta E$, an increase in the AH → B barrier, and a decrease in the BH → A barrier. This concept is consistent with the data in Figure 2, e.g., the observation that the NH → O barriers are higher than those for the OH → O case. We would expect even higher barriers for CH → O transfers. Since the proton affinities of $OH_2$ and $SH_2$ are nearly identical, little asymmetry is introduced into the potential and the OH → S and SH → O curves are nearly coincident.

**Substituent Effects.** Can we use the principles developed above to predict the effects of substituents upon the energetics of proton transfer? For example, suppose we replace one or more H atoms of our model hydride bases by alkyl groups. If this substitution is carried out in a symmetric manner, the effects are relatively minor, as indicated by the aforementioned comparison of $(H_2O–H–OH_2)^+$ and $(CH_3OH–H–HOCH_3)^+$. In order to investigate asymmetric substitutions, the transfer between oxygens in $(H_2O–H–OH_2)^+$

(21) Comparison of data computed for $(HO–H–OH)^-$ and $(H_2O–H–OH_2)^+$ with MP3/6-311G*(*) and with more sophisticated treatments (Roos, B. O.; Kraemer, W. P.; Diercksen, G. H. F. *Theor. Chim. Acta* **1976**, *42*, 77. Meyer, W.; Jakubetz, W.; Schuster, P., *Chem. Phys. Lett.* **1973**, *21*, 97) have verified the accuracy of the former approach.

was taken as a reference point and the hydrogens of the left subunit were replaced by alkyl groups.[13] The order of proton affinities for our substituted subunits is as follows: $OH_2$ < MeOH < EtOH < $Me_2O$. Using the arguments advanced above, one would expect the barriers for proton transfer from the above groups to water to increase in the same order. This was indeed found to be the case when the quantum mechanical calculations were carried out.[13] These barrier increases are quite uniform over a range of H-bond length; i.e., the curves of $E^\dagger$ vs. $R$ are parallel to one another. The constant spacing between a given pair of curves represents the increase in transfer barrier associated with the corresponding alkyl substitution. These barrier increases were found to be a linear function of the difference in proton affinity between the subunits involved. The slope of this line, ~0.4, corresponds to the Brønsted $\alpha$. These trends are not limited to the oxygen bases; similar calculations involving nitrogen bases demonstrated very analogous patterns.[13] It is possible to predict from our data the transfer barrier of any system at a given value of $R$ based simply on the result for a simple hydride system such as $(H_2O–H–OH_2)^+$ and the relative proton affinities of the actual subunits involved.

**Relaxation of Fixed Length Restraint.** When the systems studied here are not part of a rigid structure but are instead free in gas phase or solution, it is not appropriate to hold fixed the distance between the subunits. Their ionic character then leads to rather short H bonds.[8-11,14] For example, in the fully optimized geometry of $(H_2OHOH_2)^+$, $R$(OO) = 2.37 Å, short enough that the equilibrium position of the proton is precisely midway between the two O atoms. Although $R$(OO) is slightly longer in $(HOHOH)^-$ and $(CH_3OH)_2H^+$, the proton remains effectively localized in a central location. The situation is different for $(H_3NHNH_3)^+$ where there are two clearly defined minima on the potential energy surface, $(H_3NH–NH_3)^+$ and $(H_3N–HNH_3)^+$. The equilibrium $R$(NN) of 2.68 Å contracts to 2.59 Å in the transition state where the proton is midway between the N atoms. The energy barrier for this transfer that allows free variation of $R$(NN) is on the order of 1 kcal/mol. A barrier of similar small magnitude separates the two minima in $(H_2SHSH_2)^+$. Since the ground proton vibrational level is likely to be higher than this barrier, we expect oscillations of the proton around a *central* location in all the above systems.[14]

With regard to asymmetric systems,[10,15] the greater basicity of $NH_3$ leads to a single $(H_3NH–XH_2)^+$ minimum for X = O, S; i.e., there is no $(H_3N–HXH_2)^+$ minimum on the surface. On the other hand, both $(H_2OH–SH_2)^+$ and $(H_2O–HSH_2)^+$ are true minima, with the former more stable by 0.7 kcal/mol; a barrier of 2.6 kcal/mol separates them. $R$(OS) is ca. 0.15 Å shorter in the transition state than in either minimum. We conclude that the short H-bond lengths in these ionic systems lead to either single-well potentials or rather low barriers. Since the association energies of the $(AH–B)^+$ complexes from $AH^+$ and B are quite exothermic in the gas phase (ca. −20 kcal/mol), we do not expect the transfer of the proton within the complex to be a rate-limiting factor in the overall gas-phase reaction. The situation in solution will be highly dependent on the effects of solvent upon the H-bond length.

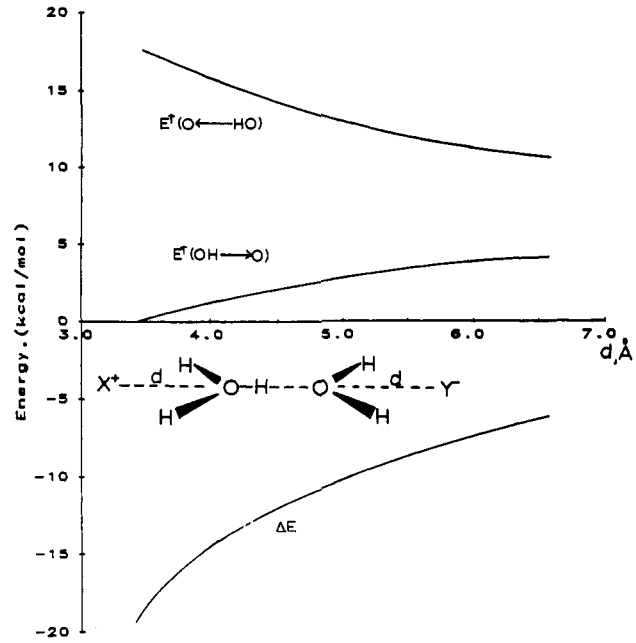


**Figure 4.** Energetic characteristics of proton transfer potential of $(H_2O–H–OH_2)^+$ in the presence of external ions. Cations approach from the left and anions from the right. Ions studied are $Na^+$, $Li^+$, $(NH_4)^+$, $Cl^-$, $HCOO^-$, and point charges of both signs.

## Influence of External Ions

The calculations to this point have dealt with proton transfers in vacuo. However, in many cases of interest the groups involved in the H bond are part of a larger system or are surrounded by other molecules. It is thus important to consider the effects of the environment upon the proton-transfer process. As a first step in this direction, a number of different ions of both positive and negative charge were placed in various locations relative to the $(H_2O–H–OH_2)^+$ and $(H_3N–H–OH_2)^+$ systems, and the proton-transfer potentials were calculated.[12] The results led to a number of insights that are expected to be useful in understanding proton transfers in condensed media.

We begin with placement of a number of different ions along the H-bond axis of $(H_2O–H–OH_2)^+$. As illustrated by the lowermost curve in Figure 4, the ions lead to negative values of $\Delta E$ in what would be a fully symmetric potential with $\Delta E$ = 0 in their absence. This effect is both of large magnitude and of long range, with $\Delta E$ still quite negative even at distances of 6 or 7 Å. The upper two curves in Figure 4 reveal a lowering of the barrier for proton transfer from left to right as the ion approaches and the opposite effect on the reverse transfer direction.

A second question concerning the relative effects of various different ions was addressed by comparison[12] of $Na^+$, $Li^+$, $(NH_4)^+$, $Cl^-$, and $HCOO^-$. It was found that for distances of greater than about 3.5 Å, these ions produce essentially identical perturbations in the transfer potential. The insensitivity of the ionic effects to the chemical nature of the ion is further underscored by identical results when the ions are replaced by fictitious "point charges", carrying no electrons or orbitals. These results offer hope that a large number of charged species within a protein or solution might be realistically modeled by an array of point charges that are compu-

tationally much less costly.

The above trends may be explained quite simply in terms of electrostatic interactions of the ion with the central proton. A cation repels the proton and, when placed on the left side, acts to "push" the proton across to the right. A second and more quantitative analysis involves a combination of the unperturbed transfer potential with an additional term computed as the Coulombic interaction between the ion and the proton. This very simple treatment provides a surprisingly accurate reproduction of the actually computed potentials. Moreover, the data indicate that the effect of the charge is *greater* than would be expected on the basis of its interaction with a naked proton. That is, rather than shielding the proton from the ion, the remainder of the H-bonded system acts to *magnify* the ion's influence by a factor of nearly 2.[12]

What are the ramifications of these results on proton-transfer processes in a molecule such as a protein? The most obvious conclusion is that the presence of ions can modify the proton-attracting power of one group relative to another. When strong enough, this principle may be used to push a proton across from one subunit to another with a normally lower proton affinity. For example, our calculations[12] indicate that a cation placed within about 3 Å of the nitrogen atom of $(H_3N–H–OH_2)^+$ can reverse the normally highly positive value of $\Delta E$ and make $(H_3N–HOH_2)^+$ more stable than $(H_3NH–OH_2)^+$. The changes in the barriers further facilitate this proton transfer by reduction of $E^\dagger(NH\rightarrow O)$.

**Dynamics.** Can we estimate the amount by which these barrier height changes affect the kinetics of proton transfer? Due to its light mass, we assume that the fastest transfer process is quantum mechanical tunneling of the proton between the two wells in the transfer potential. After evaluation of the energy levels and wave functions of the various protonic vibrational states, the rate may be calculated by standard formulae.[12b] The fastest transfers were found to take place in symmetric potentials with $\Delta E = 0$. For example, when the barrier is 7 kcal/mol, the proton is shifted across the H bond within picoseconds, in line with the experimentally observed time scale.[22] The rate is quite sensitive to $E^\dagger$, dropping by several orders of magnitude when the barrier is doubled. This observation substantiates our hypothesis that small elongations of a H bond that enlarge $E^\dagger$ offer an effective means of slowing down the proton transfer. Introduction of asymmetries into the potential, e.g., by motions of external ions, also lead to dramatic drops in the transfer rate. Values of $\Delta E$ of only several kilocalories/mole are sufficient to localize the proton in the lower of the two wells; transfer cannot occur by tunneling but only via excitation to a higher vibrational level. The inability of a proton to tunnel out of the lower energy well underscores the importance of the sign of $\Delta E$.

## Angular Distortions

The calculations described to this point have considered stretches of each H bond, i.e., variation of $R$, but not the angular deformations or "bends" present in the H bonds of many large molecules. Such distortions were introduced into our model H-bonded systems as follows.[8-11] The fully optimized $(H_nX–H–YH_m)^+$ complex, e.g., $C_{3v}$ $(H_3N–H–NH_3)^+$, was taken as a reference point containing no distortions. The $H_nX$ subunit was then rotated a specified amount $\alpha_a$ about a line perpendicular to the X–Y axis; the rotation of the $YH_m$ subunit was denoted $\alpha_b$. With the system held in this configuration, the central proton was allowed to follow the lowest energy path between the two subunits, tracing out a proton-transfer potential. Due to the angular distortions, this path did not generally coincide with the X–Y axis, and the X–H–Y atoms were therefore not collinear. The first type of distortion studied involves a rotation of only one subunit of the two. Also studied was a "conrotatory" distortion in which both subunits were rotated so as to turn their lone pairs[23] in the same direction away from the X–Y axis; rotations in opposite directions were termed "disrotatory".

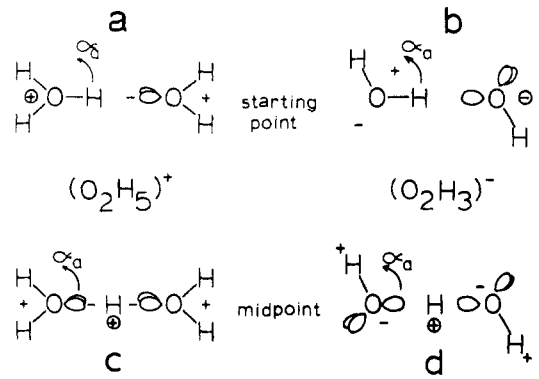


**Figure 5.** Schematic illustrations of charge patterns in $(H_2O–H–OH_2)^+$ and $(HO–H–OH)^-$. Directions of dipole moments are indicated by uncircled + and – signs; formal charges by a circled sign. Starting point refers to bottom of well in transfer potential and midpoint to the top of barrier.

The trends observed for all the cationic systems of the type $(H_nX–H–YH_m)^+$ obey the following rules.[8-10] All modes of angular deformation increase the barrier to proton transfer. The increases associated with distortion of less than about 20° are fairly small but rise quickly for greater deformations. The order observed for the barrier increases is as follows: single rotation < conrotatory < disrotatory. The magnitudes of these increases can be quite large. For example, a disrotatory deformation of 40° in $(H_3N–H–NH_3)^+$ raises the barrier from 12 to 33 kcal/mol when the $R$(NN) distance is held at 2.95 Å. A central conclusion is therefore that the transfer energetics are sensitive to *both* the length *and* the angular features of the H bond.

Are the effects of angular deformations different when the complex contains two anions as in $(HO–H–OH)^-$ rather than two neutral molecules? The answer is a resounding *yes*.[11] For example the barrier is *lowered* when one subunit of $(HO–H–OH)^-$ is rotated, contrary to the increases noted in the cation. On the other hand, another mode of distortion raises the barrier of the anion higher than does the same deformation in $(H_2O–H–OH_2)^+$. In light of the similar transfer energetics for undistorted geometries of $(HO–H–OH)^-$

(22) McMorrow, D.; Kasha, M. *J. Phys. Chem.* **1984**, *88*, 2235. Jang, D.-J.; Kelley, D. F. *Ibid.* **1985**, *89*, 209.

(23) The "lone-pair" direction in this context refers to the vector pointing from the X or Y atom of interest along the X–Y axis in the fully optimized geometry of the entire complex (see ref 8–11). While this may be accurate for the single lone pair of $NH_3$, correspondence of this vector with "true" lone-pair directions in $OH_2$ or $SH_2$ is more tenuous. The term is used in this description merely to refer to a preferred angle made by the subunit with the H-bond axis.

and $(H_2O–H–OH_2)^+$, why do the two systems behave so differently when the H bond is bent?

The explanation is rooted in the electrostatic interactions between the subunits. Figure 5 contains a simplified picture of the charge patterns in the relevant configurations of the two systems. Configurations a and b represent the "starting point" or OH–O structures of $(H_2O–H–OH_2)^+$ and $(HO–H–OH)^-$, respectively. A formal positive charge is present on the left-hand $H_2OH^+$ subunit in configuration a and a negative charge on the right-hand $OH^-$ group in b, indicated by the circled + and – signs. Also included by the uncircled + and – signs are the dipole moments that lie along the HOH bisector of each neutral $OH_2$ subunit. The orientations of the subunits in a and b represent equilibrium geometries with no angular distortions present. We consider a deformation in which the left-hand subunit is rotated counterclockwise, indicated by the curved arrows labeled $\alpha_a$. In both cases a and b, the central hydrogen is rotated off of the O–O axis, distorting the linearity of the H bond and raising the energy. However, whereas the rotation of the $OH_3^+$ subunit in a leaves the center of positive charge stationary, the rotation of $OH_2$ in b turns the positive end of its dipole *away* from the negative charge of the $OH^-$ subunit on the right, thereby adding a further destabilization. Consequently, the energy increase in the b configuration associated with a 40° distortion is 13.2 kcal/mol as compared to only 9.2 for configuration a.

We now consider the midpoint O–H–O configurations at the top of the energy barrier. Again, the undistorted geometries are illustrated in Figure 5 (c and d). The energies of both the cationic and anionic systems are raised by the rotation of the left-hand subunit that misaligns its lone pairs with respect to the central proton. However, the $\alpha_a$ rotation turns the dipole moment of the left-hand subunit away from the formal positive charge of the central proton in c but has the opposite effect of *enhancing* the alignment between the negative end of the left-hand dipole and the positively charged proton. As a result, the distortion energy of midpoint d is much less (10.4 kcal/mol) than that of c (15.3). In summary, the bottom of the well in $(H_2O–H–OH_2)^+$ is destabilized less than that of $(HO–H–OH)^-$ while the top of the barrier is destabilized by more; hence, the barrier increase associated with the angular distortion is greater in $(H_2O–H–OH_2)^+$. Indeed, the barrier in $(HO–H–OH)^-$ is actually *decreased* by this distortion, due to the greater destabilization of the bottom of the well than of the top of the barrier. It is possible to use these same fundamental concepts to predict the trends for a wide variety of different angular distortions involving rotation of one or both subunits.[11]

While the preceding discussion has focused on $E^\dagger$, it is important to note that an angular deformation such as rotation of one subunit removes the symmetry of the system and $\Delta E$ is no longer equal to zero. Moreover, the cationic $(H_2O–H–OH_2)^+$ and anionic $(HO–H–OH)^-$ systems lead to opposite signs of $\Delta E$, given the same mode of distortion. The reason for this distinction may again be attributed to electrostatics. Let us first consider the $(H_2O–H–OH_2)^+$ system in Figure 5a, where the rotation of the left-hand subunit has little effect on the charge–dipole interaction between the two subunits. When the proton is shifted across to the right-hand subunit, however, the positive charge is associated with this group and the dipole with the neutral subunit left behind. The rotation of the left-hand group misaligns its dipole from the charge, causing an additional destabilization. Hence, the right well is higher in energy than the left and $\Delta E$ is positive in sign. The situation for $(HO–H–OH)^-$ in b is quite different since the left well is greatly destabilized by the rotation of the left subunit. When the proton has transferred across to the right, the rotation of the remaining $OH^-$ does not disturb the alignment of its charge with the dipole of HOH on the right. Therefore, in the anionic case, the right well is destabilized to a *lesser* degree and $\Delta E$ is negative.

The influence of angular features of the H bond upon the relative energies of the two wells has some important ramifications for protein function. By appropriate modification of the geometry of a given H bond, a protein could control the equilibrium position of the proton within that bond. For example, the shift of a proton from one hydroxyl group to another could be easily accomplished by a conformational change that turns the second group with respect to the first and results in a negative value of $\Delta E$. It should be emphasized that the magnitudes of $\Delta E$ induced by these bending motions are not small. For example, this quantity is equal to 9 kcal/mol when a distortion or 40° is introduced into the $(HO–H–OH)^-$ system. Nor is this a short-range effect. Calculations have shown that while the latter value of $\Delta E$ = 9 kcal/mol does decrease as the H bond is lengthened beyond 2.75 Å, this reduction is rather gradual and $\Delta E$ remains as high as 7 kcal/mol, even when the O–O distance has increased to 4.0 Å.

As a final note, the changes in $\Delta E$ caused by angular deformations are not limited to the hydride systems discussed here. It has been recently demonstrated that a proton can be transferred from a carbonyl to a hydroxyl group or from an imine to an amine merely by an appropriate bend of each H bond.[20] For example, while $(H_2COH–OH_2)^+$ is lowest in energy when the hydroxyl group lies along a lone-pair direction of the carbonyl oxygen, reorientation that places the hydroxyl along the C=O axis acts to shift the proton to the former group since the most stable configuration is then $(H_2CO–HOH_2)^+$. Similarly, motion of a protonated Schiff base moiety away from the lone-pair direction of an amine tends to transfer the proton to the latter group. These results are particularly notable in that both transfers involve a shift to a group of *lower* proton affinity, suggesting that relative p$K$ values are sensitive to angular properties of the H bond.

## Conclusions and Perspectives

Ab initio calculations have demonstrated the sensitivity of proton-transfer energetics to the geometrical characteristics of each H bond. Comparison of similar systems, e.g., $(HO–H–OH)^-$ and $(H_2O–H–OH_2)^+$, points out seemingly anomalous behavior, which may be explained in terms of a small number of fundamental properties of each subunit. The effects of substituents are readily understood by their influence on the proton affinity of a given subunit. The concepts outlined in this Account make feasible predictions of transfer energetics in systems much larger than those considered here. The reader is cautioned, however, against direct extrapolation of these principles to reactions in solution

without careful consideration of solvent effects.

We have identified a number of different ways in which a macromolecule such as a protein could control the protonation states of various internal groups. The presence of an ion in the vicinity of a H bond can "push" a proton across from one group to another. Angular distortions within the bond affect $\Delta E$ and are capable of shifting the proton to a group of lower intrinsic p$K$. In addition, stretches and bends of the bond could be used to dramatically alter the rate at which a given transfer takes place by modification of the barrier.

Work is currently continuing on this problem. Calculations involving the hydrides have been largely completed, and research is now progressing to the study of larger molecules containing functional groups such as carboxyl, amide, and a model Schiff base. These larger systems with their greater complexity offer the prospect of a rich field of study and application to interesting problems in various areas of chemistry and biochemistry.

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