Mechanism of a Chemical Classic: Quantum Chemical Investigation of the Autocatalyzed Reaction of the Serendipitous Wöhler Synthesis of Urea

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Abstract: The detailed reaction pathways for the ammonium cyanate transformation into urea (Wöhler's reaction) in the gas phase, in solution, and in the solid state have exhaustively been explored by means of first-principles quantum chemical calculations at the B3LYP level of theory using the 6-31G(d,p) basis set. This serendipitous synthesis of urea is predicted to proceed in two steps; the first step involves the decomposition of the ammonium cyanate to ammonia and isocyanic or cyanic acid, and the second one, which is the main reaction step (and probably the rate-determining step), involves the interaction of NH_3 with either isocyanic or cyanic acid. Several alternative pathways were envisaged for the main reaction step of Wöhler's reaction in a vacuum involving the formation of "four-center" transition states. Modeling Wöhler's reaction in aqueous solution and in the solid state, it was found that the addition of NH_3 to both acids is assisted (autocatalyzed) by the active participation of extra H_2O and/or NH_3 molecules, through a preassociative, cooperative, and hydrogen-transfer relay mechanism involving the formation of "six-center" or even "eight-center" transition states. The most energetically economic path of the rate-determining step of Wöhler's reaction is that of the addition of NH_3 to the C=N double bond of isocyanic acid, directly affording urea. An alternative pathway corresponding to the *anti*-addition of ammonia to the C≡N triple bond of cyanic acid, yielding urea's tautomer $HN=C(OH)NH_2$, seems to be another possibility. In the last case, urea is formed through a prototropic tautomerization of its enolic form. The energies of the reactants, products, and all intermediates along with the barrier heights for each reaction path have been calculated at the B3LYP/6-31G(d,p) level of theory. The geometry optimization and characterization of all of the stationary points found on the potential energy hypersurfaces was performed at the same level of theory.

Introduction

In 1828 the German chemist Friedrich Wöhler published a four-page paper[1] on the synthesis of urea without needing a kidney, or even an animal, just trying to combine cyanic acid with ammonia. He concluded that heat had transformed the resulted ammonium cyanate into urea. Wöhler's 1828 synthesis of urea is a turning point in the history of chemistry. The significance of this work lies not just in the first synthesis of urea but also in its effects on the then popular belief—called "vitalism"—that such a preparation is impossible, because the synthesis of organic materials required the presence of a "vital force". This serendipitous synthesis of urea that had exerted the greatest influence on science in general and chemistry in particular was soon acclaimed as a chemical classic. Although this reaction is of historical importance, the method currently being widely used in industry for the synthesis of urea is based on the reaction of ammonia (NH_3) with carbon dioxide (CO_2) under high pressure and temperature.

Since 1828, when Wöhler performed the transformation of ammonium cyanate to urea accidentally for the first time in water solution, the transformation that could take place both in solution and in the solid state has extensively been studied.[2] However, only recently crystalline ammonium cyanate was isolated by J. D. Dunitz et al.,[3] and information was obtained by modern methods about its transformation to urea in the solid state. According to the authors, crystalline ammonium cyanate open to the atmosphere is transformed in 2 days into urea at room temperature.

Although much information about the rate and equilibrium of the reaction in solution has been accumulated,[2] a century of controversy and confusion concerning the mechanism of the transformation reaction still exists.[4] Two different mechanisms for the transformation of ammonium cyanate to urea have been proposed, namely, the ionic and molecular mechanisms. In the ionic mechanism the reaction

$$NH_4^+ + OCN^- \rightarrow products$$

is the rate-determining step involving probably a hydrogen-

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(2) Shorter, J. *Chem. Soc. Rev.* **1978**, *7*, 1.
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bonded intermediate complex. In the molecular mechanism the reaction

$$NH_3 + HNCO \rightarrow products$$

is the rate-determining step involving the nucleophilic attack of NH_3 on the carbon atom of HNCO. Such nucleophilic attack could result in the opening of either the $C=O$ or the $N=C$ double bond of HNCO. Despite Wöhler's reaction's historical value and its tremendous importance and contribution in the area of chemistry, it is not yet clear which one (if either) of the two proposed mechanisms, the ionic or the molecular, is correct, for both mechanisms are supported equally by the available kinetic evidence.[5] With this in mind, we tried to explore theoretically, by means of first-principles quantum chemical techniques, the reaction mechanism by which ammonium cyanate is spontaneously transformed into urea.

Computational Methods

All the calculations were performed using the Gaussian 98 program package.[6] The equilibrium and transition structures were fully optimized by Becke's three-parameter hybrid functional[7,8] combined with the Lee—Yang—Parr[9] correlation functional abbreviated as the B3LYP level of density functional theory, using the 6-31G(d,p) basis set. In all computations no constraints were imposed on the geometry. Full geometry optimization was performed for each structure using Schlegel's analytical gradient method,[10] and the attainment of the energy minimum was verified by calculating the vibrational frequencies that result in the absence of imaginary eigenvalues. All the stationary points have been identified for minimum (number of imaginary frequencies (NIMAG) = 0) or transition states (NIMAG = 1).

The vibrational modes and the corresponding frequencies are based on a harmonic force field. This was achieved with an SCF convergence on the density matrix of at least 10^{-9} and an rms force of less than 10^{-4} au. All bond lengths and bond angles were optimized to better than 0.001 Å and 0.1°, respectively. The computed electronic energies, the enthalpies of reaction, $\Delta_R H_{298}$, and the activation energies, $\Delta G^{\ddagger}_{298}$, were corrected to constant pressure and 298 K, for zero-point energy (ZPE) differences and for the contributions of the translational, rotational, and vibrational partition functions. To check the reliability of the DFT results, some single-point energy calibration calculations have also been performed at the more sophisticated QCISD(T)/6-31G-(d,p) level of theory using the B3LYP/6-31G(d,p)-optimized geometries. In general terms, the improved relative energies estimated using the QCISD(T)/6-31G(d,p) method are in reasonably good agreement with those estimated at the B3LYP/6-31G(d,p) level. For transition-state geometry determination, quasi-Newton transit-guided (QSTN) computations were performed.[11] Moreover, corrections of the transition states

have been confirmed by intrinsic reaction coordinate (IRC) calculations, while intrinsic reaction paths (IRPs)[12,13] were traced from the various transition structures to make sure that no further intermediates exist.

Results and Discussion

Considering the [C, N$_2$, O, H$_4$] system in the form of either ammonium cyanate or urea, it can be seen that there are four hydrogen and three electronegative atoms (two nitrogens and one oxygen) out of a total of eight atoms, indicating that urea can be formed in many different ways, due to the availability of many hydrogen bonds that can be formed. In effect, the exploration of the potential energy surface (PES) indicates that there are several paths for the transformation process, which comprehensively will be discussed in the following. Exploring the reaction mechanism of Wöhler's reaction in a vacuum (the gas phase) is essential for understanding the mechanism of the reaction in aqueous solution and in the solid state as well.

1. Modeling Wöhler's Reaction in a Vacuum.

1.1. Decomposition of Ammonium Cyanate in a Vacuum. As a first step of the transformation of ammonium cyanate into urea, one would expect its unimolecular decomposition to NH_3 and an isomeric CHNO molecule, probably cyanic, HOCN, **1**, or isocyanic, HNCO, **2**, acid. Actually, this is a reversible proton-transfer reaction between ammonium cation and cyanate anion. This is substantiated by the observation that crystalline ammonium cyanate in a sealed vessel under ammonia is kept essentially unchanged,[3] thus providing evidence for ammonia formation at the first stage of Wöhler's reaction. Calculations performed on an ammonium cyanate "molecule" in a vacuum gave either a $H_3N\cdots H-O-C\equiv N$ or a $H_3N\cdots H-N=C=O$ structure. Therefore, we thought it would be advisable to start the investigation of the mechanism of Wöhler's reaction in the gas phase by considering first the pathways accessible for the interaction of the NH_3 molecule with either cyanic or isocyanic acid. In both acids, due to their bent structure, the orientation of the hydrogen atom with respect to the plane defined by the unsaturated bonds would result in different products, depending on either a *syn* (*cis*) or an *anti* (*trans*) addition of NH_3 to the respective unsaturated bonds. It is noteworthy that the rate expression, rate = $k[NH_4^+][NCO^-]$, for the unimolecular decomposition of ammonium cyanate persists for the reaction of NH_3 with the CHNO isomers as well.

Among the two possible isomeric acids formed upon decomposition of the ammonium cyanate, isocyanic acid was found to be 28.2 (23.5) kcal/mol more stable than cyanic acid at the B3LYP/6-31G(d,p) (QCISD(T)/6-31G(d,p)) level of theory. In general terms, the relative stability of the CHNO isomers is not very sensitive to the level of calculation. Therefore, we decided to choose the computationally less expensive B3LYP/6-31G(d,p) procedure for the investigation of the reaction mechanism of Wöhler's synthesis of urea. However, in some cases the energetic data computed at the more sophisticated QCISD(T)/6-31G(d,p) level of theory will also be given in parentheses. To clarify whether the less stable cyanic acid could be isomerized to the more stable isocyanic acid, we computed the energetic and geometric profile of the prototropic tautomerization $H-O-C\equiv N$ (C_s) $\rightarrow$ $O=C=N-H$ (C_s) depicted schematically in Figure 1.

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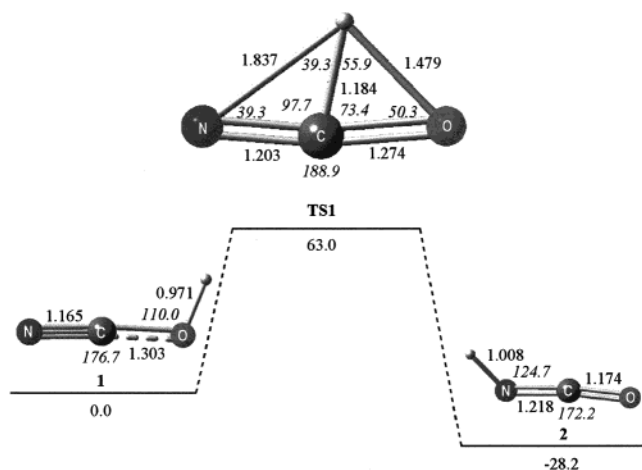
Figure 1. Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the prototropic tautomerization of cyanic to isocyanic acid computed at the B3LYP/6-31G(d,p) level of theory.
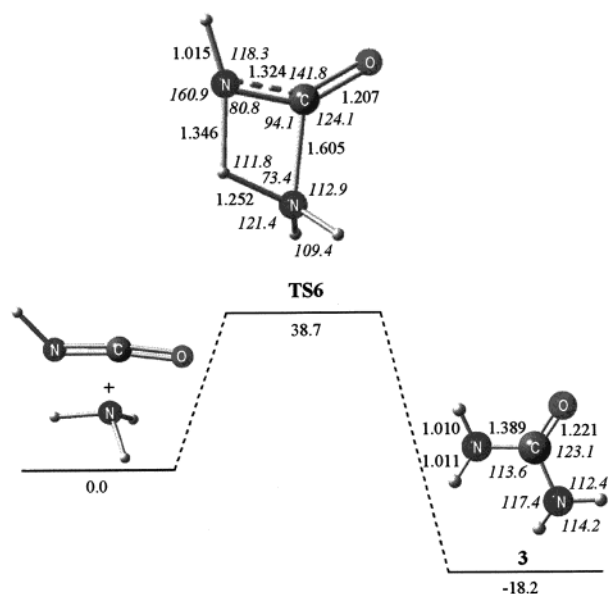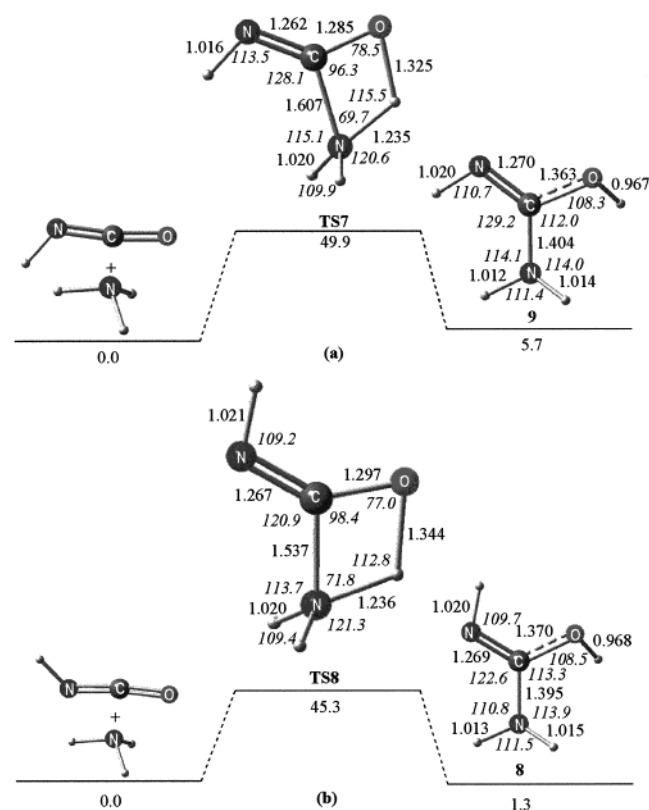

Figure 2. Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the addition of ammonia to the C=N double bond of isocyanic acid computed at the B3LYP/6-31G(d,p) level of theory.

Figure 1 illustrates that H−O−C≡N evolves to yield the more stable H−N=C=O isomer via an appropriate 1,3-H shift, through a planar transition state, **TS1**, but has to surmount a high activation barrier of 63.0 (69.7) kcal/mol. The computed heat of reaction was found to be −28.2 (−23.4) kcal/mol at the B3LYP/6-31G(d,p) level.

1.2. Conformational Analysis of Urea. The most stable conformer of urea exhibits an *anti*-conformation of C_2 symmetry with H atoms of the NH$_2$ groups pyramidalized on opposite sides of the molecule. The urea molecule can also exist[14] in a *syn*-conformation of C_s symmetry with the H atoms of the NH$_2$ groups pyramidalized on the same side. The structural parameters of the most stable C_2 conformer, **3**, are shown in Figure 2. Further details concerning the computed structural parameters of the C_s conformer **4** are furnished in the Supporting Information (Figure S1). The most stable C_2 conformer, **3**, could also

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exist in enantiomeric forms, while the C_s one, **4**—being 0.6 (1.7) kcal/mol less stable—contains an internal plane of symmetry (*meso* compound) and therefore has no enantiomers.

Further searching the conformational space of urea, we have identified another tautomeric (isomeric) form, that of the aminoiminocarbonic acid (the enol form of urea) formulated as HN=C(OH)−NH$_2$, **5**. A detailed study illustrated that there are totally four conformers of **5**, with each conformer existing in enantiomeric forms having the same energy. The equilibrium structures of the conformers of **5** computed at the B3LYP/6-31G(d,p) level of theory are given in the Supporting Information (Figure S1). The enantiomers differ in the orientation of the hydrogen atoms of the amino group with respect to the molecular plane. In one enantiomer the hydrogen atoms of the amino group are aligned in front of the molecular plane (always having the oxygen atom to the right), while in the other they are aligned behind the molecular plane. Conformers **7**−**9** are local minima in the PES 2.1 (2.2), 3.4 (2.7), and 7.8 (7.5) kcal/mol higher in energy than the global minimum corresponding to conformer **6**.

Prior to possible reaction pathways to urea formation upon interaction of ammonia with either cyanic or isocyanic acid being explored, it would be important to understand first the mechanism of the interconversion processes between conformers **6** and **9**, since all four conformers of **5** are expected to be possible intermediates in Wöhler's reaction. The details of the computed B3LYP/6-31G(d,p) geometries of transitions states **TS2**−**TS5** along with their imaginary frequencies ν_i and the activation energies of the interconversion pathways **9** → **6**, **8** → **9**, **8** → **7**, and **7** → **6** are summarized in the Supporting Information (Figure S2). Conformers **7**−**9** can be easily transformed directly or indirectly to the more stable conformer **6**, with relatively very small activation barriers, 1.3 (1.9), 23.3 (28.7), 2.8 (3.6), and 17.1 (21.5) kcal/mol for the interconversion processes **9** → **6**, **8** → **9**, **8** → **7**, and **7** → **6**, respectively. All interconversion pathways, except **8** → **9**, are slightly exothermic processes; the heats of reaction $\Delta_R H_{298}$ are predicted to be 4.4 (4.8), −2.2 (−2.2), −1.2 (−0.6), and −7.8 (−7.5) kcal/mol for the interconversion processes **8** → **9**, **7** → **6**, **8** → **7**, and **9** → **6**, respectively.

1.3. Interaction of NH$_3$ with CHNO Isomers in a Vacuum (the Main Step of Wöhler's Reaction). The relative energies, heats of reaction, and activation barriers of the rate-determining step of Wöhler's synthesis of urea in a vacuum computed at the B3LYP/6-31G(d,p) level of theory are summarized in Table 1.

Two possible pathways for the interaction of ammonia with isocyanic acid may be envisaged depending on the addition of ammonia to either the C=N or the C=O double bond of the acid. The addition of ammonia to the C=N double bond is expected to be the most favorable pathway, since it yields urea directly. The energetic and geometric profile of the addition reaction of ammonia to the C=N double bond of isocyanic acid is depicted schematically in Figure 2. It can be seen that in the addition reaction an −NH$_2$ group is being transferred to the carbon atom of the acid, while concomitantly the C=N double bond is being rectified to a single bond, through a "four-center" transition state, **TS6**. The computed activation barriers and heats of reaction were found to be 38.7 (31.3) and −18.2 (−20.2)

Table 1. Relative Energies, Heats of Reaction, and Activation Barriers (kcal/mol) of the Rate-Determining Step of Wöhler's Synthesis of Urea in a Vacuum Computed at the B3LYP/6-31G(d,p) Level of Theory

	ΔE	$\Delta_R H$	$\Delta G^{\ddagger}$
HN=CO + NH$_3$	0.0		
urea, **3**	**−18.2**	−18.2	
TS6			38.7
HNC=O + NH$_3$ (*syn*)	0.0		
urea (enolic form), **9**	5.7	5.7	
TS7			49.9
HNC=O + NH$_3$ (*anti*)	0.0		
urea (enolic form), **8**	1.3	1.3	
TS8			45.3
HOC≡N + NH$_3$ (*syn*)	0.0		
urea (enolic form), **9**	**−22.5**	−22.5	
TS9			53.3
HOC≡N + NH$_3$ (*anti*)	0.0		
urea (enolic form), **6**	**−30.2**	−30.2	
TS10			47.5

Figure 3. Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the *syn* (a) and *anti* (b) addition of ammonia to the C=O double bond of isocyanic acid computed at the B3LYP/6-31G-(d,p) level of theory.
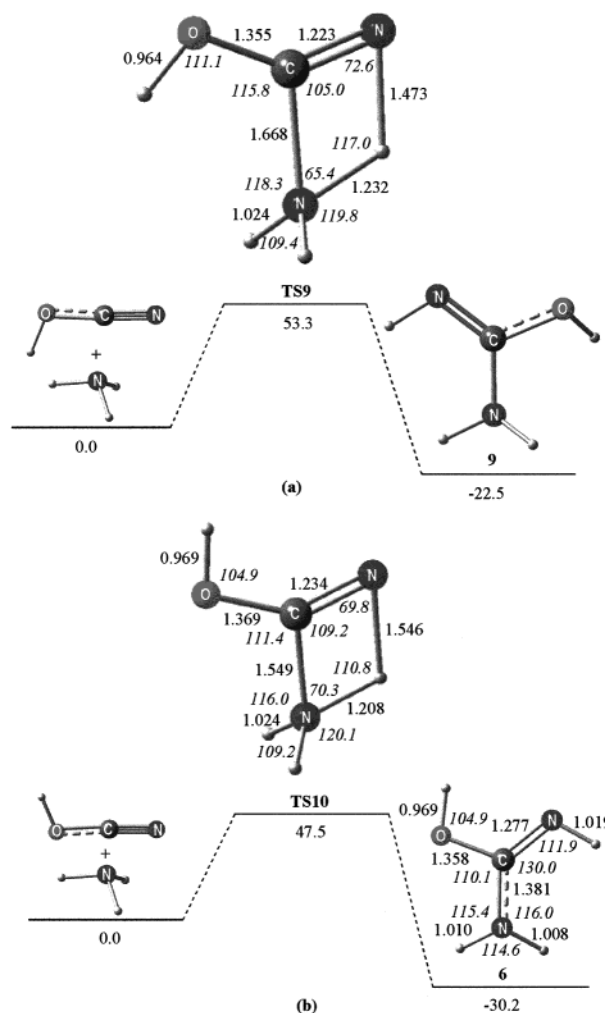

Figure 4. Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the *syn* (a) and *anti* (b) addition of ammonia to the C≡N triple bond of cyanic acid computed at the B3LYP/6-31G(d,p) level of theory.

kcal/mol, respectively. Notice that from a stereochemical point of view only one possible trajectory exists.

With regards to the ammonia addition to the C=O double bond of isocyanic acid, there are two alternative trajectories, namely, the *syn*- and *anti*-additions, with respect to the hydrogen atom of the O=C=N−H acid. The energetic and geometric profile of the addition reactions of ammonia to the C=O double bond of isocyanic acid is depicted schematically in Figure 3. In both trajectories four-center transition states **TS7** and **TS8** connect the entrance channel NH$_3$ + O=C=N−H with either species **9** for a *syn*-addition or species **8** for an *anti*-addition of

ammonia to the C=O double bond of isocyanic acid. The computed activation barriers for the *syn*- and *anti*-addition reactions are predicted to be 49.9 (42.7) and 45.3 (36.5) kcal/mol, respectively, while the heats of reaction are equal to 5.7 (3.3) and 1.3 (1.5) kcal/mol, respectively.

The last alternative pathway issuing from the entrance channel NH$_3$ + N≡C−O−H leads to the addition of ammonia to the C≡N triple bond of cyanic acid. Two different trajectories corresponding to *syn*- and *anti*-addition processes are possible, leading to the formation of conformers **9** and **6**, respectively (Figure 4). Along the reaction pathway the amino group of ammonia is attached to the carbon atom and the C≡N triple bond is concomitantly being rectified to a double one. In both trajectories four-center transition states **TS9** and **TS10** connect the entrance channel NH$_3$ + N≡C−O−H with either species **9** for a *syn*-addition or species **6** for an *anti*-addition of ammonia to the C≡N triple bond of cyanic acid. The computed activation barriers for the *syn*- and *anti*-addition reactions are 53.3 (51.5) and 47.5 (43.0) kcal/mol, respectively, while the heats of reaction are −22.5 (−20.1) and −30.2 (−27.7) kcal/mol, respectively.

It is worth noting that the only conformer of HN=C(OH)-NH$_2$ that can be directly tautomerized to urea is the more stable

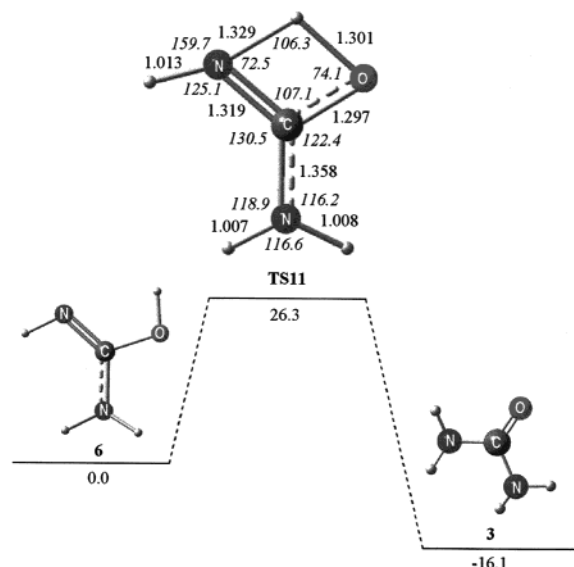**Figure 5.** Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the prototropic tautomerization of aminoiminocarbonic acid to urea computed at the B3LYP/6-31G(d,p) level of theory.

Table 2. Relative Energies, Heats of Reaction, and Activation Barriers (kcal/mol) of the Rate-Determining Step of Wöhler's Synthesis of Urea Modeled in Aqueous Solution Computed at the B3LYP/6-31G(d,p) Level of Theory

	ΔE	$\Delta_R H$	$\Delta G^{\ddagger}$
HN=CO + NH₃ + H₂O, **R3**	0.0		
6 + H₂O, **P3**	**−18.8**	−18.8	
TS14			10.7
HNC=O + NH₃ + H₂O (*syn*), **R4**	0.0		
6 + H₂O, **P4**	12.1	12.1	
TS15			31.6
HNC=O + NH₃ + H₂O (*anti*)	0.0		
urea (enolic form), **P5**	**−10.0**	−10.0	
TS16			25.8
HOC≡N + NH₃ + H₂O (*anti*), **R5**	0.0		
H₂O + urea (enolic form), H₂O + **6**	**−21.4**	−21.4	
TS17			15.4

conformer **6**, because of the favorable hydrogen atom geometrical rearrangement. Along this line we have also explored the HN=C(OH)−NH₂ → H₂NC(O)NH₂ prototropic tautomerization process. The calculations illustrated that isomer **6** evolves to urea through transition state **TS11** involving a 1,3-H shift according to the pathway shown in Figure 5. The computed activation barrier of the tautomerization process is 26.3 (33.3) kcal/mol, and the heat of reaction is −16.1(−16.1) kcal/mol.

2. Modeling Wöhler's Reaction in Aqueous Solution. Notwithstanding the solvation effects of water in aqueous solutions, the water molecules could also be involved in Wöhler's reaction, playing a catalytic role. In effect, we have thoroughly explored the catalytic effect of water in all possible pathways of the main step of Wöhler's reaction. The relative energies, heats of reaction, and activation barriers of the rate-determining step of Wöhler's synthesis of urea modeled in aqueous solution computed at the B3LYP/6-31G(d,p) level of theory are summarized in Table 2.

At first the calculations illustrated that the H−O−C≡N → O=C=N−H prototropic tautomerization is strongly assisted (catalyzed) by water, actively participating as a catalyst in the course of the 1,3-H shift rearrangement. The energy profile of
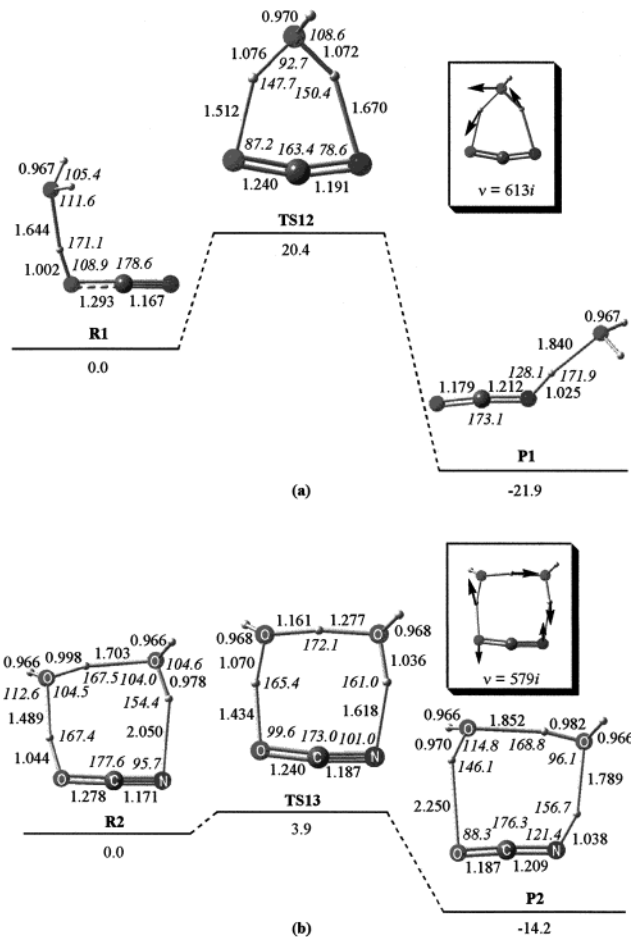

Figure 6. Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the prototropic tautomerization of cyanic to isocyanic acid assisted by one (a) and two (b) water molecules computed at the B3LYP/6-31G(d,p) level of theory.

the prototropic tautomerization catalyzed by one and two water molecules, along with selected optimized parameters for the reactant complexes **R1** and **R2**, the transition structures **TS12** and **TS13**, and the product complexes **P1** and **P2** is displayed in Figure 6. Along the first path, the initial H₂O···H−OCN reactant complex **R1** proceeds across a barrier of 20.4 kcal/mol through transition structure **TS12**, giving the H₂O···H−NCO product complex **P1**. It can be seen that the H₂O molecule assists the 1,3-H shift, dramatically lowering the activation barrier by 42.6 kcal/mol with respect to that of the uncatalyzed reaction (Figure 1). The computed heat of reaction is equal to −21.9 kcal/mol. The transition structure **TS12** involving a planar six-membered ring can be viewed as a loose association of NCO⁻ with hydroxonium, H₃O⁺, ion in such a way that the O atom of H₃O⁺ is lined up with the C atom of NCO⁻ at a separation distance of 2.451 Å. This was substantiated through the comparison of the computed Mulliken and natural charges on the associated and free H₃O⁺ ion. Thus, the net atomic (natural) charges on the O and H atoms of the associated H₃O⁺ ion found to be −0.53 (−0.91) and 0.40 (0.55), respectively, resemble closely those of the free H₃O⁺ ion, −0.38 (−0.84) and 0.46 (0.62), respectively, at the B3LYP/6-31G(d,p) level. In the vibrational mode corresponding to the imaginary frequency ($\nu = 613i$), the dominant motions involve the endocyclic protons along with the O atom of H₂O according to the normal
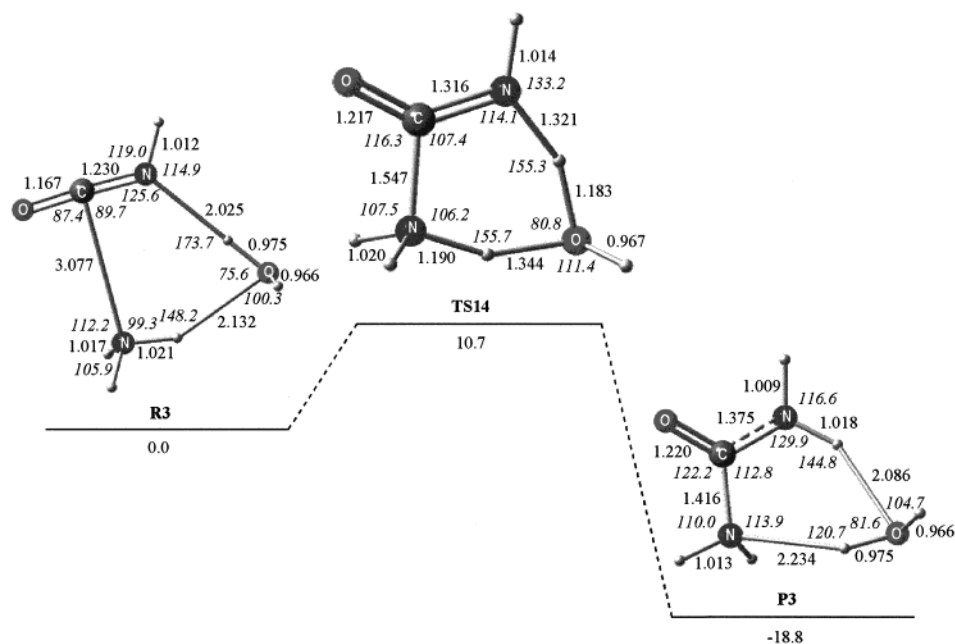
Figure 7. Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the addition of ammonia to the C=N double bond of isocyanic acid catalyzed by a water molecule computed at the B3LYP/6-31G(d,p) level of theory.

coordinate vectors shown in Figure 6. It is noteworthy that the reactant complex **R1** and the product complex **P1** are stabilized by 13.6 and 7.3 kcal/mol, respectively, with regard to the isolated interacting molecules. Along the second path, the initial $(H_2O)_2\cdots H-OCN$ reactant complex **R2** proceeds across a barrier of 3.9 kcal/mol through transition structure **TS13**, giving the $(H_2O)_2\cdots H-NCO$ product complex **P2**. It can be seen that the H_2O molecule further assists the 1,3-H shift, lowering the activation barrier by 16.5 kcal/mol with respect to that of the catalyzed reaction by one water molecule (Figure 6), thus resulting in an almost barrierless tautomerization process. The computed heat of reaction is equal to −14.2 kcal/mol. The transition structure **TS13** involves a nearly planar eight-membered ring, while the dominant motions of the vibrational mode corresponding to the imaginary frequency ($\nu = 579i$) involve the endocyclic protons along with the O and N atoms of the OCN^- moiety according to the normal coordinate vectors shown in Figure 6. It is noteworthy that the reactant complex **R2** and the product complex **P2** are stabilized by 31.3 and 17.4 kcal/mol, respectively, with regard to the isolated interacting molecules.

Let us now examine how the PES governing the addition of NH_3 to the C=N double bond of H−N=C=O acid is modified when a water molecule is involved in the reaction pathway. The energy profile along with selected optimized parameters for the reactant complex **R3**, transition structure **TS14**, and product complex **P3** is displayed in Figure 7. It can be seen that the water molecule catalyzes the addition of NH_3 to the C=N double bond of the H−N=C=O acid, lowering the activation barrier by 28.0 kcal/mol with respect to that of the uncatalyzed gas-phase reaction (Figure 2). Moreover, the computed B3LYP/6-31G(d,p) $\Delta_R H_{298}$ of −18.8 kcal/mol is almost the same as that of the uncatalyzed gas-phase reaction. A salient feature of the transition structure **TS14** is the presence of an essentially planar six-membered ring (the RMS deviation from the plane is 0.02 Å) formed through N−H···O and

N···H−O bond formation between the incoming water molecule and the interacting NH_3 and H−N=C=O molecules. The water molecule is oriented in such a way that one of its lone pairs aligns approximately along the dissociating N−H bond of NH_3. The vibrational mode corresponding to the imaginary frequency ($\nu = 1264i$) exhibits a dominant motion involving the endocyclic protons, which are transferred from NH_3 to water and from water to the HNCO molecule. It is noteworthy that the reactant complex **R3** and the product complex **P3** are stabilized by 7.1 and 10.0 kcal/mol, respectively, with regard to the isolated interacting molecules.

We now turn to explore the catalytic effect of the water molecule on the *syn*- and *anti*-addition of ammonia to the C=O double bond of H−N=C=O acid. The energy profile along with selected optimized parameters for the reactant complex **R4**, transition structures **TS15** and **TS16**, and product complexes **P4** and **P5** are displayed in Figure 8. Notice that all attempts to locate on the PES a reactant complex in the case of the *anti*-addition of ammonia to the C=O double bond of HNCO were in vain; therefore, the isolated interacting molecules are considered the reactants. It can be seen that the water molecule catalyzes both the *syn*- and *anti*-addition of ammonia to the C=O double bond of H−N=C=O acid, lowering the activation barrier by 17.8 and 19.5 kcal/mol, respectively, with respect to those of the corresponding uncatalyzed gas-phase reactions (Figure 3). The computed heats of reaction for the *syn*- and *anti*-addition reactions were found to be 12.1 and −10.0 kcal/mol, respectively. Notice that the reactant complex **R4** is stabilized with regard to the isolated interacting molecules by 16.8 kcal/mol, respectively, while product complexes **P4** and **P5** are stabilized by 4.7 and 10.0 kcal/mol, respectively. The transition structures **TS15** and **TS16** exhibit an essentially planar six-membered ring (the RMS deviation from the plane is 0.05 and 0.07 Å for **TS15** and **TS16**, respectively) formed through N−H···O and O···H−O bond formation between the incoming water molecule and the interacting NH_3 and H−N=C=O
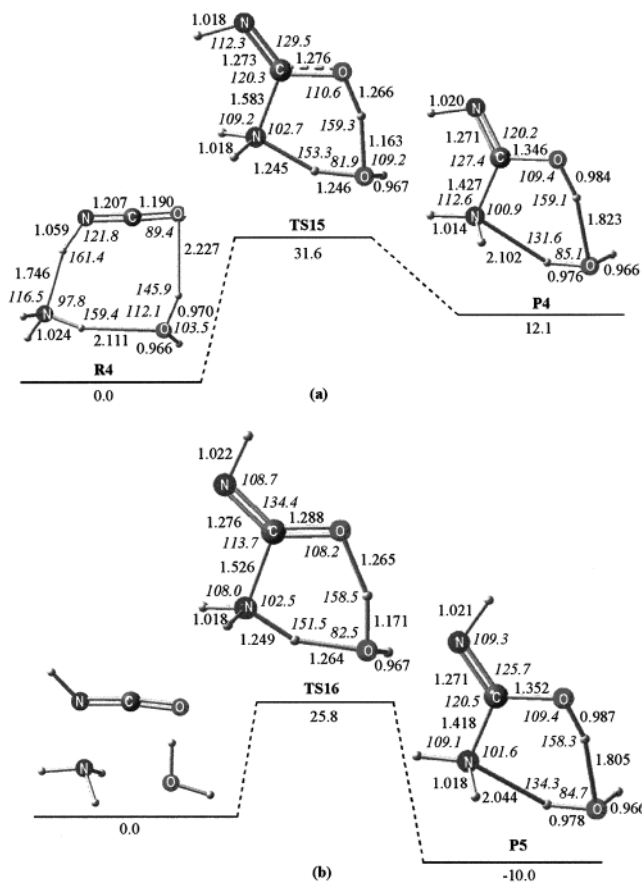
Figure 8. Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the *syn* (a) and *anti* (b) addition of ammonia to the C=O double bond of isocyanic acid catalyzed by a water molecule computed at the B3LYP/6-31G(d,p) level of theory.

molecules. The water molecule is oriented in a way analogous to that found in the transition structure **TS14**. In the vibrational modes corresponding to the imaginary frequencies (ν = 1356i and 1365i for **TS15** and **TS16**, respectively), the dominant motions involve the endocyclic protons, which are transferred from NH$_3$ to water and from water to the HNCO molecule.

Exploring the catalytic effect of the water molecule in the alternative pathway corresponding to the addition of ammonia to the C≡N triple bond of cyanic acid, we were able to locate on the PES all stationary points (reactant complex **R5** and transition structure **TS17**) shown in Figure 9 only following the trajectory for an *anti*-addition of NH$_3$ to HOCN acid. Unfortunately, it was not possible to locate a product complex on the PES; therefore, the isolated interacting molecules are considered the products of the reaction. Moreover, all attempts to locate on the PES the stationary points corresponding to reactant and product complexes following the trajectory for a *syn*-addition of NH$_3$ to HOCN acid were in vain. The computed activation barrier 15.4 kcal/mol for the *anti*-addition is lower by 32.1 kcal/mol with respect to that of the corresponding uncatalyzed gas-phase reaction. The heat of reaction was predicted to be −21.4 kcal/mol at the B3LYP/6-31G(d,p) level of theory. The transition structure **TS17** exhibits an essentially planar six-membered ring (the RMS deviation from the plane is 0.02 Å) formed through N−H···O and N···H−O bond formation between the incoming water molecule and the
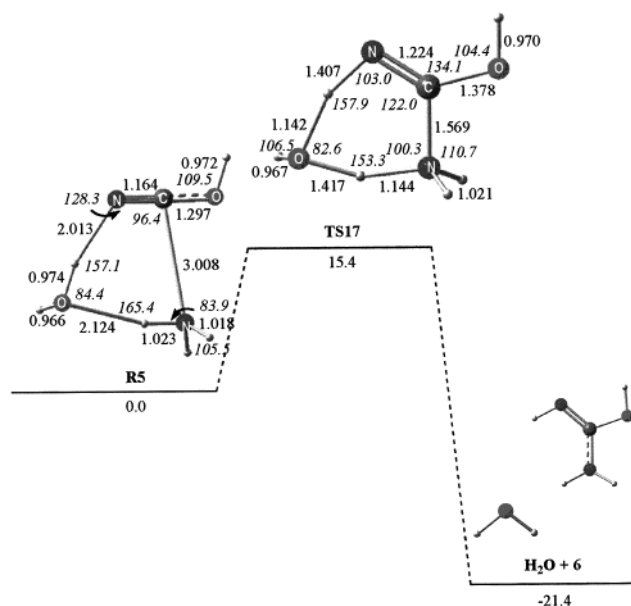

Figure 9. Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the *anti*-addition of ammonia to the C≡N triple bond of cyanic acid catalyzed by a water molecule computed at the B3LYP/6-31G(d,p) level of theory.

interacting NH$_3$ and H−O−C≡N molecules. The water molecule is oriented in such a way that one of its lone pairs aligns approximately along the dissociating N−H bond of NH$_3$. In the vibrational mode corresponding to the imaginary frequency (ν = 955i), the dominant motion involves the endocyclic protons, which are transferred from NH$_3$ to water and from water to the HNCO molecule. The reactant complex **R5** is stabilized by 8.9 kcal/mol with regard to the isolated interacting molecules.

Finally, to obtain more insight into the catalytic effect of water in Wöhler's reaction in aqueous solution, we considered the idea of a second water molecule acting as a catalyst only for the most favorable pathway, that of the addition of NH$_3$ to the C=N double bond of H−N=C=O, yielding urea directly. The energy profile along with selected optimized parameters for the reactant complex **R6**, transition structure **TS18**, and product complex **P6** is displayed in Figure 10. Along this path, an initial association of two water molecules with the H$_3$N···H−NCO complex results in a cyclic complex, **R6**, stabilized by 16.7 kcal/mol relative to the separated reactants. This complex then proceeds across a barrier of only 2.0 kcal/mol through transition structure **TS18**, giving a product complex, **P6**, associating the urea molecule with the two water molecules. The product complex **P6** is stabilized by 20.2 kcal/mol relative to the separated reactants (urea and water molecules). It can be seen that the second water molecule acting as a bifunctional acid−base catalyst facilitates the proton transfers, further lowering the activation barrier by 8.7 kcal/mol with respect to that of the catalyzed reaction by one water molecule (Figure 7). The magnitude of such a reduction in the activation barrier indicates a significant catalytic effect actually induced from the addition of a second water molecule. Obviously, the second water molecule leads to an almost barrierless Wöhler reaction in aqueous solution. The computed B3LYP/6-31G(d,p) $\Delta_R H_{298}$ was found equal to −21.7 kcal/mol. The transition structure **TS18** involves a nonplanar cyclic system of eight atoms (the RMS deviation from the plane is 0.24 Å) formed through N−H···O
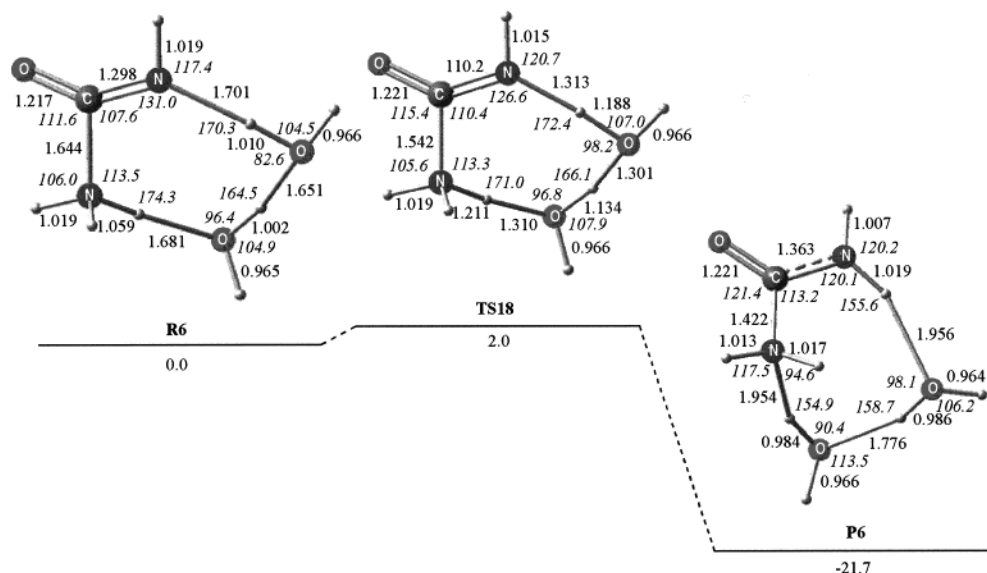
Figure 10. Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the addition of ammonia to the C=N double bond of isocyanic acid catalyzed by two water molecules computed at the B3LYP/6-31G(d,p) level of theory.

and N···H−O bond formation between the incoming water dimer and the interacting NH₃ and H−N=C=O molecules. The hydrogen bonding in the cyclic structure is better accommodated with proton donor−acceptor arrangements. The B3LYP/6-31G-(d,p)-optimized ∠N−H···O, ∠O−H···O, and ∠N···H−O hydrogen bond angles are 171.0°, 166.1°, and 172.4°, respectively, with their near linearity subjecting the eight-membered ring to a reduced strain. The ∠O−H···O−H torsion angle in the water dimer is −21.6°, while the ∠N···H−O−H and ∠N−H···O−H torsion angles related to the making and breaking of N−H bonds are −7.9° and 5.7°, respectively. Moreover, the exocyclic H atoms in the water dimer are staggered with respect to each other. The vibrational mode corresponding to the imaginary frequency ($\nu = 1259i$) exhibits the dominant motions involving the endocyclic protons participating in the H-bonds formed, which are being transferred in a cyclic way from the N atom of NH₃ to the N atom of the HNCO molecule. Obviously, the proton transfer from the N atom of NH₃ to the N atom of the HNCO molecule is assisted by, or in concert with, the proton transfer within the water dimer. Such a proton relay constitutes the basis of a bifunctional acid−base catalytic action identified previously for reactions subject to catalysis by the solvent.[15−21]

Unfortunately, due to our present computational resources and the extremely high CPU demands, further investigation of the macroscopic influence of the solvent on the activation barrier's reduction in aqueous solution was not possible. However, although the electrostatic effects of the bulk environment are expected to play an important role in stabilizing the highly polarized water-chain transition structure, experimental and computational studies of water catalysis in analogous addition reactions, such as the hydration of CO₂, showed that

the reaction proceeds via a cooperative and concerted mechanism involving at least two catalytically active water molecules in aqueous solution.

A complete treatment of the mechanism of Wöhler's reaction in aqueous solution needs to consider the catalytic effect of the solvent molecules on the prototropic tautomerization HN=C(OH)−NH₂ → H₂NC(O)NH₂ as well. Along this line we thoroughly explored how the energy profile of the 1,3-H shift of conformer **6** is modified by the active participation of one and two water molecules. The energy profile along with selected optimized parameters for the reactant complexes **R7** and **R8**, transition structures **TS19** and **TS20**, and product complexes **P7** and **P8** for the tautomerization process assisted by one and two water molecules, respectively, is displayed in Figure 11. Along this path, an initial association of one and two water molecules with conformer **6** results in cyclic reactant complexes **R7** and **R8**, stabilized by 15.5 and 29.6 kcal/mol relative to the separated reactants, respectively. These complexes then proceed across a barrier of only 4.1 and 2.9 kcal/mol, through transition structures **TS19** and **TS20**, giving the product complexes **P7** and **P8**, actually being the urea molecule associated with one and two water molecules, respectively. Notice that the products **P7** and **P8** are stabilized by 11.5 and 24.6 kcal/mol with respect to the interacting species, respectively. It can be seen that the first water molecule lowers the activation barrier by 22.2 kcal/mol with respect to that of the uncatalyzed reaction (Figure 5), while the second water molecule further reduces the activation barrier, but only by 1.2 kcal/mol. Obviously, the active participation of only one water molecule is the most important factor, drastically assisting the 1,3-H shift in the prototropic tautomerization HN=C(OH)−NH₂ → H₂NC(O)NH₂. The computed B3LYP/6-31G(d,p) $\Delta_R H_{298}$ was found to be −12.1 and −11.1 kcal/mol for the exothermic tautomerization processes catalyzed by one and two water molecules, respectively.

The transition structure **TS19** (Figure 11a) involves a planar six-membered ring (the RMS deviation from the plane is 0.006 Å) formed through N···H−O and O−H···O bond formation between the incoming water molecule and the HN and OH

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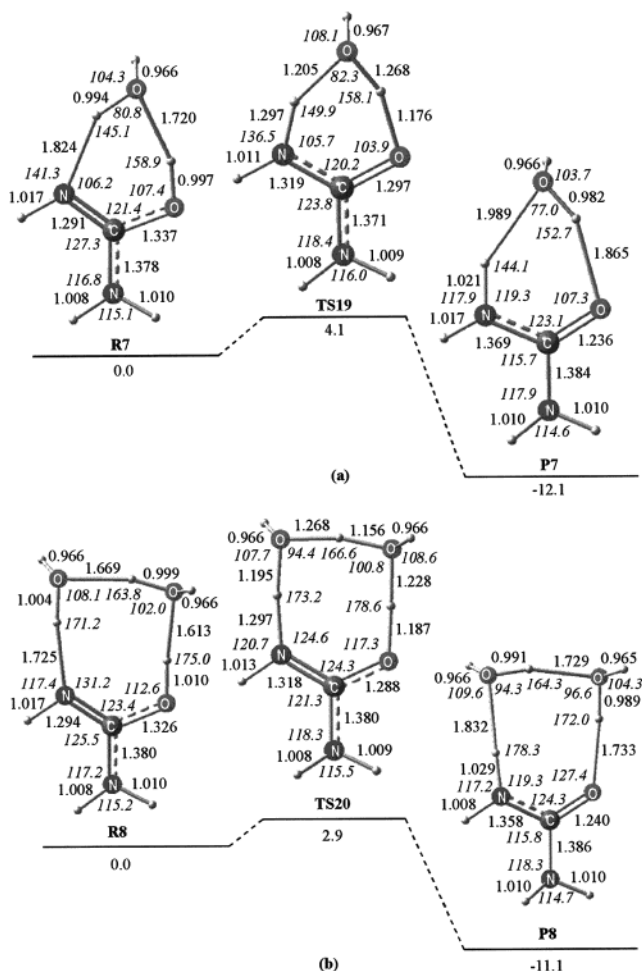
Figure 11. Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the prototropic tautomerization of aminoiminocarbonic acid to urea assisted by one (a) and two (b) water molecules computed at the B3LYP/6-31G(d,p) level of theory.

moieties of the HN=C(OH)—NH$_2$ tautomer. The optimized ∠N···H—O and ∠O—H···O hydrogen bond angles are 149.9° and 158.1°, respectively. The water molecule is oriented in such a way that one of its lone pairs aligns approximately along the dissociating O—H bond of the HN=C(OH)—NH$_2$ tautomer. In the vibrational mode corresponding to the imaginary frequency ($\nu = 1483i$), the dominant motion involves the endocyclic protons, which are transferred from —OH to water and from water to the =NH group of the HN=C(OH)—NH$_2$ tautomer. The transition structure **TS20** (Figure 11b) also involves an essentially planar eight-membered ring (the RMS deviation from the plane is 0.015 Å) formed through N···H—O and O—H···O bond formation between the incoming water dimer and the HN and OH moieties of the HN=C(OH)—NH$_2$ tautomer. The optimized ∠N···H—O, ∠O—H···O, and ∠O···H—O hydrogen bond angles are 173.2°, 166.6°, and 178.6°, respectively. The ∠O—H···O—H torsion angle in the water dimer is −112.9°, while the ∠N···H—O—H and ∠H—O···H—O torsion angles related to the forming of the N—H bonds and breaking of the H—O bonds are 0.8° and 0.6°, respectively. Moreover, the exocyclic H atoms in the water dimer are staggered with respect to each other. In the vibrational mode corresponding to the imaginary frequency ($\nu = 1372i$), the dominant motions involve the endocyclic protons participating in the H-bonds formed,

which are being transferred in a cyclic way from the O atom to the N atom of the HN=C(OH)—NH$_2$ tautomer. Obviously, the 1,3-H shift in the HN=C(OH)—NH$_2$ tautomer is assisted by, or in concert with, the proton transfer within the water dimer in the same way as found for related reactions subject to catalysis by the solvent.[15−27]

3. Modeling Wöhler's Reaction in the Solid State. Extending our interest in the investigation of the mechanism of Wöhler's reaction in the solid state, we pursued the idea of the autocatalysis of the reaction by the intermediates formed upon decomposition of ammonium cyanate (e.g., NH$_3$, HNCO, or HOCN). Along this line we addressed the issue of autocalysis of the possible pathways of Wöhler's reaction by ammonia, acting as catalyst. Considering that the concentration of the catalytically active NH$_3$ molecules in the total mass of the solid is quite low, compared to the concentration of the catalytically active H$_2$O molecules in aqueous solution, one would expect Wöhler's reaction to be accomplished slower in the solid state. In fact, the experiment showed that transformation of ammonium cyanate to urea in the solid state is much slower; the decomposition process is completed in 2 days,[3] while in aqueous solution it proceeds rapidly.[2]

Crystalline ammonium cyanate is spontaneously decomposed to NH$_3$ and cyanic or isocyanic acid.[3] According to the so far known experimental evidence, it is not clear which of the two acids, if either, is formed. Inspection of the recently[3] determined crystal structure of ammonium cyanate suggests that cyanic acid (HOCN) should be the most possible product formed upon decomposition of ammonium cyanate. This is based on the fact that in crystalline NH$_4$NCO hydrogen bonds are formed only between the oxygen atoms of the anions NCO$^-$ and the hydrogen atoms of the cations NH$_4^+$, while there are no analogous interactions between hydrogen and nitrogen atoms of the anions.[3] However, further experimental evidence revealed that crystalline ammonium cyanate is transformed to crystalline urea through an amorphous intermediate.[3] Along this line one could not exclude the possibility for the more stable isocyanic acid to be directly formed upon decomposition of ammonium cyanate, for all possible hydrogen bonds can be formed in the amorphous solid. In light of the above considerations one has to explore two alternative pathways for the catalyzed transformation of ammonium cyanate to urea in the solid state, namely, (i) the addition of ammonia to the C=N double bond of isocyanic acid, leading directly to urea, and (ii) the addition of ammonia to the C≡N triple bond of cyanic acid, yielding the most stable conformer, **6**, of the imino enol tautomer HN=C(OH)—NH$_2$, **5**, of urea, which can subsequently be tautomerized to urea. Notice that isocyanic acid could result either directly from the decomposition of ammonium cyanate or from the prototropic isomerization of the less stable cyanic acid. The calculations illustrated that the prototropic tautomerization H—O—C≡N → O=C=N—H is strongly assisted (catalyzed) by ammonia, actively participating as a catalyst in the course of

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Table 3. Relative Energies, Heats of Reaction, and Activation Barriers (kcal/mol) of the Prototropic Tautomerization of Cyanic to Isocyanic Acid Computed at the B3LYP/6-31G(d,p) Level of Theory

	ΔE	$\Delta_R H$	$\Delta G^{\ddagger}$
HOCN, **1**	0.0		
HNCO, **2**	**−28.2**	−28.2	
TS1			63.0
HOCN + H$_2$O, **R1**	0.0		
HNCO + H$_2$O, **P1**	**−21.9**	−21.9	
TS12			20.4
HOCN + 2H$_2$O, **R2**	0.0		
HNCO + 2H$_2$O, **P2**	**−14.2**	−14.2	
TS13			3.9
HOCN + NH$_3$, **R9**	0.0		
HNCO + NH$_3$, **P9**	**−19.1**	−19.1	
TS21			12.3
HOCN + 2NH$_3$, **R10**	0.0		
HNCO + 2NH$_3$, **P10**	**−11.7**	−11.7	
TS22			0.7

the 1,3-H shift rearrangement. The relative energies, heats of reaction, and activation barriers of the prototropic tautomerization of cyanic to isocyanic acid in a vacuum, in aqueous solution, and in the solid state computed at the B3LYP/6-31G(d,p) level of theory are summarized in Table 3. The energy profile of the prototropic tautomerization catalyzed by one and two NH$_3$ molecules, along with selected optimized parameters for the reactant complexes **R9** and **R10**, transition structures **TS21** and **TS22**, and product complexes **P9** and **P10** is displayed in Figure 12. Along these paths, the initial reactant complexes **R9** and **R10** proceed across barriers of 12.3 and 0.7 kcal/mol through transition structures **TS21** and **TS22**, giving the product complexes **P9** and **P10**, respectively. It can be seen that the first NH$_3$ molecule assists the 1,3-H shift, dramatically lowering the activation barrier by 50.7 kcal/mol with respect to that of the uncatalyzed reaction (Table 3). The second NH$_3$ molecule further lowers the activation barrier by 11.6 kcal/mol, resulting in an almost barrierless prototropic tautomerization (Figure 12b). The transition structure **TS21** involving a planar six-membered ring can be viewed as a loose association of NCO$^-$ with NH$_4^+$ in such a way that the N atom of NH$_4^+$ is lined up with the C atom of NCO$^-$ at a separation distance of 2.593 Å. In the vibrational mode corresponding to the imaginary frequency (ν = 201i), the dominant motions involve all atoms except the C atom according to the normal coordinate vectors shown in Figure 12 as well. The transition structure **TS22** involving a planar eight-membered ring can be viewed as a loose association of the NCO$^-$ anion with the (NH$_3$)$_2$ dimer, forming a symmetric transition state. In the vibrational mode corresponding to the imaginary frequency (ν = 700i), the dominant motion involves all endocyclic protons, which are transferred from the O atom to the N atom of the CHNO isomer according to the normal coordinate vectors shown in Figure 12 as well. It is noteworthy that the reactant complexes **R9** and **R10** and the product complexes **P9** and **P10** are stabilized by 18.7, 33.1, 9.6, and 44.4 kcal/mol, respectively, with regard to the isolated interacting molecules.

Let us now explore first how the PES governing the addition of NH$_3$ to the C=N double bond of H−N=C=O acid is modified when an ammonia molecule is involved in the reaction pathway. The energy profile along with selected optimized parameters for the reactant complex **R11**, transition structure **TS23**, and product complex **P11** is displayed in Figure 13a. It
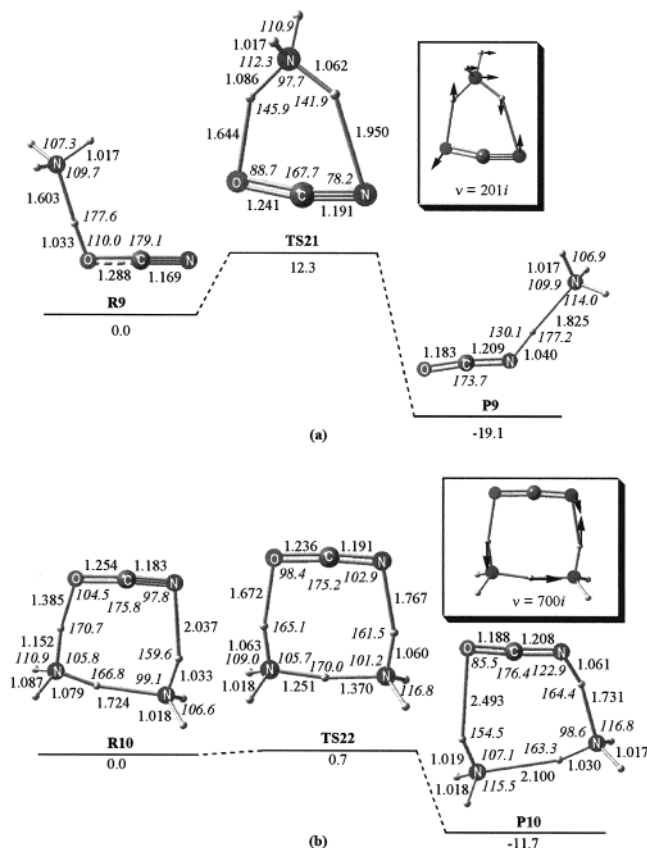

Figure 12. Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the prototropic tautomerization of cyanic to isocyanic acid assisted by one (a) and two (b) ammonia molecules computed at the B3LYP/6-31G(d,p) level of theory.

can be seen that the NH$_3$ molecule catalyzes the addition of NH$_3$ to the C=N double bond of the H−N=C=O acid, lowering the activation barrier by 24.2 kcal/mol with respect to that of the uncatalyzed gas-phase reaction (Figure 2). Moreover, the computed B3LYP/6-31G(d,p) $\Delta_R H_{298}$ of −20.5 kcal/mol is almost the same as that of the uncatalyzed gas-phase reaction. The transition structure **TS23** is similar to **TS14** involved in the respective reaction pathway catalyzed by a water molecule. The salient feature of **TS23** is the presence of an essentially planar six-membered ring (the RMS deviation from the plane is 0.04 Å) formed through N−H···N and N···H−N bond formation between the incoming NH$_3$ molecule and the interacting NH$_3$ and H−N=C=O molecules. In the vibrational mode corresponding to the imaginary frequency (ν = 1013i), the dominant motion involves the endocyclic protons, which are transferred from NH$_3$ to NH$_3$ and from NH$_3$ to the HNCO molecule. The reactant complex **R11** and the product complex **P11** are stabilized by 32.5 and 24.8 kcal/mol, respectively, with regard to the isolated interacting molecules.

Next, we explored the second possible pathway related to the addition of NH$_3$ to the C≡N triple bond of H−O−C≡N acid. The energy profile along with the selected optimized parameters for the reactant complex **R12**, the transition structure **TS24**, and the product complex **P12** is displayed in Figure 13b. It can be seen that the NH$_3$ molecule catalyzes the addition of NH$_3$ to the C≡N double bond of the cyanic acid, lowering the activation barrier by 28.5 kcal/mol with respect to that of the uncatalyzed gas-phase reaction (Figure 4b). Moreover, the
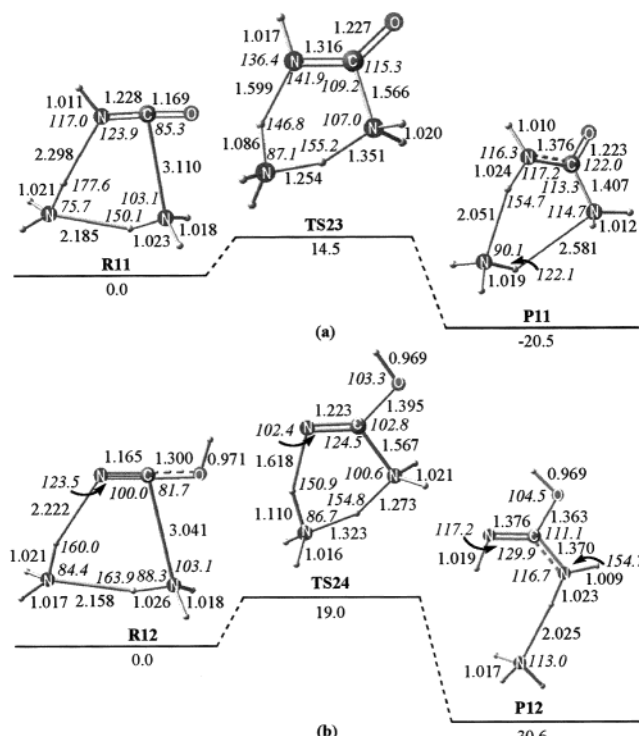
Figure 13. Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the addition of ammonia to the C=N double bond of isocyanic acid (a) and to the C≡N triple bond of cyanic acid (b) catalyzed by an ammonia molecule computed at the B3LYP/6-31G(d,p) level of theory.

computed B3LYP/6-31G(d,p) $\Delta_R H_{298}$ of −30.6 kcal/mol is almost the same as that of the uncatalyzed gas-phase reaction. The transition structure **TS24** is similar to **TS17** involved in the respective reaction pathway catalyzed by a water molecule. **TS24** adopts a perfect planar six-membered ring formed through N−H···N and N···H−N bond formation between the incoming NH₃ molecule and the interacting NH₃ and HOCN molecules. In the vibrational mode corresponding to the imaginary frequency ($\nu = 1103i$), the dominant motion involves the endocyclic protons, which are transferred from NH₃ to NH₃ and from NH₃ to HOCN. The reactant complex **R12** and the product complex **P12** are stabilized by 6.2 and 6.6 kcal/mol, respectively, with regard to the isolated interacting molecules.

Comparing the two possible pathways for the transformation of ammonium cyanate to urea in the solid state catalyzed by ammonia, it can be concluded that both pathways are competitive, with the first one being slightly favored, for its barrier height is 4.5 kcal/mol lower than the barrier height of the second alternative pathway, within the B3LYP/6-31G(d,p) approach.

Finally, we thoroughly explored how the energy profile of the 1,3-H shift of conformer **6** is modified by the active participation of one and two ammonia molecules. The relative energies, heats of reaction, and activation barriers of the prototropic tautomerization of the enolic form of urea to urea in a vacuum, in aqueous solution, and in the solid state computed at the B3LYP/6-31G(d,p) level of theory are summarized in Table 4. The energy profile along with selected optimized parameters for the reactant complexes **R13** and **R14**, the transition structures **TS25** and **TS26**, and the product complexes **P13** and **P14** for the tautomerization process assisted by one and two NH₃ molecules, respectively, is displayed in Figure

Table 4. Relative Energies, Heats of Reaction, and Activation Barriers (kcal/mol) of the Prototropic Tautomerization of the Enolic Form of Urea to Urea Computed at the B3LYP/6-31G(d,p) Level of Theory

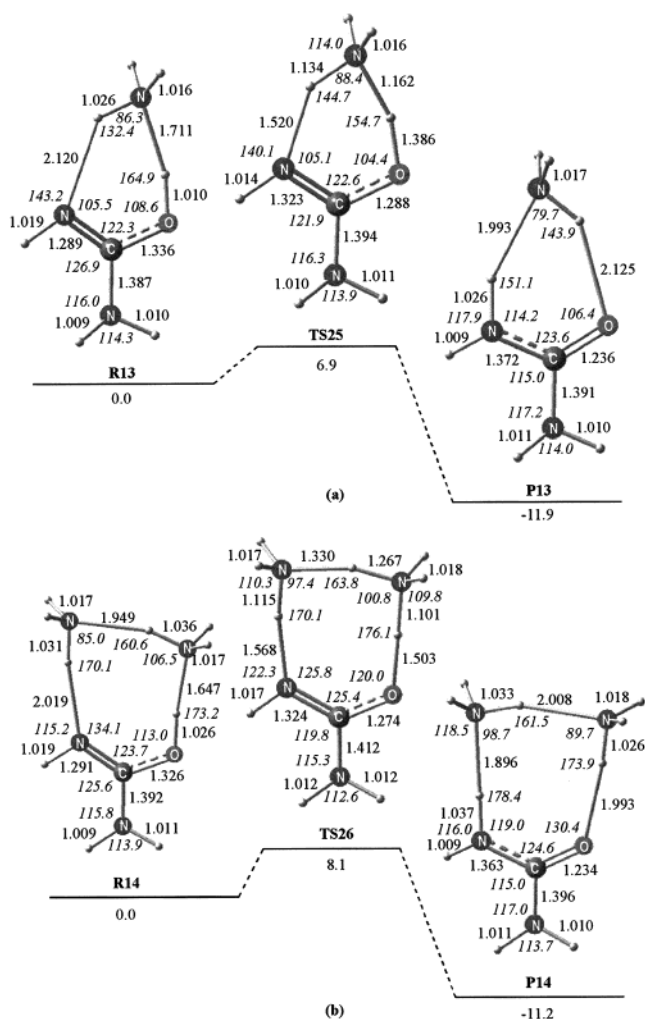|	ΔE	$\Delta_R H$	$\Delta G^{\ddagger}$
HN=C(OH)NH₂, **6**	0.0		
H₂NC(O)NH₂, **3**	**−16.1**	−16.1	
TS11			26.3
HN=C(OH)NH₂ + H₂O, **R7**	0.0		
H₂NC(O)NH₂ + H₂O, **P7**	**−12.1**	−12.1	
TS19			4.1
HN=C(OH)NH₂ + 2H₂O, **R8**	0.0		
H₂NC(O)NH₂ + 2H₂O, **P8**	**−11.1**	−11.1	
TS20			2.9
HN=C(OH)NH₂ + NH₃, **R13**	0.0		
H₂NC(O)NH₂ + NH₃, **P13**	**−11.9**	−11.9	
TS25			6.9
HN=C(OH)NH₂ + 2NH₃, **R14**	0.0		
H₂NC(O)NH₂ + 2NH₃, **P14**	**−11.2**	−11.2	
TS26			8.1

Figure 14. Reaction enthalpies $\Delta_R H_{298}$ (kcal/mol), barrier heights $\Delta G^{\ddagger}_{298}$ (kcal/mol), and geometric (bond lengths in angstroms, bond angles in degrees) reaction profile of the prototropic tautomerization of aminoiminocarbonic acid to urea assisted by one (a) and two (b) ammonia molecules computed at the B3LYP/6-31G(d,p) level of theory.

14. Along this path, an initial association of one and two NH₃ molecules with conformer **6** results in cyclic reactant complexes **R13** and **R14**, stabilized by 13.3 and 22.1 kcal/mol relative to the separated reactants, respectively. These complexes then proceed across a barrier of only 6.9 and 8.1 kcal/mol, through

transition structures **TS25** and **TS26**, giving the product complexes **P13** and **P14** (actually the urea molecule associated with one and two ammonia molecules, respectively), stabilized by 9.0 and 17.2 kcal/mol with respect to the interacting molecules, respectively. It can be seen that the first and second NH_3 molecules lower the activation barrier by 19.4 and 18.2 kcal/mol, respectively, compared to that of the uncatalyzed gas-phase reaction (Table 4). Obviously, the second NH_3 molecule does not further assist the proton migration; therefore, the active participation of only one water molecule is the most important factor in catalyzing the 1,3-H shift tautomerization process. The computed B3LYP/6-31G(d,p) $\Delta_R H_{298}$ values were found to be -11.9 and -11.2 kcal/mol for the exothermic tautomerization processes catalyzed by one and two NH_3 molecules, respectively. These values compare well with the corresponding values of the catalyzed 1,3-H shift tautomerization process by one and two water molecules.

The transition structure **TS25** (Figure 14a) involves a planar six-membered ring (the RMS deviation from the plane is 0.006 Å) formed through $N\cdots H-O$ and $O-H\cdots O$ bond formation between the incoming water molecule and the HN and OH moieties of the $HN=C(OH)-NH_2$ tautomer. The optimized $\angle N\cdots H-O$ and $\angle O-H\cdots O$ hydrogen bond angles are 149.9° and 158.1°, respectively. The water molecule is oriented in such a way that one of its lone pairs aligns approximately along the dissociating $O-H$ bond of the $HN=C(OH)-NH_2$ tautomer. In the vibrational mode corresponding to the imaginary frequency ($\nu = 1483i$), the dominant motion involves the endocyclic protons, which are transferred from $-OH$ to water and from water to the $=NH$ group of the $HN=C(OH)-NH_2$ tautomer. The transition structure **TS26** (Figure 14b) also involves an essentially planar eight-membered ring (the RMS deviation from the plane is 0.015 Å) formed through $N\cdots H-O$ and $O-H\cdots O$ bond formation between the incoming water dimer and the HN and OH moieties of the $HN=C(OH)-NH_2$ tautomer. The optimized $\angle N\cdots H-O$, $\angle O-H\cdots O$, and $\angle O\cdots H-O$ hydrogen bond angles are 173.2°, 166.6°, and 178.6°, respectively. The $\angle O-H\cdots O-H$ torsion angle in the water dimer is $-112.9°$, while the $\angle N\cdots H-O-H$ and $\angle H-O\cdots H-O$ torsion angles related to the forming of the $N-H$ bonds and breaking of the $H-O$ bonds are 0.8° and 0.6°, respectively. Moreover, the exocyclic H atoms in the water dimer are staggered with respect to each other. In the vibrational mode corresponding to the imaginary frequency ($\nu = 1372i$), the dominant motions involve the endocyclic protons participating in the H-bonds formed, which are being transferred in a cyclic way from the O atom to the N atom of the $HN=C(OH)-NH_2$ tautomer. Obviously, the 1,3-H shift in the $HN=C(OH)-NH_2$ tautomer is assisted by, or in concert with, the proton transfer within the water dimer

in the same way as found for related reactions subject to catalysis by the solvent.[15-27]

Conclusions

In this paper we have reported a comprehensive study of the mechanism of Wöhler's reaction in a vacuum and developed models describing possible reaction pathways for the reaction in aqueous solution and in the solid state. The results can be summarized as follows.

Wöhler's reaction is predicted to proceed in two steps. The first step corresponds to the decomposition of crystalline ammonium cyanate to ammonia and isocyanic or cyanic acid. The second step (main reaction step), being the rate-determining step, corresponds to the interaction of NH_3 with either isocyanic or cyanic acid.

For the main step of the reaction several alternative pathways were envisaged depending on the trajectory followed by ammonia during its interaction with the isocyanic or cyanic acid. All alternative pathways proceed through a concerted preassociative mechanism involving the formation of four-center transition states. Interestingly, in aqueous solution and in the solid state the interaction of NH_3 with either isocyanic or cyanic acid is assisted (autocatalyzed) by the active participation of extra H_2O (solvent) and/or NH_3 molecules, through a preassociative, cooperative, and hydrogen-transfer relay mechanism involving the formation of "six-center" or even "eight-center" transition states.

The most energetically economic path of the main step of Wöhler's reaction modeled in a vacuum, in aqueous solution, and in the solid state corresponds to the addition of NH_3 to the $C=N$ double bond of isocyanic acid, yielding urea directly (C_2 symmetry). Moreover, all favorable pathways are strongly exothermic; therefore, the transformation of ammonium cyanate into urea is thermodynamically favored.

Finally, there is a very small possibility of initial attack of the nitrogen atom of ammonia to the carbon atom of cyanic or isocyanic acid in the solid state and in aqueous solution, where hydrogen bonds dominate among all molecules.