Intrinsic Barriers for Proton Transfer Reactions Involving Electronegative Atoms, and the Water Mediated Proton Switch: An Analysis in Terms of Marcus Theory

J. Peter Guthrie

Contribution from the Department of Chemistry, University of Western Ontario, London, Ontario, Canada N6A 5B7

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Abstract: The intrinsic barrier for proton transfer reactions along a preformed hydrogen bond is approximately 1 kcal/mol. The apparent intrinsic barrier for simple apparently bimolecular proton transfers is higher, typically about 5 kcal/mol, because the process involves an intervening water molecule. Analysis of this process by multidimensional Marcus theory shows that the reaction is commonly stepwise, and the apparent barrier arises from the need to form a transient unstable complex of hydronium ion and two basic species or hydroxide ion and two acidic species. A similar analysis leads to predictions of the rate constants for water mediated proton switch reactions.

Introduction

Proton transfers involving electronegative atoms are known to be fast and diffusion controlled except for small values of ΔpK_a, the difference between the pK_a values of the protonated forms of the species acting as donor and acceptor.[1] Nevertheless, there appears to be a substantial intrinsic barrier for this proton transfer process, and analysis of the available data in terms of Marcus theory[2−4] leads to values of 5 kcal/mol.[5−8] In Marcus theory the intrinsic barrier is the free energy of activation for a process with $\Delta G° = 0.0$. This posed a problem: in treating concerted reactions by a two-dimensional extension of Marcus theory,[9,10] we found that the intrinsic barrier for direct proton transfer had to be small, ca. 1 kcal/mol, if the reactions were indeed to be concerted and the observed free energies of activation were to be matched. There is a general prejudice among organic chemists that the intrinsic barrier for proton transfer along a hydrogen bond should be small.[8,11−14] Studies of proton transfer from acids of strength comparable to hydronium ion show that these reactions are superfast;[15,16] i.e.,

the actual proton transfer step is faster than diffusional encounter. This is consistent with a small intrinsic barrier, and not one as large as 5 kcal/mol. The resolution of this problem is implicit in a recent paper by Berg and Jencks,[17] which examined the barrier for loss of a solvating water or alcohol molecule hydrogen bonded to an amine. If the barrier to removing the water in hydrogen bonded contact with a molecule is larger than the barrier to removing a water farther away, then the last step in diffusion together of two molecules can be slower/more difficult that the preceding steps. Furthermore, if the two molecules both hydrogen bond to water, then removal of the last solvent molecule from between them will be particularly slow. This offers an explanation both of the high barrier seen for simple proton transfers, such as those studied by Eigen,[1] and for the observation that most such proton transfers occur by way of a bridging water molecule,[18] although proton abstraction from a weakly hydrogen bonding carbon acid is a direct process.[19]

Hine showed[13] that proton transfers through a short chain of water molecules could be stepwise and still be fast enough to match the observed rates, but implicitly assumed a very low intrinsic barrier for each proton transfer step.

We now wish to show that the apparent intrinsic barrier to "simple" proton transfers involving electronegative atoms and the apparent intrinsic barriers for water mediated proton switch reactions can be calculated from a simple model of desolvation limited by hydrogen bond energies, and a very low intrinsic barrier for proton transfer along a hydrogen bond.

Results and Discussion

Model and Calculations Based on It. We will analyze proton transfer reactions in terms of reaction squares or reaction cubes. A reaction square is an Albery[20]−More O'Ferrall[21]

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1996.
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(6) (a) Gilbert and Jencks showed that proton transfers from O to O can be fitted using reasonable assumptions about diffusion rates and a rate constant for the isoenergetic proton transfer step of 10^{10} s^{-1}, which corresponds to an intrinsic barrier of 3.8 kcal/mol. (b) Gilbert, H. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7931−7947.
(7) (a) Bednar and Jencks showed that proton transfers involving HCN, like other "normal" acids can be fitted using reasonable assumptions about diffusion rates and a rate constant for the isoenergetic proton transfer step of 10^9 s^{-1}, which corresponds to an intrinsic barrier of 5 kcal/mol. (b) Bednar, R. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1985**, *107*, 7117−7126.
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−Jencks[22] diagram where the x and y coordinates represent the two bond forming/breaking processess which must both occur to transform the starting materials to products. Free energy is a third dimension at right angles to these two and can be represented by contours. For a reaction where three bond making/breaking processes are required to transform starting materials to products, we need a reaction cube[23] in which the x, y, and z dimensions represent the three reaction coordinates and the free energy is a fourth dimension orthogonal to the three shown. It is difficult to plot energy or even supply contours in this case, because of the difficulty of seeing multiple three dimensional energy contours within a cube. It is, however, possible to draw a contour showing the inaccessible region of the diagram, by choosing a contour energy just above that of the transition state.

In discussing the stepwise components of possibly concerted proton transfer reactions, we must calculate free energies of the various encounter complexes and intermediates. We use an admittedly oversimplified model, which at least has the virtue of explicitly setting out the assumptions used. To estimate the free energy changes for these corner species we assume that $\Delta G_{complex} = \Delta G_{ion\ pair} + \Delta G_{h-bond} + \Delta G_{encounter}$.

Ion pairing is neglected at high ionic strength (1 M or greater) and is scaled to a value of $\Delta G_{overall} = 0.1$ kcal/mol[24] for 1:1 ion pair formation in water at low ionic strength. This is the free energy for formation of an ion pair from spherically symmetrical singly charged anion and cation. We partition this free energy into the statistical and electrostatic contributions using the equation[25] derived by Fuoss[26] and Eigen,[27] picking an interaction distance to give $\Delta G_{overall} = \Delta G_{encounter} + \Delta G_{electrostatic} = 0.1$ kcal/mol in water. The corresponding contributions can be calculated from the terms in this equation as $\Delta G_{encounter} = 1.29$ and $\Delta G_{electrostatic} = -1.19$. Simple electrostatic calculations are used to calculate the electrostatic interaction energy for geometries other than the contact ion pair, using standard bond angles (109.5° for tetrahedral, 120° for trigonal geometries) and a single contact distance, r, for both bonding and nonbonding distances. There seems to be little point in being more precise unless one does a *much* more elaborate calculation. The saving point is that in aqueous solution electrostatic effects are small. We are also implicitly assuming the same effective dielectric constant for all configurations considered. Since electrostatic effects are of modest importance in aqueous solution, the crude approximations used here are not totally unreasonable and allow some account to be taken of electrostatic effects on complex stability.

Equilibrium constants for hydrogen bonding are calculated using the equation of Stahl and Jencks,[28] but corrected for encounter complex formation, because we only want to count encounter once, and a particular intermediate may have several interactions present. However, since Stahl and Jencks worked at high ionic strength, their treatment neglects ion pairing. We explicitly correct for ion pairing at low ionic strength as described above. Stahl and Jencks developed their equation for simple hydrogen bonded pairs, with statistical corrections for the number of hydrogens and the number of basic atoms. Their equilibrium constant is the sum of two effects: hydrogen bonding and encounter complex formation $\Delta G_{encounter}$. We calculate the energy of hydrogen bond formation by subtracting

$\Delta G_{encounter}$ for bringing two reactants together. We estimate $\Delta G_{encounter}$ after Hine[14] by calculating the probability of the key atom in one reactant being in a volume equal to that of an oxygen atom relative to the other reactant; the equilibrium constant so calculated is 0.0085 M^{-1}.

Free energies for encounter complex formation were estimated following Hine.[14] As described above, for encounter complex formation involving one position for the second reactant relative to the first, we calculate $K = 0.0085$ M^{-1}. This is taken as K_{chem} in Hine's[29] notation. Then, following Hine[29] we calculate the symmetry correction for each particular case, using symmetry numbers for reactants and products. In this case we must take note of various possible chiral centers present in the complex but absent in the reactants. Since the complexes are held together by hydrogen bonds, which are longer than covalent bonds, the energy differences for different diastereomers involving adjoining chiral oxygens are trivially different in energy, so we include a factor of 2 for each such chiral center. A water molecule, hydroxide ion, or hydronium ion hydrogen bonded to two different species will in general be a chiral center, and should be counted as such in assessing the probability of formation of an encounter complex. An alternative way of assessing the probability of formation of an encounter complex is to consider a diamond lattice model for the local structure of water, and count the number of possible sites in the lattice which one species could occupy and still count as an equivalent complex. This gives roughly equivalent numbers but is much harder to work through and explain in complicated systems.

Bimolecular Acid−Base Reactions. For the example of acetic acid reacting with aniline,[1] the observed free energy of activation is 5.7 kcal/mol. We now analyze the proton transfer event in terms of the mechanism in **1**, and the reaction square

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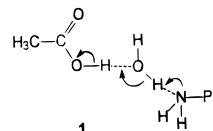
in Figure 1. We must calculate the free energy of each corner and then examine the implications of possible values of the intrinsic barrier for the proton transfer steps. The two stepwise alternatives lead to the anilinium−hydroxide−acetic acid, and aniline−hydronium−acetate triples, respectively.

The energy of each corner species is then calculated as the sum of the hydrogen bond, electrostatic and statistical contributions. Details of these calculations have been described above. The energies of the corner species so calculated are found in Table S1, Supplementary Material.

We now calculate the free energy of activation using two-dimensional Marcus theory,[2−4,9,10] the corner energies just calculated, and a value for the intrinsic barrier for proton transfer along a hydrogen bond. Assuming intrinsic barriers of 1 kcal/mol, $\Delta G^{\ddagger}$ is calculated to be 5.95 kcal/mol. With an intrinsic barrier of 0.5 kcal/mol, $\Delta G^{\ddagger}$ is calculated to be 5.34 kcal/mol. The reaction is predicted to be essentially stepwise, with the rate limiting process being transfer of a proton from acetic acid to the intervening water. The model is consistent with the facts provided the intrinsic barrier is low, i.e., ≤1 kcal/mol.

The alternative, a further diffusion step leading to direct proton transfer, can be shown to be much slower. We estimate the hydrogen bond strength between water and acetic acid or aniline from the difference in free energy of transfer for model compounds and isosteric analogs for which the relevant

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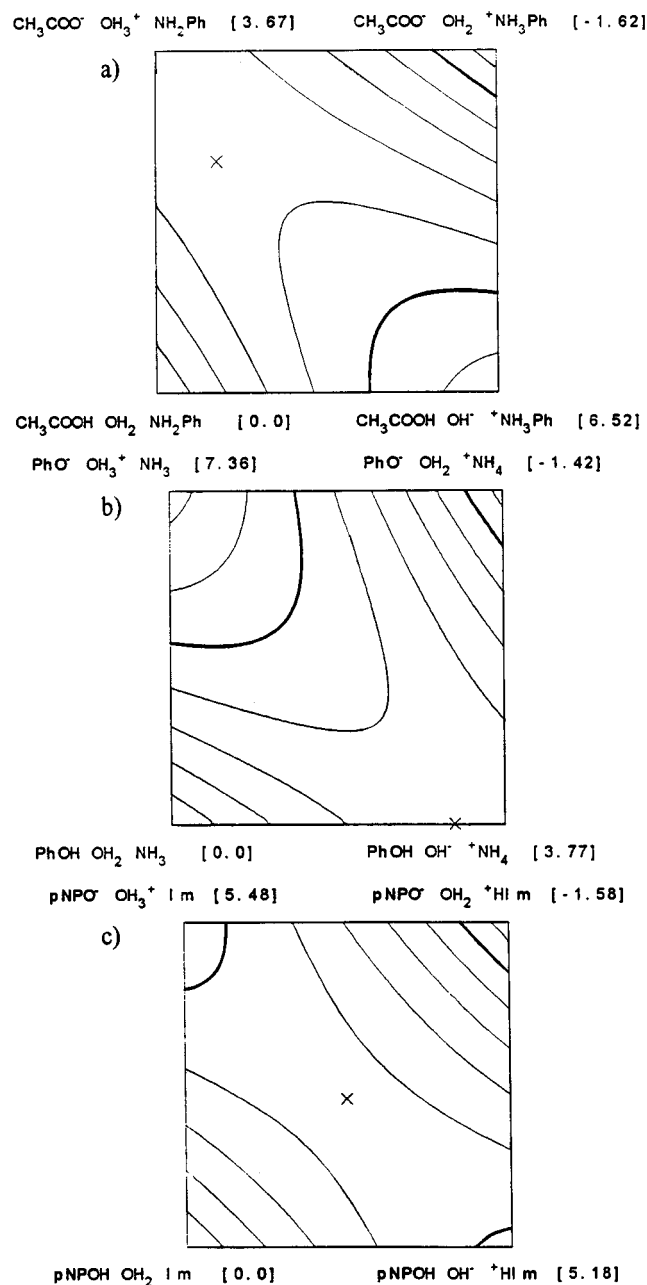
Figure 1. Proton transfer through an intervening water from (a) acetic acid to aniline, (b) ammonia to phenol, and (c) *p*-nitrophenol to imidazole.
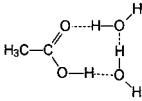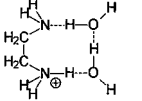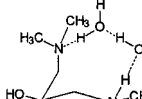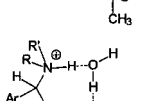
Table 1. Predicted and Observed Activation Energies for Proton Transfer and Water Mediated Proton Switch Reactions[a]

reaction	calculated DG*	observed DG*
Ph-NH₂ . H₂O . HOCOCH₃	5.95[c]	5.98[b]
NH₃ . H₂O . HOPh	5.93[c]	5.98[b]
Im . H₂O . HOpNP	7.04[c]	5.57[b]
(structure)	5.75[c]	6.96[d]
(structure)	9.03[c]	8.16[e]
(structure)	8.36[c]	8.57[e]
(structure)	7.44[c]	8.21[g]
(structure)	9.93c	9.25h

[a] All in aqueous solution at 25 °C. [b] Based on data from Eigen[1] and Maass.[38] These experiments were done at low ionic strength.[38] [c] Calculated by multidimensional Marcus theory, as described in the text. [d] Reference 35. [e] Reference 19. [f] Substituents on the carbinolamine nitrogen, other than the acidic proton, are not shown. [g] Reference 33. [h] Reference 39.

irrelevant, and transfer through a bridging water is seen. Similarly good fits are seen for other proton transfer reactions; see Table 1.

Water Mediated Proton Switch. We turn now to the water mediated proton switch process[33] to see if the apparent intrinsic barriers for this are also predicted by our model. In a water mediated proton switch, a proton migrates from one atom of a molecule to another, by way of intervening water molecules, without generating diffusionally free hydronium or hydroxide ions. These reactions have apparent intrinsic barriers of 7.2–13.1 kcal/mol.[34] For the *H*–O exchange reaction of acetic acid, the observed rate constant is 4.8×10^7,[35] $\Delta G^{\ddagger} = 6.98$; the exchange process involves two water molecules.[35] Proceeding as before, we use the mechanism in **2**, and calculate the energies

(structure 2)

2

of the corners for what is now a reaction cube; see Figure 2. The energies for the corner intermediates are estimated as already described and are found in Table S1. With an intrinsic barrier of 1 kcal/mol we obtain $\Delta G^{\ddagger} = 5.75$ kcal/mol, satisfactorily close to the observed value. The reaction is predicted to be essentially stepwise, with the transfer of a proton between the two solvent molecules being largely rate limiting.
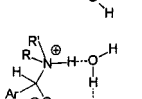
hydrogen bonding is impossible: from acetic acid[30] and methyl formate,[30] $\Delta G_{h-bond} = -3.15$ kcal/mol for acetic acid to water; from *N,N*-dimethyl aniline[31] and isopropyl benzene,[30] $\Delta G_{h-bond} = -3.20$ for water to aniline. Then following Berg and Jencks[17] ($\Delta G_{act} = -\Sigma\Delta G_{hb} + \Delta G_{cav} + \Delta G_{disp} = 3.15 + 3.20 + 0.6 + 1.3$ (latter two values from ref 17) = 8.25 kcal/mol), the free energy of activation for loss of the intervening water will be at least 8 kcal/mol, leading to a rate constant of $\leq 10^7$ s⁻¹, which is much too slow to compete with the stepwise process in Figure 1. Thus the fact that loss of the intervening water would lead to a proton transfer process with a rate constant of 10^{12} s⁻¹ is

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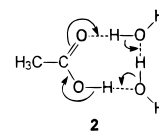
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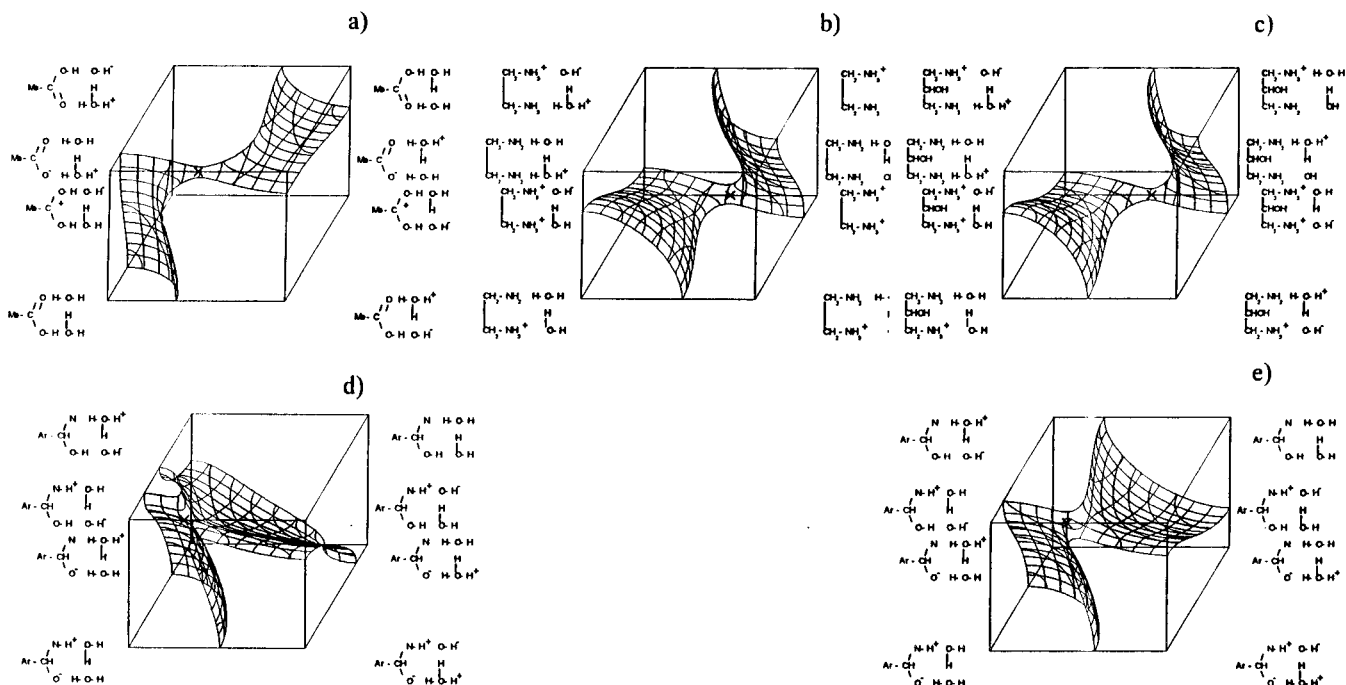(35) Luz, Z.; Meiboom, S. *J. Am. Chem. Soc.* **1963**, *85*, 3923–3925.

Figure 2. Water mediated proton switch from (a) one oxygen to the other of acetic acid, (b) one nitrogen to the other of ethylenediamine, (c) one nitrogen to the other of 2-hydroxy-1,3-propanediamine, (d) the zwitterionic to the neutral form of the adduct of methoxyamine and *p*-chlorobenzaldehyde, and (e) the zwitterionic to the neutral form of the adduct of piperazine and pyridine-4-carboxaldehyde. Surfaces are drawn for energies <0.1 kcal/mol higher than the calculated transition states.

For the water mediated proton switch of ethylenediamine monocation, for which the observed $\Delta G^{\ddagger}$ is 8.2 kcal/mol, we assume two bridging water molecules and construct a reaction cube. Although it might seem possible to have only one bridging water molecule, this requires that the ethylenediamine be eclipsed. Molecular mechanics calculations carried out using the MM3(89)[1,36] program as supplied by QCPE give a barrier of 4.6 kcal/mol for going from a conformation with the amines gauche to one with the amines eclipsed. For the one water molecule model a concerted path with a free energy of activation = 5.1 kcal/mol is predicted, leading to a total free energy of activation of 9.7 kcal/mol. In the two water molecule model the reaction is essentially stepwise, with an activation energy of 9.03 kcal/mol. Athough the two models lead to predictions too similar for confident decision, the two water moledule model looks preferable.

Similarly the proton exchange rate for 2-hydroxy-*N,N,N′,N′*-tetramethyl-1,3-propanediamine is assumed to involve two bridging water molecules. To have only one bridging water requires a chair-like conformation with prohibitive steric interactions, amounting to 6.87 kcal by MM3. The predicted free energy of activation for the one water molecule model is 5.01 kcal leading to an overall barrier of 11.9 kcal/mol, which is much higher than for the two water molecule model. For the two water molecule model this reaction also is essentially stepwise, with a predicted free energy of activation of 8.36 kcal/mol for an intrinsic barrier of 1 kcal/mol.

For the water mediated proton switch converting zwitterionic to neutral intermediates in the addition of methoxylamine to *p*-chlorobenzaldehyde,[33] mechanism **3**, for which the rate

3

constant is 6.2×10^6 s^{-1}, $\Delta G^{\ddagger}_{obs} = 8.21$ kcal/mol, a similar analysis leads to $\Delta G^{\ddagger}_{pred} = 7.44$ kcal/mol, and the process is predicted to be stepwise.

Although the rate determining step for these proton transfers through water has a very small intrinsic barrier, it is the proton transfer and not diffusional encounter which is the overall rate limiting process because there are energetically unfavorable proton transfer steps before the rate determining step. The "corner intermediates" cannot separate by diffusion because there are available to them energetically favorable proton transfer processes with essentially no kinetic barrier. These "intermediates" will not have sufficiently long lifetimes to allow diffusional separation. The very low intrinsic barriers which we postulate are still consistent with observable deuterium kinetic isotope effects.

Most proton transfer reactions are, in fact, through intervening solvent molecules;[18] data are available for ammonium ion, carboxylic acids, and phenols.[18] One exception to this is proton transfer from ammonium to ammonia.[37] Although any exception is disconcerting, it seems likely that the special feature here is the small size of ammonia and ammonium; the contribution of dispersion forces is likely to be negligible, which will lower the barrier to the final diffusion step. The model we have used implies that for the exchange process involving direct proton transfer from ammonia to ammonium, the rate limiting process will be largely diffusional and not the proton transfer itself.[37]

(36) As contained in MM3 (89) as obtained from QCPE. Allinger, N. L.; Yuh, Y. H.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8551.

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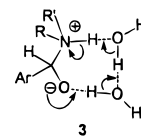(38) Maas, G. Dissertation, Universitaet Goettingen, 1962.

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For eight proton transfer reactions and proton switch reactions, given in Table 1, the root-mean-square (rms) deviation of calculated and predicted values is 0.85 kcal/mol for an intrinsic barrier of 1 kcal/mol. Minimizing the deviations by adjusting the value of the intrinsic barrier led to an rms deviation of 0.81 kcal/mol for an intrinsic barrier of 0.88 kcal/mol, but we doubt that the model justifies any attempt at greater precision than 1 kcal/mol.

The model presented in this paper is admittedly crude, particularly in its treatment of electrostatic effects. This imposes uncertainties of about 1 kcal in the energies of the various corner intermediates which we postulate and hence in the calculated free energies of activation. Nevertheless, it leads to satisfactory predictions with a simple physical model and requires only calculations which can be carried out on a desktop computer.

We conclude that there is only a very small intrinsic barrier to proton transfer along a preformed hydrogen bond. The multidimensional Marcus theory approach has been shown to give valid predictions of rates of elimination reactions of simple alkyl halides, with neither adjustable parameters nor the use of any information from elimination reactions.[10]

Supporting Information Available: Table S1, energies of the "corner intermediates", and Table S2, pK_a values for species discussed (10 pages). See any current masthead page for ordering and Internet access instructions.

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