Theoretical Perspectives on Proton Transfer and Bifunctional Catalysis

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Simple proton transfer (PT) is a three-centre, four-electron process in which the positively charged proton moves between electronic lone pairs on the donor and acceptor groups. It is helpful to analyse the process further as the resultant of two individual components : - deprotonation of the donor A-H+, and protonation of the acceptor :B. Each of these heterolytic components may be described qualitatively by self-consistent-field molecular-orbital (SCF MO) theoretical methods - since each species has a closed-shell electronic structure and there is no change in the number of electron pairs - and may be represented by a Morse-curve energy profile (figure 1).

Superimposition of energy profiles for the component processes generates a profile for the overall PT occurring linearly between donor and acceptor groups separated by a particular distance. A relatively long A··B distance leads to a double-well energy profile in which hydrogen-bonded species A-H+··B and A··H-B+ are separated by a central barrier. A relatively short A··B distance leads to a single-well energy profile for a proton-bound dimer A··H+··B, whereas an intermediate A··B distance leads to a flat energy profile for PT (figures 2 and 3).

An early ab *initio* SCF MO theoretical study relating to PT was made by Clementi [1]. The potential energy (PE) surface for the system NH_4Cl, with respect to the geometrical coordinates Cl··H and H··NH_3, shows a minimum for the ion-pair complex $NH_4^+Cl^-$ which may be approached along valleys corresponding to the separated species, either NH_4^+ + Cl- or NH_3 + HCl. A diagonal section across the PE surface for constant Cl·N distance = 5.0 Å yields a double-minimum energy profile for PT: a substantial barrier separates the gas-phase ions from the more stable neutral molecules. However, a diagonal section for constant Cl·N distance = 3.25 Å yields a single-well energy profile.
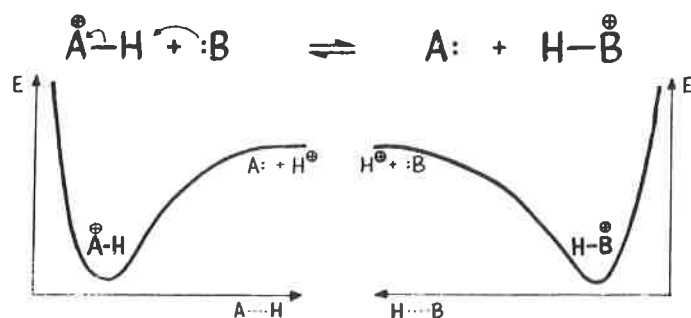
An example of a simple PT in a system whose energy minimum is an asymmetrical hydrogen-bonded complex is provided by NH_4^+··NH_3, which was the subject of an important theoretical study by the groups of Delpuech (Nancy) and Veillard (Strasbourg) [2]. Their SCF calculations with a double-zeta plus polarization (DZP) basis yielded a N··N distance in the hydrogen-bonded complex very similar to the result of a recent study [3] which

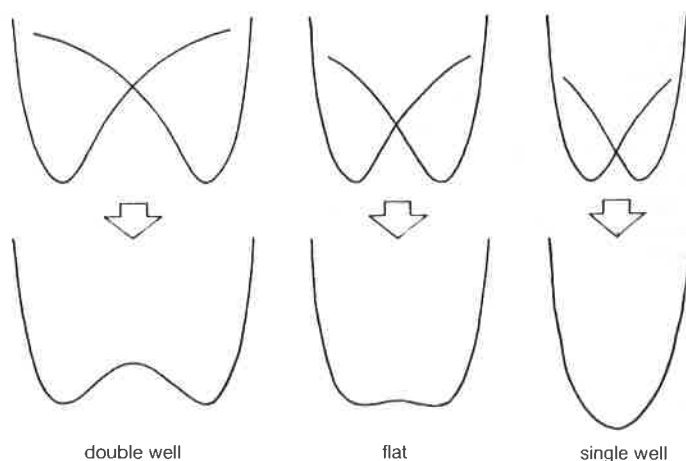double well   flat   single well

FIGURE 2.

FIGURE 3.

FIGURE 1.
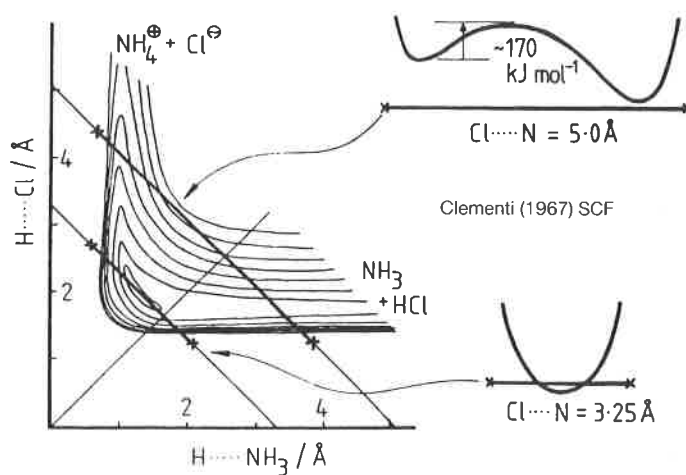
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included electron correlation at the MP2/6-31G(d) level and only 3% different from the still more recent X-ray crystallographic determination [4]. Veillard and co-workers [2] calculated a small barrier to the symmetrical PT of 12 kJ.mol⁻¹, which may be compared with a value of 11 kJ.mol mol⁻¹ at the MP4SDQ/6-311++G(d,p)//MP2/6-31G(d) level [5].

calc.	2·778Å	Veillard	(1972)	SCF/DZP
	2·731Å	Ikuta	(1987)	MP2/6-31G*
expt.	2·695Å	Berthold (1988)		X-ray

Scheiner has reviewed his extensive theoretical studies of PT [6]. To summarize the results of his group and of others, in regard to the factors which influence the barrier height to PT, it is generally found that increasing the size of the basis set in SCF MO calculations leads to an increase in the barrier height, whereas introducing electron-correlation effects tends to decrease the barrier height. Often these factors roughly compensate for each other, so that quite reasonable results may be obtained from SCF calculations using basis sets of only modest size. The longer is the distance between the donor and acceptor groups, the larger is the barrier to PT. Usually PT occurs along the path of an approximately linear pre-existing hydrogen bond. Angular deformation away from collinearity of A⋯H⁺⋯B tends to increase the barrier to PT, but if A and B are anionic groups (e.g. HO⁻⋯H⁺⋯OH⁻) angular bending leads to a smaller barrier; this difference in behaviour is due to the nature of the electrostatic interactions between the groups in the respective systems [6] (figure 4).
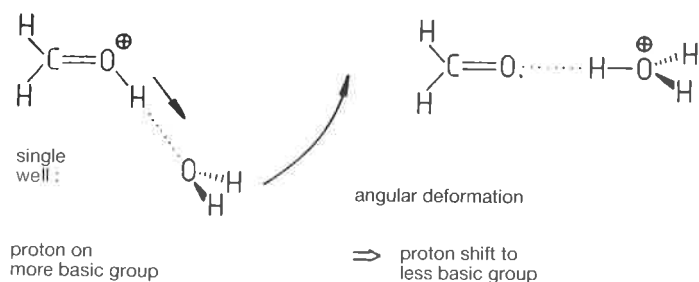

single well :

proton on more basic group

angular deformation

⟹ proton shift to less basic group

FIGURE 4.

The proton-bound dimer of formaldehyde and water, CH₂=OH⁺⋯OH₂, exists in a single-well potential with the proton more closely attached to the more basic oxygen atom of the carbonyl group [7]. However, if the hydrogen bond is constrained to be collinear with the carbonyl bond, the proton is predicted to shift to the less basic (lower proton affinity) site on water [8]. PT may thus be induced by a geometrical change which imposes this constraint. This result could have implications for enzymic catalysis.

At a particular hydrogen-bond distance between donor and acceptor groups, the barrier height for PT between nitrogen atoms NH → N is lower than for PT between oxygen atoms OH → O. Because the N-H bond in NH₄⁺ is slightly longer than the O-H bond in H₃O⁺, the energy profiles for the components of the NH₄⁺⋯NH₃ PT have, in effect, a smaller separation than those for H₃O⁺⋯OH₂, leading to a lower barrier [9]. Owing to the difference in proton affinity between nitrogen and oxygen bases, PT in the direction OH → N is facile, but has a substantial barrier in the reverse direction O ← HN [6].
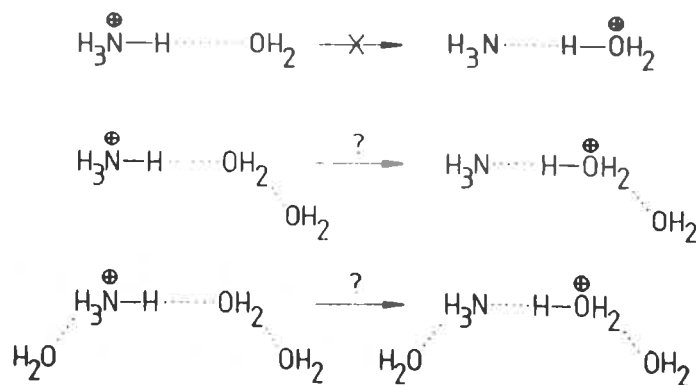
Delpuech, Veillard and their co-workers [10] investigated the effects of specific solvation upon the NH₄⁺⋯OH₂ PT equilibrium. A single solvating water molecule, hydrogen bonded to the acceptor water, was found to make the hydroxonium form considerably less unstable than the unsolvated H₃N⋯H-OH₂⁺ species, but a second solvating water molecule, hydrogen bonded to the donor ammonium, tended to restore the preference for the left-hand side of the equilibrium. It was predicted that additional solvation in this incremental manner would lead slowly to convergence upon the energetics of the equilibrium in the aqueous phase. At that time it was not feasible to search PE surfaces, calculated by *ab initio* SCF MO methods, for transition structures of reacting systems as large as these specifically solvated species. Consequently it was not possible to obtain meaningful results for barrier heights to PT in these systems, or to address issues of kinetics and catalysis in a meaningful way. Nonetheless, these authors did consider the possibility of PT being mediated by a solvent water molecule intervening between the donor and acceptor groups : the mediating molecular of water is itself both a proton acceptor and a proton donor. It was assumed by Delpuech and Veillard that the symmetrical species H₃N⋯H₃O⁺⋯NH₃ would represent a transition state; however, this species could equally well be an intermediate occurring along the pathway for a stepwise mechanism.

concerted
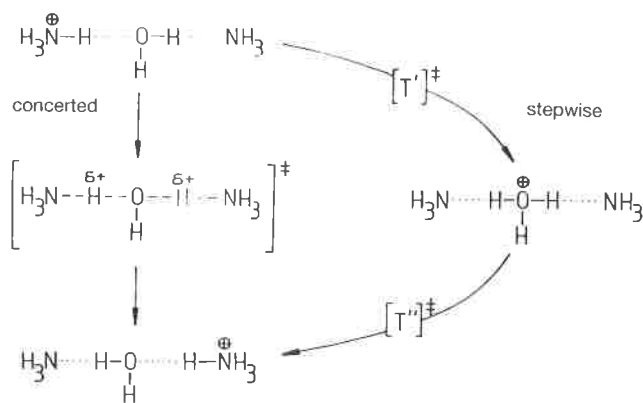
stepwise

The question of concerted *vs.* stepwise mechanisms for double PT between a variety a donor and acceptor groups A-H⁺ and B, mediated by a variety of intervening groups S-H, was thoroughly investigated by Schowen and co-workers [11] using the INDO semiempirical SCF MO method. A concerted mechanism is one in which the two PTs are coupled and occur synchronously. There are two possibilities for stepwise mechanisms : either the group A donates its proton first, generating A⋯HSH⁺⋯B as an intermediate, or the group B accepts a proton first, generating A-H⁺⋯S⁻⋯H-B⁺ as an intermediate. The reactant and product complexes and these intermediates may be located at the corners of a diagram on which the edges represent the individual proton-transfer steps PT' and PT". A concerted mechanism (figure 5) corresponds to a diagonal path across the PE surface between the
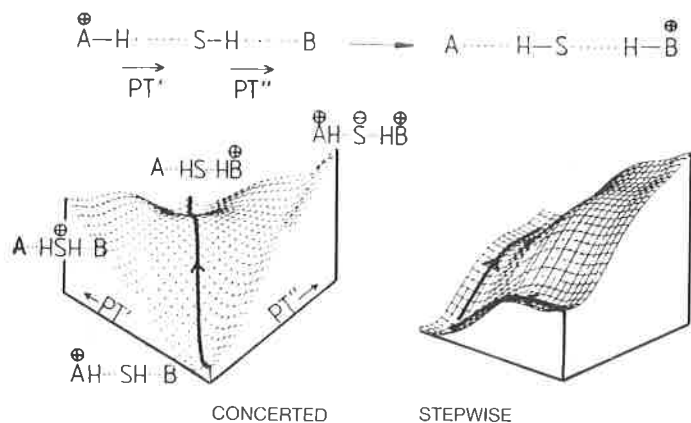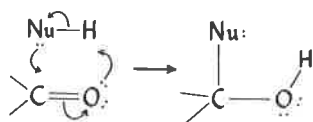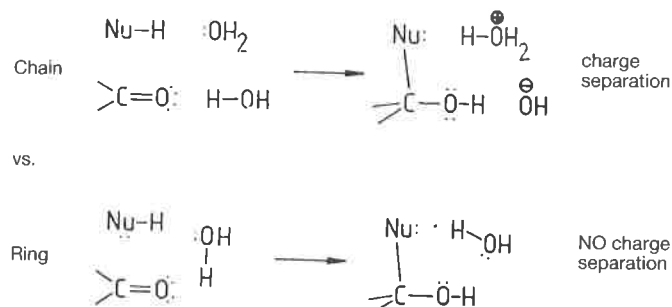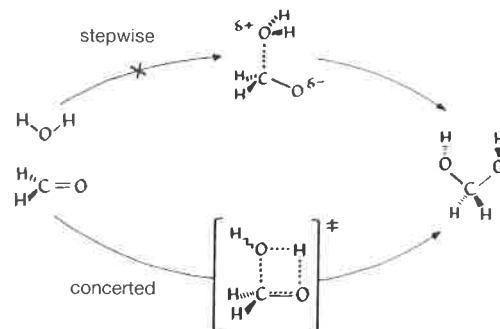
FIGURE 5.

Ab initio SCF/STO-3G calculations for addition of water to formaldehyde revealed that the gas-phase reaction occurs not by a stepwise mechanism involving a zwitterionic intermediate but by a concerted mechanism involving a four-centre transition structure [13]. Several ways were considered by which one extra molecule of water might facilitate the addition : general acid catalysis

reactant complex A-H+···S-H··B and the product complex A···HS·H-B+, and occurs when both intermediates have high energies. The energetics of the individual PT steps depend upon the component hydrogen-bond distances A···S and S···B, just as for simple PT. Shorter distances A···S tend to favour a concerted double PT, whereas longer distances tend to favour a stepwise mechanism. A relatively small change in the overall geometry can cause a change in mechanism. The chemical identities of the groups A, S and B are less important in determining the mechanism than are the geometrical features of the component hydrogen bonds. These theoretical findings may have implications for biological systems : for example, the charge-relay chain once thought to be involved in the catalytic mechanism of serine proteases [12].

(proton donation to $CH_2=O$), general base catalysis (proton acceptance from the nucleophilic H_2O), or bifunctional catalysis. The first two possibilities gave only small reductions in the barrier height, but the latter mode of participation was predicted to lower the barrier height dramatically [13]. The transition structure FW2≠, involving two molecules of water, was found to be 41 kcal.mol-1 (173 kJ.mol-1) lower in energy than the transition
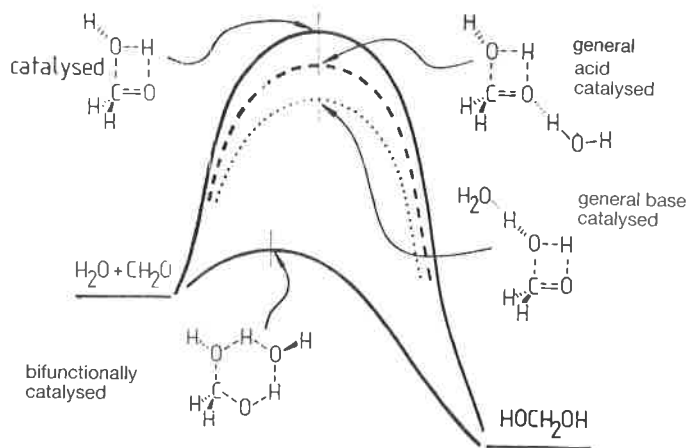

Proton Transfer (PT) is often a component of multibond reactions which also involve the making and breaking of bonds between atoms other than hydrogen, i.e. heavy-atom reorganisation (HAR). For example the addition of a neutral nucleophile Nu-H to a carbonyl group under neutral conditions involves PT as a essential component. In a protic solvent such as water, this process could be facilitated if one molecular of solvent could accept a proton from Nu-H and another molecule of solvent could donate a proton to the carbonyl oxygen. However, this scheme would lead to a separation of charges to the ends of the chain of molecules, which would be energetically unfavourable. In contrast, if a solvent molecular participates bifunctionally as both a proton acceptor (from Nu-H) and a proton donor (to the carbonyl O) then a double PT may occur, together with the nucleophilic addition, without any unfavourable separation of charges.

structure FW1≠ for the uncatalysed addition at the STO-3G [14]. Inspection of the atomic displacements occurring in the reaction-coordinate vibrational mode shows that the double PT is concerted and that it occurs together with the HAR processes [14] (figure 6).

Bifunctional participation of a water molecule, as a proton acceptor and as a proton donor, in a six-membered cyclic transition structure has now been reported in many theoretical studies. Besides nucleophilic addition to double-bonded species, another class of reactions which are catalyzed in this manner are tautomeric equilibria. The barrier height for the lactam⇌lactim equilibrium between 2-pyridone and 2-hydroxypyridine is very substantially reduced by either one [15, 16] or two [16] molecules of water participating in a cyclic hydrogen-bonded arrangement. The barrier height of 41 kJ mol-1 calculated for the two-water catalysed process by a configuration interaction (CI) method appears to agree well with the enthalpy of activation of 46 kJ.mol-1 determined by Dubois and co-workers [17] for tautomerism of 6-methoxy-2-pyridone in water. The role of bulk solvent, as considered by a reaction-field continuum model, was not important for these specifically solvated species and did not affect the relative energetics significantly [16].
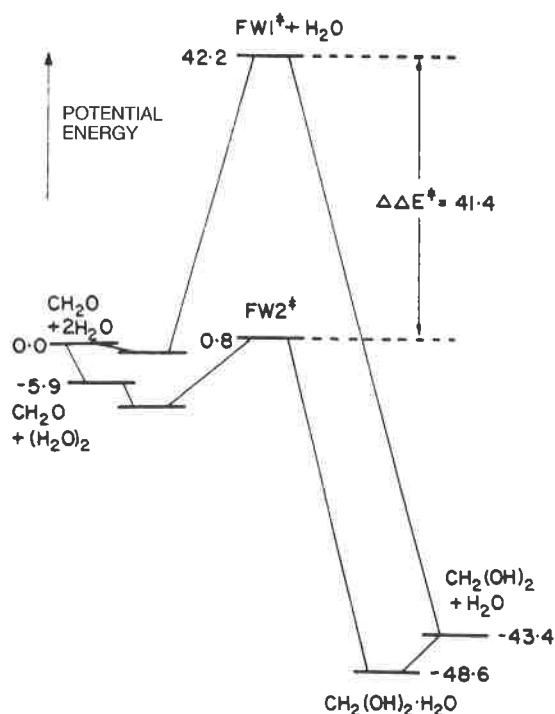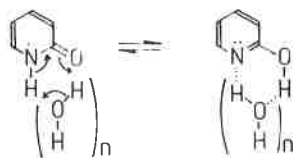
FIGURE 6.

reduction in barrier height/kJ mol⁻¹ (vs. n = 0) :

|		
n = 1	> 155	Bertran (1981) CNDO/2
	179	Bertran (1985) STO-3G
	129	Hillier (1987) CI/3-21G
n = 2	$\triangle E^{\neq} = 41$	Hillier (1987) CI/3-21G
cf.	$\triangle H^{\neq} = 46$	Dubois (1983) Expt.

The barrier-height reduction for prototropy of formic acid catalysed by one molecule of water acting bifunctionally is almost certainly overestimated at the SCF/3-21G level, being twice the value calculated at the MP2/6-31G* with electron correlation [18]. Whereas the enthalpy of activation may be considered to be approximately the same in aqueous solution as for a specifically-solvated gas-phase process, the entropies of activation will be quite different. A simple and very approximate method for scaling gas-phase entropies to aqueous-phase values (cf. ref [14]) may be applied to the two-water catalysed process to yield activation parameters very close to those determined experimentally by dynamic NMR methods for prototropy of acetic acid in aqueous solution [19].

Formic acid prototropy : bifunctional catalysis by H₂O
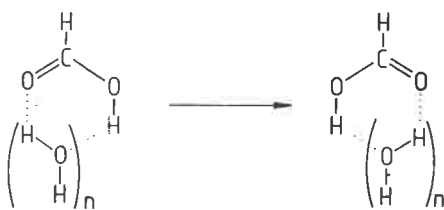
n = 1 : barrier reduction/kJ mol⁻¹ ∼ 169 (SCF/3-21G)
                                          84 (MP2/6-31G*)

n = 2 :	$(\triangle H^{\neq})_{aq}$	$(\triangle S^{\neq})_{aq}$/J K⁻¹mol⁻¹	
calc.	15	-57	Petts & Williams [18]
expt.	13	-55	Luz & Meiboom (1963)
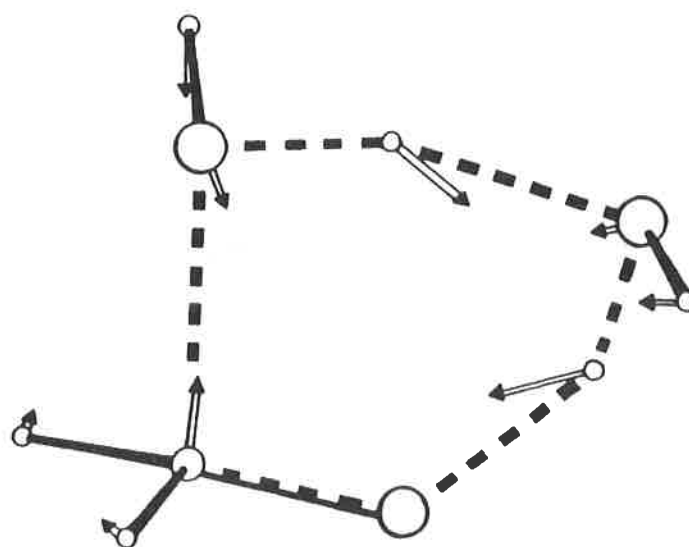
The degenerate prototropic rearrangement of formamidine is also predicted by SCF MO calculations [20] to be catalysed bifunctionally by a water molecule.

Formamidine prototropy : bifunctional catalysis by H₂O
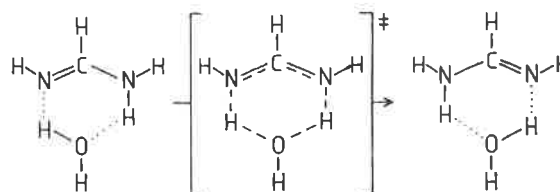
barrier reduction ∼ 157 kJ mol⁻¹
Csizmadia (1983) ⎫ SCF
Fukuiu   (1984) ⎭

In all these systems the double PT is predicted to be concerted and is coupled with HAR processes. Another concerted double PT, which has been the subject of many theoretical studies [21], is the prototropic rearrangement occurring within the dimer of formic acid. Calculations at the SCF/STO-3G level for the analogous degenerate rearrangement of the formamidine dimer predicted this also to be a concerted process [22], but very recent results from higher-level theoretical methods have revealed the D_{2h} symmetrical species to be a local minimum - and not a transition structure - thus implying that the two PTs occur in a stepwise fashion [23].
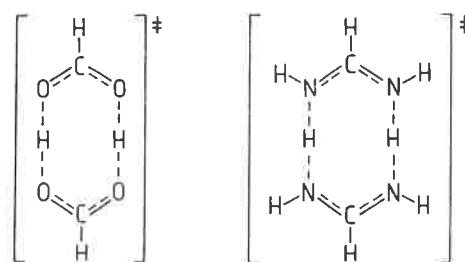

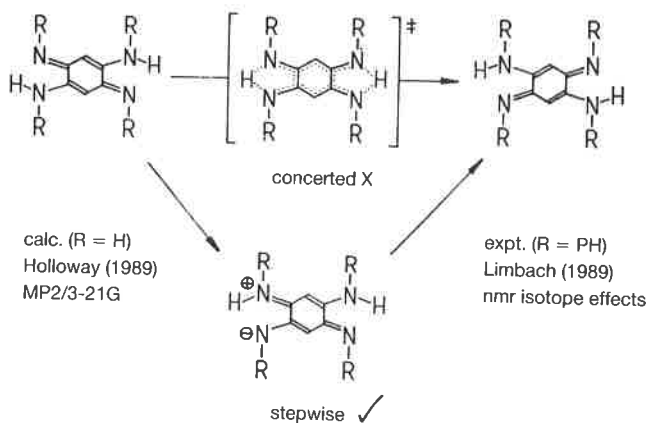formic acid

Schaefer (1987)
SCF/DZP : concerted

formamidine

Ahlberg (1989) STO-3G : concerted
Ahlberg (1990) 6-31G* : stepwise

Ahlberg has suggested the reason for the difference in behaviour between the formic acid and formamidine dimers may be the longer, weaker hydrogen bonds formed in the nitrogenous system [23]. This would accord with the view that it is geometrical features which determine the concerted *vs.* stepwise character of double PT processes [11]. The mixed dimer of formic acid with formamidine has been studied recently [24] at the SCF/3-21G level : a stepwise mechanism for the prototropic rearrangement is predicted, with a very low barrier to formation of the C_{2v} symmetrical carboxylate-formamidinium ion-pair intermediate.

3-5 kJ mol⁻¹

stepwise proton transfers

2-8 kJ. mol⁻¹

Williams (24) SCF/3-21G
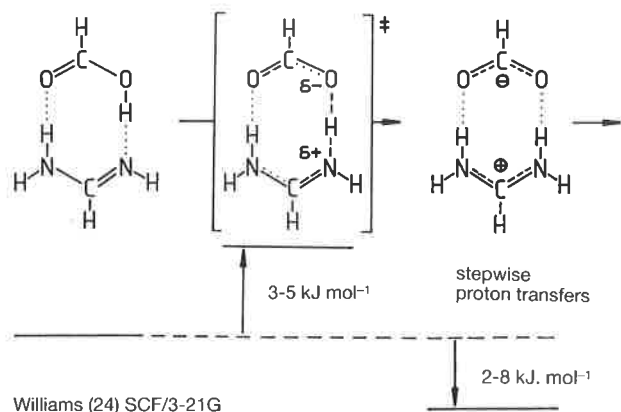
Finally, recent MP2/3-21G calculations [25] agree with the results of NMR studies of isotopic effects upon the degenerate prototropic rearrangement of azophenine [26]. The double PT occurs by a stepwise mechanism involving a zwitterionic intermediate.

concerted X

calc. (R = H)
Holloway (1989)
MP2/3-21G

expt. (R = PH)
Limbach (1989)
nmr isotope effects

stepwise ✓

In summary, the following points may be listed which emerge from theoretical studies of PT and bifunctional catalysis :

- for simple, single PT the barrier height depends upon the hydrogen-bonded distance between the donor and acceptor groups ;

- PT may be induced by geometrical change ;

- specific solvation may modify the energetics of equilibria and of kinetics ;

- protic solvents, such as water, may participate bifunctionally in PT processes ;

- this bifunctional participation leads to catalysis of nucleophilic additions and of tautomerism ;

- PT and heavy-atom reorganisation are coupled in these processes ;

- for double PT the mechanism may be either concerted or stepwise, depending upon the hydrogen-bonded distances.

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