The Mechanism of Exchange of Intramolecularly Hydrogen-bonded Protons in a Diamide

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Two alternative mechanisms for the exchange of intramolecularly hydrogen-bonded protons in a diamide have been theoretically studied by means of the AM1 method. Direct abstraction, and rotation about the C–N bond followed by abstraction, have been considered for both the base-catalysed and the acid-catalysed exchange. From the results obtained in this paper it can be concluded that the base-catalysed exchange takes place by direct abstraction, the internal hydrogen bond clearly retarding the proton exchange. Conversely, the internal hydrogen bond does not appreciably retard acid-catalysed proton exchange.

It has been found that primary amide hydrogen protons buried in the interior of a protein are slow to exchange. Much of the retardation arises because the interior is inaccessible to solvent. Part of that retardation arises because the protons are internally hydrogen bonded. With the aim of evaluating the effect of those internal hydrogen bonds on NH exchange, Perrin *et al.*[1] designed the system shown in Fig. 1. Such a system is a diamide, with the two primary amide groups forced to hydrogen bond with each other. Two NH protons, labelled H_Z, are hydrogen bonded to the opposite carbonyl groups, while the other two protons, labelled H_E, are not internally hydrogen bonded.

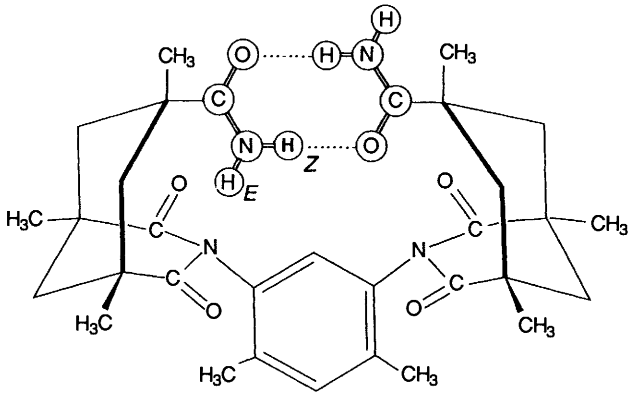

Fig. 1 Diamide experimentally studied in ref. 1

Two alternative mechanisms have been proposed for exchange of internally hydrogen bonded protons (H_Z in system **1**): (*a*) direct abstraction through a transition state with a three-centre bond; (*b*) rotation about the C–N bond, which would transfer H_Z to the *E* site in system **1** from which it can then be readily abstracted. From the study, by NMR saturation transfer methods, of kinetics of the proton exchange, Perrin *et al.*[1] conclude that the internal hydrogen bond in diamide **1** retards base-catalysed exchange of H_Z *ca.* 30-fold. That exchange is viewed as occurring by direct abstraction of the proton from the hydrogen bond. In contrast, the internal hydrogen bond does not retard the acid-catalysed exchange of H_Z at all, as both H_Z and H_E protons undergo acid-catalysed exchange at nearly the same rate. This result that implies a nearly free rotation about the C–N$^+$ bond is somewhat unexpected, given that it is not clear why the hydrogen bond formed by H_Z in the *N*-protonated species is less resistant to breaking than that in the neutral diamide.

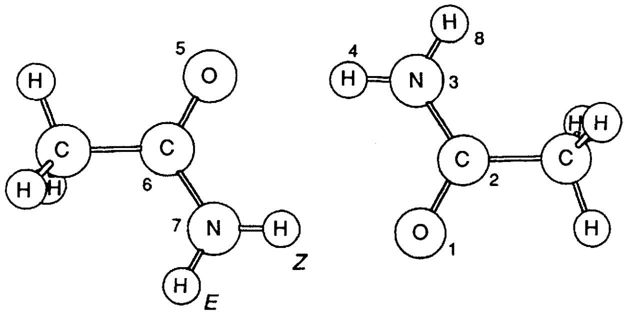

Fig. 2 Neutral diamide adopted in this paper as a model of the one displayed in Fig. 1

The goal of this work is to discuss theoretically the mechanism of exchange of intramolecularly hydrogen-bonded protons in a diamide taken as a model of the system shown in Fig. 1. In particular, we will try to clarify the difference in behaviour between the base- and acid-catalysed proton exchange processes.

Methodology.—Systems up to 37 atoms were considered. Due to the size of the systems chosen the use of *ab initio* methods is quite beyond our computational capabilities. The calculations were then carried out by using the standard AM1 procedure,[2] as implemented in the AMPAC[3] package of computer programs.

As a model of the diamide shown in Fig. 1 we have chosen the structure displayed in Fig. 2. This neutral dimer will be the substrate for the base-catalysed proton exchange, while the corresponding *N*-protonated species will act as the substrate for the acid-catalysed exchange.

The second reason for choosing AM1 as the quantum method for our calculations was that, with a few exceptions, AM1 seems to be an effective method for studying proton transfers in chemistry and biochemistry. However, the failure of the AM1 methodology to allow for orbital expansion on atoms bearing large negative charges is well known.[4] It results in too positive heats of formation when the formal charge in an anion is largely concentrated on a single atom. This is the case for OH^- where the error on the deprotonation enthalpy is 21.5 kcal mol^{-1}. This error reduces to only 4.0 kcal mol^{-1} when we substract the heats of formation of CH_3OH and CH_3O^-. Therefore, the CH_3O^- anion has been used in this paper as a proton-acceptor.

All minima geometries were carried out by minimizing the energy with respect to all geometrical variables by using the DFP method[5] incorporated in AMPAC and without making any assumptions. The location of transition states was done by using the McIver–Kormornicki gradient minimization tech-

Table 1 Energy barriers (in kcal mol^{-1}) for rotation about the C_6–N_7 bond

Species	Energy barrier
Neutral monomer	9.25
N-Protonated monomer	0.69
Neutral diamide	10.40[a] 10.68[b] 10.34[c]
N-Protonated diamide	0.88[d] 0.35[e] 0.89[f]

[a] Structure shown in Fig. 2. [b] Structure shown in Fig. 2 but substituting the methyl groups in positions 2 and 6 by two *tert*-butyl groups. [c] Structure shown in Fig. 2 but substituting the H_8 by a methyl group. [d] *N*-Protonated species corresponding to the neutral species mentioned in footnote *a*. [e] *N*-Protonated species corresponding to the neutral species mentioned in footnote *b*. [f] *N*-Protonated species corresponding to the neutral species mentioned in footnote *c*.

Table 2 Main interatomic distances/Å for several structures mentioned in the text

	M[a]	TS[b]	M^{+}[c]	TS^{+}[d]
O_1C_2	1.25	1.25	1.26	1.26
C_2N_3	1.37	1.37	1.36	1.36
N_3H_4	1.00	0.99	0.99	0.99
O_5H_4	2.07	2.11	2.54	2.53
O_5C_6	1.25	1.24	1.22	1.22
C_6N_7	1.37	1.43	1.52	1.52
O_1H_Z	2.07	2.42	2.12	2.36
O_1H_E	3.63	2.42	3.55	2.68
O_1H_S	—	—	3.25	3.67
N_7H_Z	1.00	1.01	1.03	1.03

[a] Minimum energy structure for the neutral dimer shown in Fig. 2. [b] Transition state for the rotation around the C_6–N_7 bond in the neutral diamide. [c] Minimum energy structure for the *N*-protonated diamide. [d] Transition state for the rotation around the C_6–N_7 bond in the *N*-protonated diamide.

nique.[6] The characterization of both kinds of stationary points, minima and transition states, was carried out by diagonalizing their Hessian (force constant) matrices and looking for zero or one-negative eigenvalues, respectively.

Results and Discussion

Firstly we present the results obtained in the study of the rotation mechanism process that exchanges H_Z and H_E atoms for the structure shown in Fig. 2.

In order to understand in more detail the characteristics of the rotation mechanism in the dimer we analyse first the rotation process around the C–N bond in the monomer. In agreement with the experimental geometry of formamide,[7] each monomeric unit that forms the dimer of Fig. 2 presents a planar $H_ZH_EN_7C_6O_5$ group. That structure is a consequence of the formation of a delocalized π-system arising from a linear combination of p-type atomic orbitals perpendicular to the H_2NCO plane and centred on the N, C, and O atoms. The Mülliken bond order between N and C is 1.117 which corresponds to some double bond character. This double bond character is expected to make the rotation process difficult. Accordingly, the located transition state structure for rotation lies 9.25 kcal mol^{-1} above reactants. In this transition state structure, the three atoms attached to the N_7 atom already adopt a disposition close to the typical triangular pyramid centred at the nitrogen atom, like in the NH_3 molecule. The amount of energy required to reach the top of the barrier corresponds then to the breaking of the π bond.

We will focus next on the neutral dimer shown in Fig. 2. The main geometrical parameters corresponding to the minimum energy structure and the transition state structure for rotation around the C_6–N_7 bond are presented in Table 2. The atoms are numbered in accordance with Fig. 2.

The neutral dimer minimum energy structure is the one shown in Fig. 2. The ring of eight atoms is planar owing to some double bond character existing between C_2–N_3 and C_6–N_7 that has already been discussed for the monomer. The corresponding bond orders are 1.170 for both bonds. The two monomers that form the dimer are bonded by two hydrogen bonds between O_1–H_Z and O_5–H_4.

In comparing the values for the distances in the minimum energy structure and in the transition state structure, we observe that there is no significant change of the ring distances apart from the C_6–N_7 and the O_1–H_Z bonds. Both increase, by 0.06 Å for the first one and 0.4 Å for the second one. The enlargement of the C_6–N_7 bond is in agreement with breaking a π bond, while the O_1–H_Z distance increases because there is a breaking of the hydrogen bond when the H_Z atom comes out from the ring plane while rotating. Both bond breaking processes are expected to make the rotation process in the dimer molecule difficult. The corresponding energy barrier is 10.40 kcal mol^{-1}. This value represents an increment of only 1.15 kcal mol^{-1} in comparison with the rotation barrier in the monomer. The hydrogen bond breaking does not then seem to contribute significantly to the rotation barrier. In fact, the reason why there is not much difference between the energy barrier of rotation in the monomer and in the dimer molecule is that although the O_1–H_Z intramolecular hydrogen bond breaks while rotating, a new O_1–H_E hydrogen bond forms at the same time. In Table 2 we can observe that at the transition state both, O_1–H_Z and O_1–H_E distances, are the same.

We conclude that the energy required to surpass the rotation barrier in the neutral dimer molecule essentially accounts for the necessity of breaking a π bond, in the same way that it occurs in the monomer.

Depending on which is the site of protonation, two mechanisms have been proposed for acid-catalysed proton exchange in amides[1,8,9]: (i) the imidic acid mechanism that proceeds *via* the intermediate $RC(OH){=}NH_2^{+}$ and (ii) the *N*-protonation mechanism which takes place *via* the *N*-protonated intermediate $RCONH_3^{+}$. The first mechanism is favoured for amides with electron-withdrawing substituents, but the *N*-protonation mechanism is more likely for the model structure of Fig. 1 with its electron-donating alkyl groups, and this is the mechanism we adopted for our calculations. We will discuss next the rotation process in the *N*-protonated dimer molecule.

In Table 2 some of the internuclear distances for the *N*-protonated minimum energy structure and the transition state structure for rotation around the C_6–N_7 bond are given. It must be noted that for the *N*-protonated species an additional hydrogen atom attached to N_7 has been included. This atom is labelled as H_S.

Comparing the distance values in Table 2 for the minimum energy structure of the *N*-protonated diamide and for the corresponding neutral system, we can observe that the protonation process has broken the symmetry of the molecule. Both, O_5–H_4 and O_1–H_Z hydrogen bonds are longer in the charged species than in the neutral system but they are no longer equivalent. The O_5–H_4 distance is 0.42 Å longer than the O_1–H_Z hydrogen bond. In addition, the Mülliken bond order between C_6–N_7 of only 0.754 (compared to the above-mentioned value in the neutral molecule) is a clear indication that there is no double bond character between those two atoms in the protonated structure.

The energy barrier for rotation we obtain in the *N*-protonated molecule is only 0.88 kcal mol^{-1}. This low barrier is in agreement with previous theoretical[10] and experimental[11,12] results showing strong evidence of rapid rotation around the C–N^{+} single bond in several amides. Hopkinson *et al.*[10] calculated several years ago a barrier for rotation in formamide of *ca.* 1 kcal mol^{-1}.

If it is obvious that the rotation process in the charged dimer does not proceed *via* the breaking of any π-bond, in contrast to what we had observed in the neutral dimer, it is also clear that H_Z is required to move out of the intramolecular hydrogen bond it was forming with the O_1 atom, as for the neutral dimer rotation. The reason why the *N*-protonated system is nearly a free rotor can be asserted from the distance values in Table 2. At the transition state structure the O_1–H_Z bond is beginning to disappear (the O_1–H_Z distance has increased 0.24 Å from reactants) but, at the same time, there is a new hydrogen bond being formed (between H_E and O_1, in Table 2). The amount of energy required to break the intramolecular hydrogen bond is nearly compensated by the formation of another intramolecular hydrogen bond. It has to be noted that the O_1–H_Z bond is shorter than the O_1–H_E one, in contrast to what happens in the neutral transition state for the rotation.

There have been reported in the literature several substituent effects on the rotational rates of both neutral amides and the corresponding *N*-protonated molecules.[13,14] In particular, it has been observed that the rotational rate is increased in several neutral amides by bulky substituents that can sterically destabilize the planar structure of the molecule.[13] In order to test whether the above-mentioned rotational barriers for the neutral dimer and the *N*-protonated system were dependent on our simplified model of the structure in Fig. 1, we re-calculated those barriers substituting the methyl groups in positions 2 and 6 of Fig. 2 by two *tert*-butyl groups, and obtained in that way a structure more similar to the diamide of Fig. 1. The new rotational barriers are 10.68 kcal mol^{-1} and 0.35 kcal mol^{-1} for the neutral dimer rotation and the *N*-protonated dimer rotation, respectively. Those values show no significant change due to the effect of the bulkier substituents (see Table 1). This fact can be explained on the grounds that the *tert*-butyl groups maintain ring planarity at the minimum energy structure.

Having checked that the rotational barriers obtained are not modified on substituting the methyl groups by *tert*-butyl substituents, we kept the methyl groups at positions 2 and 6 in all our subsequent calculations in order to save computational time.

Next we discuss the base- and acid-catalysed mechanisms of proton exchange. We present first the results obtained in the study of the base-catalysed proton exchange between the neutral model structure shown in Fig. 2 and CH_3O^-, comparing the barrier for abstraction of H_Z and H_E.

However, as CH_3O^- approaches the H_Z proton of our neutral diamide model, we observed that the ring system of the molecule rotated so that the H_8 proton could form a new hydrogen bond with the entering methoxy group. This rotation movement could be real or it could be an artifact of the AM1 model we were using, as AM1 tends to favour hydrogen-bond formation. Whatever the reason, we concluded that our model structure of Fig. 2 was not useful for our purposes because the main objective of this work was to study the effect of only one hydrogen bond (the H_Z–O_1 intramolecular bond) in the H_Z proton exchange process against H_E abstraction.

For that reason we decided hereafter to substitute H_8 in the dimer of Fig. 2 with a methyl group, thus eliminating any chance of hydrogen bond formation between that end of the ring system and the entering methoxy group. We re-calculated the rotation barriers for the new structure (both for the neutral and the protonated species) without observing any significant change that could alter the conclusions discussed above (see Table 1).

In the approach of CH_3O^- to both H_Z and H_E, the supermolecule first forms a stable hydrogen bonded complex. The calculated abstraction barriers measured from the corresponding intermediates are 3.42 kcal mol^{-1} and 6.96 kcal mol^{-1} for H_E and H_Z exchanges, respectively. A 3.5 kcal mol^{-1} energy difference confirms that H_E abstraction is more favourable in our neutral dimer model than H_Z abstraction. This energy difference could justify the retardation of *ca.* 30-fold in the base-catalysed exchange of H_Z *versus* the H_E abstraction. Comparing with the rotational barriers mentioned above it is also clear that exchange of H_Z proceeds by direct abstraction of the proton from the hydrogen bond, instead of by rotation about the C_6–N_7 bond, which transfers H_Z to the *E* site, from which it could be abstracted.

Regarding the acid-catalysed mechanism, the experimental findings that indicate no retardation of the H_Z exchange *versus* the H_E abstraction[1,14] can be interpreted by means of two results from the present work. Firstly, in the acid-catalysed mechanism the protons, H_Z as well as H_E, exchange without any barrier in our model. That is an indication that direct abstraction of H_Z or H_E is very easy, in good agreement with experimental results which suggest that those acid-catalysed exchanges are diffusion controlled processes.[8] Secondly, the interconversion between H_Z and H_E by rotation takes place through a very low barrier.

Conclusions

We can summarize in the following points the main conclusions of our theoretical work regarding the exchange of the internally hydrogen bonded proton H_Z in a structure like the one shown in Fig. 1.

First, the base-catalysed exchange takes place by direct abstraction. This is a consequence of the partial double bond character of the C–N bond that implies a high barrier for rotation that would transfer H_Z to the *E* site. In addition, the direct exchange of the H_Z proton requires an energy barrier 3.5 kcal mol^{-1} higher than the H_E abstraction, probably due to the fact that H_Z is an internally hydrogen bonded proton. This result explains why the base-catalysed exchange of H_Z is clearly retarded *versus* the H_E exchange.[1]

Secondly, the nearly free rotation about the C–N single bond of the *N*-protonated diamide explains why the acid-catalysed abstraction of H_Z is not appreciably retarded by the internal hydrogen bond.

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