

Bent Hydrogen Bonds and Proton Transfers

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The transfer of a proton from one group to another is probably the most common and fundamental reaction in all of chemistry, second only to electron transfer. As experimental techniques have advanced, it has become feasible to study aspects of the proton transfer process that were previously inaccessible. It is possible to investigate the reaction in the gas phase, free of complicating solvent effects.¹⁻³ The time frame accessible to experimental inquiry has been shortened dramatically in recent years, even into the picosecond scale.⁴⁻⁸

Ab initio quantum chemical calculations are capable of probing various facets of the proton transfer reaction, extracting information unavailable to experimental measurements. For example, one can systematically vary the relative orientations of the reactants and monitor the electronic distributions at any arbitrary stage of the very rapid proton transfer process, even those configurations which do not represent stationary points on the potential energy surface. Calculations have been applied to proton transfers in a diversity of situations, such as zeolites,^{9,10} DNA base pairs,^{11,12} anionic complexes,^{13,14} intramolecular H bonds,¹⁵⁻¹⁷ and enzyme models.^{18,19}

Work in this laboratory over the years has been devoted to extracting the fundamental principles that guide the proton transfer process, using ab initio methods as our chief tool. Much of our motivation is derived from enzymes, where a proton transfer is very commonly a part of the entire reaction mechanism.²⁰⁻²³ We wish to learn how it is that the enzyme is able to control the transfer of the proton so that it occurs at just the correct step in the reaction pathway. It has also been our goal to understand how protons can be "pushed" by the protein from one group to another, as occurs in membrane proteins such as bacteriorhodopsin.²⁴

Since the accuracy of the type of quantum mechanical calculation that may be applied is inversely related to the size of the system under study, it is necessary to make judicious choices of small models which faithfully mimic the properties of the system of interest. For this purpose, a residue which forms a H bond through a hydroxyl group, e.g., Ser, can be modeled by a smaller hydroxyl-containing molecule such as HOH or MeOH. The carboxyl group which is the "business end" of Glu and Asp can be mimicked by formic or acetic acid. Similarly, a small molecule which contains an amide functionality, such as for-

mamide or acetamide, can serve as an adequate representation of the peptide linkage or the functional groups of Asn and Gln. An additional advantage of modeling by small molecules is the ability to analyze the behavior of the functional groups themselves, without complexities arising from the remainder of the residues or protein.

As an example, if one considers the proton transfer between two hydroxyl-containing residues, it might be natural to choose a system like (H₂O...H⁺...OH₂) as a starting point. Once a given system has been chosen for study, it is common for theorists to fully optimize all aspects of its geometry. In the case of an ionic H bond, this sort of prescription typically leads to a very short intermolecular separation, on the order of perhaps 2.4 Å.^{25,26} In such a short H bond, the equilibrium position of the proton lies midway between the two oxygen atoms. While this computation faithfully reproduces the proton-bound water dimer itself, it is not representative of the situation where two hydroxyl-containing groups are H-bonded within the context of a protein. It is very rare to find H bonds this short. Indeed, the many factors that contribute to the final equilibrium structure of the entire protein prevent the individual H bonds from achieving the

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Steve Scheiner was born in 1951 in New York City, where he earned his B.S. degree in chemistry from the City College of New York in 1972. He then went on to Harvard University, where he received his Ph.D. in 1976 in chemical physics, working under the tutelage of William Lipscomb. After two years as a Weizmann Fellow at The Ohio State University, he took a faculty position at Southern Illinois University, where he is currently a professor of chemistry. He is interested in all facets of structure-function relationships and is currently exploring excited-state processes.

geometries they would adopt were the rest of the protein absent. This contention is supported by surveys of protein structures²⁷ where H bonds of any given type exhibit a wide range in H-bond length. This being the case, it is important to consider how the length of a H bond influences the proton transfer process occurring within. A review of earlier calculations²⁸ discussed the rapid rise of the energy barrier to transfer with increasing intermolecular separation, and analyzed this behavior in terms of properties of the donor and acceptor groups individually.

Just as the overall structure of the protein imposes restrictions on the length of a given H bond, so too are angular aspects subject to external forces. It is for this reason that wide variations are seen in H-bond angles when protein structures are analyzed,²⁷ even though there is only one distinct set of angles that minimizes the energy of a H bond containing a given pair of groups. It is hence essential to determine how proton transfers are affected by the angular characteristics of the H bond and to understand the underlying reasons for the perturbations observed. This Account summarizes the principles that have been unearthed by ab initio calculations, beginning with simple systems containing N and O atoms, and progressing to larger and more complex groups such as carboxyl and amide, both in vacuo and within environments that more closely model a protein or other large molecule.

Nitrogen Atoms

Previous work in the literature has demonstrated that electrostatic forces are largely responsible for the attractive interaction between a pair of molecules in a H bond. These Coulombic interactions are even more dominant when the H bond is an ionic one and one of the groups is formally charged, as in $(\text{H}_2\text{OH}^+-\text{OH}_2)$.²⁹ These electrostatic attractions are supplemented by other terms, which tend to cancel one another. For example, the exchange repulsion between the electron clouds of the two subunits is roughly equal and opposite to the attraction resulting from mutual polarizations of these clouds, termed polarization/charge transfer. So for most intents and purposes, one can make surprisingly accurate predictions about the effects of geometric distortions, based primarily on considerations of electrostatic interactions.

Amine. These points can best be illustrated by a series of examples. Consider first the proton-bound ammonia dimer, shown in Figure 1. Its optimum geometry has a fully linear H bond wherein the bridging proton lies along the N-N axis. The single lone pair of the NH_3 molecule is collinear with the molecule's C_3 symmetry axis; both point directly toward the bridging proton of the donor molecule in $(\text{H}_3\text{NH}^+-\text{NH}_3)$, pictured in **1a**. The result of the proton transfer across to the acceptor group on the right leaves a structure (**1b**) equivalent to **1a** and so of equal energy.

Remembering that free NH_3 is a model of an amine group, within the confines of a protein the N atoms

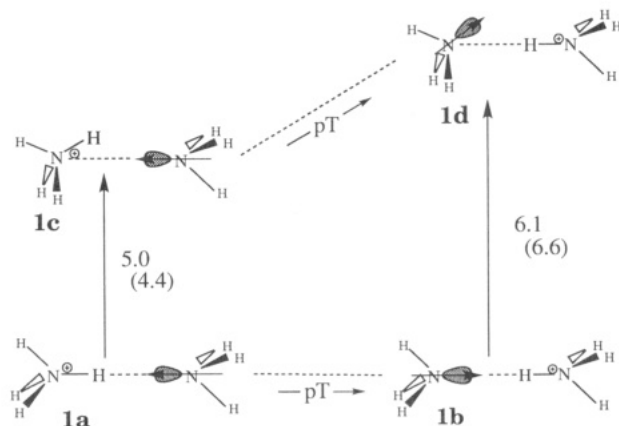


Figure 1. Proton transfers in linear and bent conformations of $(\text{H}_3\text{N}-\text{H}^+-\text{NH}_3)$. Distortion energies of each configuration are given in kilocalories/mole, followed by the electrostatic component in parentheses. The left-hand molecule is rotated by 40° in **1c** and **1d**, with $R(\text{NN}) = 3.25 \text{ \AA}$. Arrows represent the dipole moment of the neutral subunit. The center of positive charge of H_3NH^+ is approximately coincident with the N nucleus.

would be bound directly to the superstructure of the macromolecule, which would typically prevent the perfect linear arrangement of the H bond in **1a** and **1b**. The "bending" that occurs in proteins, or in any large superstructure, can be reproduced by forcing each NH_3 unit to turn relative to its partner. This rotation is effected by turning the three peripheral hydrogens, leaving the central nitrogen stationary, and causing the C_3 axis of the molecule to deviate from the N-N axis by some angle α .

Let us consider the example where the molecule on the left is rotated. In order to enlist the aid of concrete data, we take 40° as a sample rotation and keep the two nitrogen atoms 3.25 \AA from one another. In the case where the bridging hydrogen is covalently bound to the rotated molecule on the left, **1c** illustrates that the proton follows the C_3 axis to prevent energetically costly distortion of the basic tetrahedral geometry of $(\text{H}_3\text{NH})^+$. But the removal of this hydrogen from the N-N axis takes a toll on the strength of the H bond. The energy of the entire system is calculated to rise by 5.0 kcal/mol .³⁰ Perhaps more importantly, the same rotation of the left subunit causes an even larger energy increase of 6.1 kcal/mol in $(\text{H}_3\text{N}^+-\text{HNH}_3)$, following proton transfer, **1d**. As a result, transfer of the proton from left to right is energetically uphill, once the left-hand subunit has been rotated. Put another way, angular deformation of one subunit tends to pull the proton toward it. This finding is particularly intriguing as the two subunits are chemically identical (NH_3) and therefore of nominally equivalent proton-attracting power. If correct, the calculations suggest that the relative pK of groups engaged in a H bond is not invariant but rather subject to angular aspects of the geometry of that bond. The 1.1 kcal/mol difference here is roughly equivalent to 1 pK unit at 298 K .

It therefore becomes imperative to analyze the difference in distortion energy of **1c** and **1d**. One can achieve insights by partitioning the interaction energy between the two subunits into a number of components, each with physical significance. The Kitaura-

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Morokuma (KM) scheme^{31,32} has provided useful notions about chemical processes in the past and has been applied to the present problem. This approach first considers the interaction before the electron clouds of the two subunits are able to distort one another, thereby yielding a classical electrostatic interaction between these static clouds, plus a quantum mechanical "exchange repulsion", similar to steric repulsion in closed-shell cases such as these. After releasing the electron clouds to respond to the partner's presence, one can extract second-order terms which are identified as polarization (redistributions within a given subunit) and charge transfer (between subunits).

A partitioning of the interaction between $(\text{H}_3\text{NH})^+$ and NH_3 in **1a** indicates most of it to be of electrostatic origin.³⁰ Specifically, Coulombic forces account for 22.2 of the total 24.5 kcal/mol interaction energy. The other components are each less than 4 kcal/mol, and there is much cancellation between repulsive exchange and the second-order terms which are attractive. More importantly for our purposes, the *changes* in electrostatic energy arising from the rotation of the left-hand subunit mimic those of the full distortion energy, as witnessed by the similarity between the values in and out of parentheses in Figure 1. So the question as to why the proton transfer toward the rotated molecule is favored reduces to understanding why the electrostatic forces of the optimal linear arrangement are more destabilized for **1d** than for **1c**.

One may analyze the electrostatic interaction by considering the various multipole moments of each subunit. $(\text{H}_3\text{NH})^+$ is charged and has no dipole moment, while its neutral partner, NH_3 , is uncharged. The dipole moment of the latter, indicated by the arrow in Figure 1, is collinear with the N lone pair and C_3 axis. The leading term of the electrostatic interaction between the two subunits will hence be of ion-dipole character. One can see in Figure 1 that the **1a** \rightarrow **1c** rotation does not interfere with the ability of the dipole moment of the neutral NH_3 to point directly toward the center of positive charge of its partner $(\text{H}_3\text{NH})^+$. However, once the proton has transferred from left to right, the rotation of the left-hand subunit (**1b** \rightarrow **1d**) causes a misalignment of the dipole moment of the neutral on the left. Computation of the electrostatic energy confirms the greater destabilization of the R^{-2} ion-dipole term in the **1b** \rightarrow **1d** transition, as compared to **1a** \rightarrow **1c**.³⁰

The reader is cautioned that the above description is a simplification of a complex issue. The KM energy decomposition scheme makes several arbitrary assumptions, like any other attempt to partition a quantum mechanical observable like total energy into nonobservable quantities. The multipole series may converge slowly, particularly for close approach of the two subunits. And there are terms other than ion-dipole that are of considerable magnitude. For example, the ion-quadrupole term makes a contribution to the destabilization energy of **1d** comparable to that of ion-dipole.³⁰ Nonetheless, consideration of only the basic geometric dispositions of the dipole moment and centers of positive charge provides a remarkably

accurate indicator of the direction in which a given angular distortion is apt to push the bridging proton.

Imine. The foregoing analysis of $(\text{H}_3\text{NH}^+\cdots\text{NH}_3)$ has been concerned with a pair of chemically identical subunits. Calculations have revealed that the same considerations apply too when one subunit is intrinsically more basic than the other. Consider the case where the NH_3 molecule on the right of Figure 1 is replaced by methyleneimine, $\text{NH}=\text{CH}_2$. The latter has a higher proton affinity so the analogue to **1b** is more stable than that of **1a**, i.e., the proton prefers association with the imine to association with the amine, prior to any geometric distortion. Despite the presence of a double bond to the N, the same principles are in operation as for $(\text{H}_3\text{NH}^+\cdots\text{NH}_3)$. Again, the rotation of the left-hand subunit induces the proton to shift toward the left, this time overcoming the natural predilection of the proton for the more basic imine on the right. Taking $R = 2.75 \text{ \AA}$ as an example, the proton prefers association with the imine by 2.5 kcal/mol when the H bond can adopt a fully linear arrangement. A 55° rotation of the amine model NH_3 reverses the situation, and it is now the latter group which is preferred, also by 2.5 kcal/mol.^{33,34} The distortion has thus induced a total 5 kcal/mol perturbation in the proton transfer potential, equivalent to 3–4 pK units.

These calculations have unearthed a principle that may have profound implications for protein function. It appears that proton position is not bound by considerations of pK or proton affinity alone. By a minor change in its conformation that alters the angular characteristics of a H bond connecting two residues, it is possible for a protein to push a proton from one to the other, even if the recipient has a lesser pK_b. This idea might provide a means for an enzyme to control at just what point in its catalytic cycle a proton will be transferred. It also suggests a mechanism by which to couple conformational energy, governing the local H-bond geometry, with "protonic energy" which pushes protons in directions they would normally not go.

One might expect that if a misorientation of the NH_3 group causes the proton to shift toward it, a similar rotation of the partner imine would act to enhance its attraction for the proton. Calculations confirmed this supposition and provided numerical estimates. Again taking 2.75 \AA as a sample $R(\text{N}\cdots\text{N})$ separation, a 51° rotation of the imine, which takes the $\text{C}=\text{N}$ double bond into coincidence with the $\text{N}\cdots\text{N}$ axis, increases the preference of the proton for the imine by 2.3 kcal/mol over and above the 2.5 kcal/mol which exists when the N lone pair is aligned along the H-bond axis.³³ An energy decomposition analysis³⁵ demonstrated again the close similarity between the total distortion energies and those in the electrostatic component alone. As in the simpler case of $(\text{H}_3\text{NH}^+\cdots\text{NH}_3)$, the change in exchange repulsion associated with bending the H bond is nearly canceled by modifications of the attractive charge transfer and polarization components. More detailed analysis of the multipole terms in the electrostatic energy is complicated by a number of

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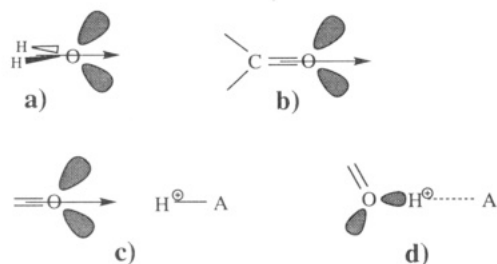


Figure 2. Directions of the dipole moments (arrows) and lone electron pairs in (a) HOH and (b) H₂CO. (c) The interaction of neutral H₂CO with a proton donor AH⁺. (d) The situation following proton transfer to the carbonyl oxygen, accompanied by rotation of the carbonyl group.

factors. Firstly, it is unclear what point to take as the origin in evaluating the moments of a molecule like CH₂=NH. Further, the dipole moment of the imine is not coincident with the N lone pair, nor is the center of positive charge of CH₂=NH₂⁺ located on the N nucleus. Nonetheless, the calculations reveal strong similarities with the simpler (H₃NH⁺...NH₃) case. Again in (H₃NH⁺...NHCH₂), it is primarily the interactions of the charge of H₃NH⁺ with the lower-order moments of the neutral that are responsible for the destabilization of this configuration upon rotating the neutral subunit.

Oxygen Atoms

Proton transfers involving oxygen atoms add a new wrinkle to the analysis. Rather than having a single lone pair with a collinear molecular dipole moment as nitrogen has, the O atom contains two lone pairs. As illustrated in Figure 2, the moment bisects the two lone pairs, whether the O atom is involved in single bonds as a hydroxyl or the double bond of a carbonyl. If one assumes idealized sp³ hybridization of the pairs in the former, the dipole is separated by 55° from each lone pair; sp² hybridization of the carbonyl oxygen predicts a 60° deviation.

The separation between moment and lone pairs provides a "turning force" as the proton moves back and forth to the oxygen atom. Consider the proton shared between a carbonyl oxygen and some arbitrary partner, designated simply as A in Figure 2. When the proton is located on A, there is a predilection for the neutral oxygen base to orient its dipole moment toward the positively charged partner subunit, thereby allowing maximal electrostatic interaction, indicated in Figure 2c. But as the proton approaches the oxygen, it is attracted toward one of the lone pairs. (It is for this reason that C–O–H bond angles within molecules are usually in the neighborhood of 100–110°, far from 180°.) Were the proton to simply move toward the lone pair with no other reorientations, it would be far removed from the O–A axis and severely weaken the H bond. An alternative, which permits retention of a strong H bond at the same time placing the proton on the O lone pair, rotates the O base, as illustrated in Figure 2d.

The combination of this turning force with the electrostatic effect can make for a powerful influence upon the proton transfer energetics. This point can be illustrated by the simple model system pairing a carbonyl oxygen with water. Figure 3 represents the proton transfer under two different sets of circum-

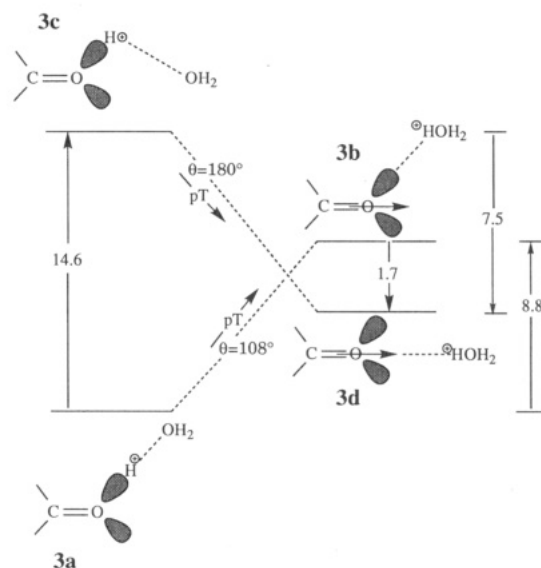


Figure 3. Proton transfers between H₂CO and HOH for two intermolecular orientations, characterized by $\theta(\text{C}=\text{O}\cdots\text{O})$. Energetics are in kilocalories/mole. $R(\text{OO}) = 2.75 \text{ \AA}$.

stances. In both cases, the distance between the oxygen atoms is held fixed at 2.75 Å. In the first case, the intermolecular angle $\theta(\text{C}=\text{O}\cdots\text{O})$ is set to 108°, the value that is optimal for the (H₂COH⁺...OH₂) configuration in **3a**. The proton is then allowed to transfer across to the acceptor water, leading to geometry **3b**. This process is calculated to be energetically uphill by 8.8 kcal/mol, not surprising since the proton affinity of H₂CO exceeds that of H₂O.³⁶

The other situation begins with **3c**, again with the proton first located on the carbonyl oxygen, but this time the water oxygen is placed along the C=O direction, i.e., $\theta = 180^\circ$. As illustrated in Figure 3, the proton weakens the H bond by coming off of the O–O axis, so that it can position itself along one of the O lone pairs, destabilizing the system by 14.6 kcal/mol. After the proton has transferred across to the water, the misorientation of the carbonyl lone pairs in **3d** is no longer a problem. In fact, this arrangement is a definite advantage since the dipole moment of the carbonyl group can now point directly toward the positive charge of the ⁺HOH₂ entity. This alignment contrasts with **3b**, where the C=O dipole is misoriented by 72°, and accounts for the overall greater stability of **3d** by 1.7 kcal/mol, as indicated in Figure 3.

The net result of the nonlinear H bond in (H₂COH⁺...OH₂) when $\theta = 180^\circ$ and the favorable alignment of the dipole moment in (H₂CO...⁺HOH₂) is that the latter is more stable than the former by 7.5 kcal/mol. In other words, the change in position of the hydroxyl group of water, from $\theta = 108^\circ$ to $\theta = 180^\circ$, has reversed the natural proton affinities of the carbonyl and hydroxyl groups.³⁴ Whereas the proton prefers association with the carbonyl oxygen when the hydroxyl lies along a C=O lone pair direction, a transfer across to the hydroxyl is favored, despite the lower proton affinity of this group, when the hydroxyl is located along the C=O bond direction. The energetic amount of this shift is sizable, changing from 8.8 to –7.5 kcal/mol, a total of 16.3 kcal/mol, or 12 pK units.

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As in the above case of the simpler transfer between two amines, a rigorous decomposition of the ($\text{H}_2\text{-COH}^+\leftrightarrow\text{OH}_2$) system reveals that the changes in energy that accompany the reorientations pictured in Figure 3 are indeed largely electrostatic in origin.³⁵ The interaction between the dipole moment of H_2CO and the charge of $^+\text{HOH}_2$ is very much more favorable when $\theta = 180^\circ$ as compared to 108° and is the single most important factor in the reversal of proton position. Despite its apparent ability to act as an excellent indicator, the ion-dipole term does not quantitatively reproduce the changes that occur in the full energy, as there are a number of other contributing factors, some of them sizable. Caution should hence be exercised in drawing quantitative conclusions based solely on this single term.

Carboxyl, Carboxylate, and Amide. The principles uncovered by the calculations are not confined to simple models like H_2O or NH_3 , but are also applicable to larger groups, some more representative of protein residues. Consider, for instance, the carboxyl group of the Asp and Glu residues which commonly participates in proton transfers within enzymes. Calculations have demonstrated that the properties of this group can be understood and predicted by considering it as separate $=\text{O}$ and $-\text{OH}$ functionalities, bonded to the same carbon atom. Each of the latter behaves similarly, within COOH , as in the simpler prototypes, i.e., $\text{H}_2\text{C}=\text{O}$ and HOH , respectively. Of course, there is a certain degree of mutual perturbation, but each item can be dealt with and understood separately. For example, the most notable discrepancy between the $=\text{O}$ atom on H_2CO and that on HCOOH is the greater proton affinity of this atom within the context of the full carboxyl group. It is hence not surprising to find that, for any given H-bond length, the energy barrier to remove the extra proton from $\text{HC}(\text{OH})\text{OH}^+$ is a few kilocalories/mole higher than for H_2COH^+ .³⁷ A particularly useful finding is the consistency of this discrepancy. That is, the energy barrier to remove a proton from $\text{HC}(\text{OH})\text{OH}^+$ is 2–3 kcal/mol higher than if a proton is pulled off of H_2COH^+ , for just about any H-bond length, e.g., regardless of whether the interoxygen distance is 2.5 or 3.0 Å.

Just as the neighboring OH produces a minor but predictable perturbation upon the distance dependence of the proton transfer barrier of $=\text{O}$ in HCOOH , so too are the angular aspects of the H bond amenable to analysis. For example, it was emphasized in Figure 3 that varying the angle of approach of a proton acceptor molecule toward the carbonyl oxygen can shift the equilibrium position of the proton from one group to the other. More specifically, the proton prefers association with the carbonyl when the acceptor molecule lies along a carbonyl lone pair direction, but transfer to the acceptor is favored if it is placed along the $\text{C}=\text{O}$ axis. The difference in energy between these two proton positions, ΔE , varies smoothly from 8.8 to -7.5 kcal/mol as θ varies between 108° and 180° , passing through 0 at $\sim 152^\circ$, at which point the carbonyl and water have equal attracting power for the bridging proton. When H_2CO is replaced by HCOOH , the result is much the same.³⁷ Again an increase in θ reverses the sign of ΔE . However, due

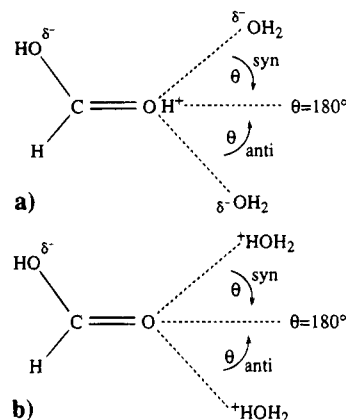


Figure 4. Schematic diagram of syn and anti configurations of the proton-bound complex of HCOOH and H_2O . The bridging proton is associated with (a) HCOOH and (b) H_2O .

to the higher proton affinity of the carbonyl oxygen of HCOOH , it is a little more difficult to remove the extra proton. Hence, ΔE is consistently 3–5 kcal/mol more positive in the carboxyl case, and the two curves of ΔE vs θ are nearly parallel to one another throughout the full range of θ . The higher proton affinity of HCOOH delays the onset of the 0 value of ΔE until $\theta \sim 165^\circ$.

The presence of the OH on HCOOH leads to some interesting options for the angular dependence that are not possible with the simpler H_2CO . The two “sides” of the $=\text{O}$ atom are not equivalent in HCOOH . As indicated in Figure 4, approach of a proton from one direction is syn to the OH group, and the other anti. While the choice affects the energetics of proton transfer, the differences can be understood on the basis of simple physical principles. In the case of syn approach, for example, the change from positive to negative ΔE occurs more gradually; i.e., it takes more of an increase in $\theta(\text{C}=\text{O}-\text{O})$ toward 180° to pull the proton off of the carbonyl oxygen and onto the acceptor molecule.

An important factor contributing toward this difference is the electrostatic interaction between the hydroxyl oxygen of HCOOH and the oxygen of the acceptor water.³⁷ When the bridging proton is located on the HCOOH , both of these oxygens are partially negatively charged, as indicated in Figure 4a. Their mutual repulsion destabilizes the $(=\text{OH}^+\leftrightarrow\text{O})$ geometry wherein the proton is associated with the carboxyl. Following transfer, the acceptor is a positively charged $^+\text{HOH}_2$ moiety, so the interaction with the OH is now a stabilizing force (Figure 4b). The combination of destabilization of $(=\text{OH}^+\leftrightarrow\text{O})$ and stabilization of $(=\text{O}\leftrightarrow^+\text{HO})$ tends to lower ΔE , their energy difference, i.e., to push the proton toward the water.

We now consider how this interaction between the two oxygen atoms is affected by the $\theta(\text{C}=\text{O}-\text{O})$ angle for the syn and anti cases. Considering first syn, as θ is increased toward 180° , the two oxygen atoms become further separated so their electrostatic interaction weakens. Hence, the tendency toward smaller ΔE is attenuated with larger θ , explaining the more gradual drop in this quantity for the syn geometry of HCOOH . In the case of anti approach, Figure 4 illustrates that increasing θ brings the two pertinent oxygen atoms into closer proximity. Hence the above trend is reversed, and ΔE drops more quickly. A more

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rigorous examination of the various components of the interaction energy³⁵ confirms the dominating influence of electrostatics in explaining these trends. Consistent with the simplified analysis in Figure 4 based upon selected atomic charges, the full electrostatic energy rises more quickly for the anti vs syn ($=\text{OH}^+\cdots\text{O}$) configuration as θ is increased, whereas the opposite is true for ($=\text{O}\cdots\text{HO}$).

Besides addition of a proton to the carboxyl group, removal is of interest as well since carboxylate anions occur with some regularity in enzyme systems. A prototype system was hence designed by binding together the HCOO^- and HO^- anions by a proton.³⁸ Despite the difference between this complex and that where both subunits HCOOH and HOH are neutral, one sees once again the same dependence upon intermolecular angle. Keeping constant the intermolecular separation, as the HO^- proton acceptor moves toward the $\text{C}-\text{O}$ axis of the carboxylate, there is an increasing tendency for the shared proton to move away from the latter. The change in ΔE with increasing $\theta(\text{C}=\text{O}\cdots\text{O})$ is in fact quantitatively quite similar for the carboxyl and carboxylate groups.

Another sort of angular distortion which has been considered is one that takes the acceptor out of the plane of the COO group. It is here that an interesting discrepancy was noted. This deformation tends to draw the proton toward the neutral HCOOH and away from the HOH molecule. In contrast, the same motion pushes the proton in the opposite direction when the analogous HCOO^- and HO^- anions are involved.³⁸ This initially puzzling finding can be rationalized simply on the basis of the interaction between the charge of the ionic subunit and the dipole moment of the neutral. Consider first the proton bridging the pair of neutral molecules. When the proton is on the hydroxyl group, its displacement out of the COO plane of ($\text{HC}(\text{OH})\text{O}\cdots\text{HOH}_2$) removes the ion from the plane wherein lies the dipole moment of the neutral HCOOH , thereby destabilizing this configuration. The same displacement has much less effect after the proton has transferred to the formic acid since the charge now resides on the carboxyl, ($\text{HC}(\text{OH})\text{OH}^+\cdots\text{OH}_2$). The preferential destabilization of the former configuration amounts to a push of the proton toward the carboxyl. When the proton bridges the two anions, on the other hand, it is the subunit to which it is bound that is neutral, and the other is ionic. Now when the proton is on the carboxylate, the out-of-plane motion of the hydroxyl in ($\text{HCOOH}\cdots\text{OH}^-$) strongly destabilizes the system while the same motion is less perturbing to ($\text{HCOO}^-\cdots\text{HOH}$). The result is a push of the proton away from the carboxylate group.

Similar sorts of behavior have been noted when the carbonyl oxygen is part of an amide group, instead of carboxyl. The amide is particularly relevant as the functional segment of the peptide linkage in proteins, or as a model of Asn or Gln. Specifically, as the proton transfers across from the amide to a proton-accepting water molecule, $\theta(\text{C}=\text{O}\cdots\text{O})$ is inclined toward values closer to 180° where the $\text{C}=\text{O}$ bond moment can better interact with the developing positive charge of $^+\text{HOH}_2$.³⁹ This tendency persists for $R(\text{O}\cdots\text{O})$ distances at least as large as 3.0 Å.

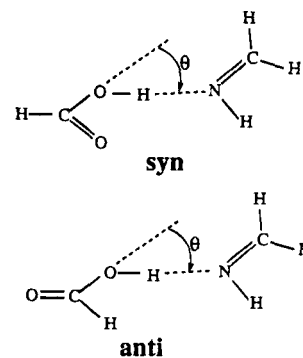


Figure 5. Syn and anti configurations of the complex pairing HCOOH with NHCH_2 , showing the definition of the intermolecular orientation angle θ .

Effects of Surrounding Molecules

The calculations described above have all been carried out with no other molecules in the vicinity. While such in vacuo calculations are necessary to extract the fundamental principles that govern the proton transfer process, it is equally important to understand how the system is affected by immersion in an environment akin to the interior of a protein or appropriate solvation. One of the more important aspects of surrounding molecules is their ability to shift their internal electronic distributions in response to the electric field generated by a perturbing system. A crude but effective means of modeling this phenomenon is through a self-consistent reaction field formalism wherein the system of interest is placed within a cavity, hollowed out of a medium composed of a polarizable continuum, characterized by dielectric constant ϵ .⁴⁰

Due in part to its relevance to a proton-pumping protein called bacteriorhodopsin, calculations were carried out for the H-bonded complex between HCOOH and the imine $\text{H}_2\text{C}=\text{NH}$. Configurations were considered in which the imine nitrogen is either syn or anti to the noninteracting oxygen atom of the carboxyl group, as illustrated in Figure 5. As in the cases where water acts as proton acceptor, the angle made by the nitrogen acceptor and the $\text{C}-\text{O}$ group can have an effect upon the relative energies of the two wells in the proton transfer potential. But reorientation cannot overcome the huge amount of energy that is needed to produce the charge separation that would ensue were the proton to transfer across to the nitrogen and generate the ($\text{HCOO}^-\cdots\text{HNHCH}_2$) ion pair. Taking the syn arrangement as an example, the neutral pair is favored over the ion pair by about 20 kcal/mol.⁴¹

The situation changes when the system is immersed in a polarizable medium which can stabilize the large dipole moment of the ion pair, in an amount that corresponds to the magnitude of the dielectric constant. Considering again the syn geometry, when the dielectric constant has risen to 2, the ion and neutral pairs have comparable energies; by the time $\epsilon \sim 3$, it is the ion pair that is favored.

It is particularly interesting to consider the amount of this energy switching for various intermolecular orientations. Specifically, when θ in Figure 5 is equal

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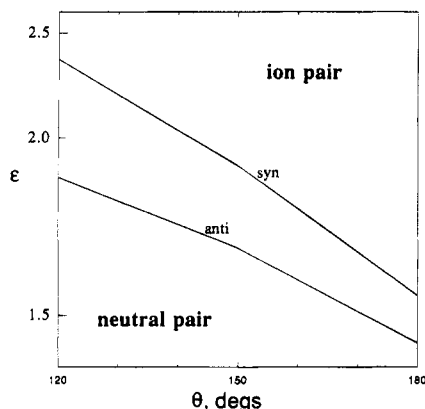


Figure 6. Stability regimes of neutral and ion pairs of HCOOH-NHCH₂, in terms of θ (C=O...O) and dielectric constant, ϵ , of medium, with $R(\text{O}\cdots\text{N}) = 2.75 \text{ \AA}$. Note that the vertical axis is not linear in ϵ .

to 120°, the increase in ϵ from 1 to 3 preferentially lowers the energy of the ion pair vs the neutral pair by 25 kcal/mol. This change is even more dramatic for $\theta = 180^\circ$, where the same increase in ϵ lends an additional preference to the ion pair of over 50 kcal/mol. In other words, the change in angle has a progressively larger effect upon the relative stabilities of the two wells in the proton transfer potential as the polarizability of the medium increases. Whereas the earlier results had indicated that a proton could be pushed from one group to another by angular changes within a vacuum, the present data suggests that this same trend can be enhanced within the context of a polarizable medium such as a protein in certain circumstances. There is a great deal of energy involved in this effect, potentially amounting to tens of pK units.⁴¹

The dual dependence of the preferred configuration upon both angle and dielectric constant is presented as a sort of "phase diagram" in Figure 6. Consider first the bottom section of the figure, where the dielectric constant of the medium is small, which

minimizes its ability to stabilize the ion pair, thereby leading to the lower energy of the neutral pair. As ϵ increases, the transition to the ion pair is marked by the crossing of the border into the ion pair region. Note that it takes less of a polarizability to transform the anti configuration than for syn. But probably most important is the observation that the switch from neutral to ion pair depends also upon the intermolecular orientation angle θ . Taking the syn orientation as an example again, the ion pair becomes preferred at around $\epsilon = 2.3$ for $\theta = 120^\circ$, but the switch occurs for smaller $\epsilon \sim 1.6$, when the angle is 180°. Another way of viewing this diagram is via changes in θ at fixed ϵ . For any ϵ in the range between 1.5 and 2.3, it is possible to effect a proton transfer, i.e., transition from neutral to ion pair, by increasing only the angle. This same sort of coupling between polarizability of the surroundings and intermolecular orientation should be general for any system where the latter angle affects the system's net dipole.

Conclusions

It has been learned that the angular aspects of a H bond can have a profound influence upon the energetics of proton transfer, even to the point of forcing a proton onto a group that is less basic than its partner. Surrounding molecules can amplify this effect to the point where angular reorientations cause shifts in relative stability of more than 30 kcal/mol. Most importantly, the relationship between H-bond angles and energetics can be understood on the basis of simple physical principles such as charge-charge or ion-dipole interactions, without need of high-level ab initio calculations. There is thus reason for optimism that the ideas expressed herein may enable predictions in complex problems such as enzyme mechanisms where quantum mechanical calculations are out of the question.

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