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Experimental and Theoretical Evidence for a Concerted Catalysis by Water Clusters in the Hydrolysis of Isocyanates

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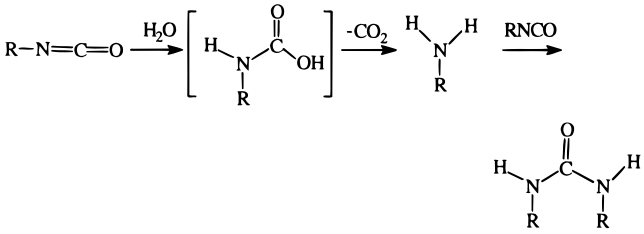
A kinetic and mechanistic investigation of the catalyzed hydration of isocyanates was undertaken. Both experimental and theoretical results showed that the hydrolysis reaction involves a chain of water molecules. The detailed hydration mechanism by water and water clusters ($H{-}N{=}C{=}O + n(H_2O) \rightarrow H_2NCOOH + (n-1)H_2O$, $n = 1{-}3$) has been modeled by ab initio methods, both in the gas phase and in aqueous solution. While two water molecules in the form of a dimer seem to play the key role in hydrating the isocyanate, a third water molecule may be needed to bridge the gap from the point of attack on the isocyanate to the water dimer and to facilitate further the hydration. In accordance with these facts, experimental results imply a second-order dependence on water during its nucleophilic addition to phenyl isocyanate, over a wide concentration range. In this specific case, water oligomers higher than the dimer seem to make no appreciable contribution to the rate of the hydrolysis reaction. The nucleophilic addition occurs in a concerted way across the N═C bond of the isocyanate rather than across the C═O bond. This preferential reaction mechanism could be rationalized in terms of Fukui functions for both nucleophilic and electrophilic attacks. Although a charge separation occurs in the transition state, electrostatic solvent effects are not quite important in reducing only marginally the energy barriers.

Introduction

The chemistry of isocyanates (RN═C═O), where R can be either an alkyl or an aromatic group, dates back over more than 150 years. The first recorded preparation of this type of compounds was by Wurtz[1] in 1848. Later on in the nineteenth century, a more systematic investigation of the chemistry of isocyanates was carried out by scientists such as Hofmann[2] and Curtius[3]. Bayer and co-workers[4] recognized that diisocyanates are ideally suited for the preparation of polymers, such as polyurethanes, by a simple reaction. Nowadays there is a widespread use of aliphatic and aromatic isocyanates and diisocyanates in the polymer industry and in agricultural and pharmaceutical chemistry.[5] In a recent book,[5] no less than 1100 reaction schemes involving isocyanates as starting materials have been selected. Despite such a wealth of available literature, the mechanism of even one of the simplest reactions, namely the hydrolysis, remains controversial. Isocyanates normally react rapidly with water, under mild conditions, giving 1,3-disubstituted ureas and carbon dioxide as the overall products (Scheme 1). This involves initial formation of the labile carbamic acid, which breaks down to give the amine and carbon dioxide. In the presence of a base, such as hydroxide, the principal product is the primary amine.

Scheme 1



Our interest in this problem was prompted by several experimental studies on the hydrolysis of aliphatic and aromatic isocyanates. Mader[6] is believed to have been the first to perform isocyanate hydrolysis reactions in aqueous solution. From his studies, it was concluded that the buffer-independent hydration of 4-(dimethylamino)-phenyl isocyanate could occur by either hydronium ion catalyzed, hydroxide ion catalyzed, or uncatalyzed routes. Moodie and co-workers[7] failed, however, to observe acid catalysis for phenyl isocyanate and deduced that a catalysis resulting from the hydronium ion was negligible. They also suggested that the value of 7.35×10^3 mol^{-1} dm^3 s^{-1} for the acid-catalyzed rate constant, reported by Mader[6] for 4-(dimethylamino)phenyl isocyanate, is too large to be simply explained in terms of the substituent effects. Instead, they argued that the rate constant found by Mader at low pH was due to the uncatalyzed reaction of 4-(dimethylamino)phenyl isocyanate, which was protonated rather at the amino group

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[1] Wurtz, A. *C. R. Acad. Sci. Paris* **1848**, *27*, 242.

[2] (a) Hofmann, A. W. *Ber.* **1870**, *3*, 653. Hofmann, A. W. *Ber.* **1870**, *3*, 765. Hofmann, A. W. *Ber.* **1871**, *4*, 246. Hofmann, A. W. *Ber.* **1885**, *18*, 765.

[3] Curtius, T. *Chem. Ber.* **1890**, *23*, 3029.

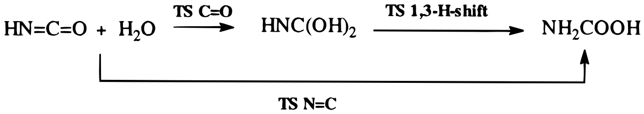
[4] (a) Bayer, O. *Modern Plastics* **1947**, *24*, 149, 250. (b) Bayer, O. *Angew. Chem.* **1947**, *59*, 257.

[5] Ulrich, H. *The Chemistry and Technology of Isocyanates*, Wiley: New York, 1996.

[6] Mader, P. M. *J. Org. Chem.* **1968**, *33*, 2253.

[7] (a) Moodie, R. B.; Sansom, P. J. *J. Chem. Soc., Perkin Trans. 2* **1981**, 664. (b) Castro, E. A.; Moodie, R. B.; Sansom, P. J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 737.

Scheme 2



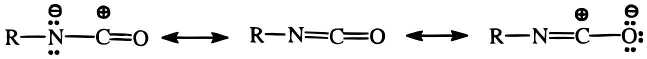
of the phenyl substituent. As for a mechanism, the uncatalyzed reaction was proposed to incorporate two water molecules, one of which behaves as a general acid and the other as a general base. Hydronium ion catalyzed hydrolysis of methyl isocyanate was also examined and the rate constant of 0.16 $\text{mol}^{-1}\ \text{dm}^3\ \text{s}^{-1}$ derived. These authors[7] also believed that this greater value for the methyl over phenyl isocyanate was due to the development of some positive charge on the nitrogen during the transition state. The solvent isotope effects, $k(H_2O)/k(D_2O) \cong 1.65$, also suggested some preequilibrium protonation followed by attack of two molecules of water. Satchell[8] examined the kinetics of the spontaneous hydrolysis of 4-chlorophenyl isocyanate at low water concentration, in diethyl ether solution (nonaqueous solvent), and found pseudo-first-order rate constants that are dependent on $[H_2O]^3$. This result has therefore been interpreted in terms of cyclic transition states involving trimeric water across the C=N bond, rather than a medium effect on monomeric water addition. Nucleophilic catalysis for the hydrolysis of isocyanates has generally been rejected[9] on the basis of substrate isotope effects, solvent isotope effects, and the kinetics of related reactions.

From a theoretical point of view, there has only been one report[10] on the hydrolysis of isocyanate. Semiempirical calculations performed using the MINDO/3 method showed that the addition of a single water molecule across both the N=C and C=O bonds has a prohibitively high barrier, whereas addition of a water dimer shows a marked preference for addition across N=C (leading directly to the carbamic acid). Addition of a water trimer was also considered, but the effect of the third water is rather negative. Note, however, that the stationary points were not fully optimized and the MINDO/3 method is known to give unrealistic results for hydrogen-bonded structures. Finally, it is worth noting that the hydrolysis of methyl isocyanate was likely to be the main reaction that occurred in the Bhopal incident.[11]

Overall, despite the extensive information, some points of discussion concerning the detailed mechanism of the hydrolysis of isocyanates still have to be cleared up: (i) Does the addition of water occur in a concerted way (across the N=C bond of isocyanate) or is a two-step process favored involving an attack across the C=O bond of the isocyanate, followed by an 1,3-H-shift (Scheme 2)? (ii) Does the excess water play an important catalytic role during the hydrolysis reaction? (iii) If a water cluster is actively involved in the process, then what is the actual number of water molecules playing a key factor?

In the present work, an attempt is made to tackle the above questions by a combined kinetic and theoretical investigation on the mechanistic details of the isocyanates hydrolysis. From the theoretical viewpoint, calculations were carried out using high-level ab initio methods and large basis sets. Besides the classical attack of two water molecules on the isocyanate, the attack of three water molecules was also investigated theoretically. A major part of the theoretical study concerns the number of water molecules treated explicitly and the modeling of the bulk solvent effect. It is shown that the polarization of the solvent, modeled by a dielectric continuum, plays a less important role for the reaction.

Scheme 3



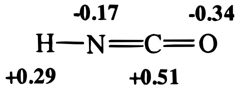
The experimental part concerns the study of the hydrolysis of 1-(phenylcarbamoyl)imidazole, an adduct of phenyl isocyanate, at 30 and 25 °C. This is followed by an examination of the competing reaction of morpholine for the isocyanate, liberated from the urea as a result of the hydrolysis reaction. Note that that masked isocyanate has been evolved to interpret the hydrolysis of isatoic anhydride.[12] Finally, the hydrolysis of a pure isocyanate is studied at various water concentrations and a method is developed for measuring the rates of hydrolysis at low water concentrations.

Overall, this combined experimental and theoretical study has enabled us to establish the key factors which give rise to concerted catalysis in the hydration of isocyanates.

Results and Discussion

A. Qualitative Consideration. Before discussion of the actual hydration process is started, it is instructive to look at the reactivity of isocyanates. The latter can best be understood by considering the electronic structure of the isocyanate functional and the effect of various groups attached to its nitrogen atom. Simple resonance structures indicate that the electron charge density is greatest on the oxygen and smallest on the carbon (see Scheme 3).

To know what computational chemistry shows regarding the charge distribution of isocyanate (Scheme 3), a Mulliken population analysis has been performed at the MP2/6-311++G(d,p) level of theory. As shown below, calculations predict a net charge of −0.34 on the oxygen, being the most negative of all atoms, and +0.51 on the carbon, being the most positive center.



$$\underset{+0.29}{H}-\overset{-0.17}{N}=\underset{+0.51}{C}=\overset{-0.34}{O}$$

Consequently, most nucleophilic reactions involving isocyanates are initiated by attack at the positive carbon center. If steric factors are ignored, any electron-withdrawing group attached to the NCO moiety will increase the positive charge on the carbon atom, which results in increased reactivity of the isocyanate toward nucleophilic attack. Conversely, electron-donating groups will reduce its reactivity. Similarly, the reactivity of the attacking group, at the isocyanate carbon, will increase as its nucleophilicity increases. Nucleophilic addition to

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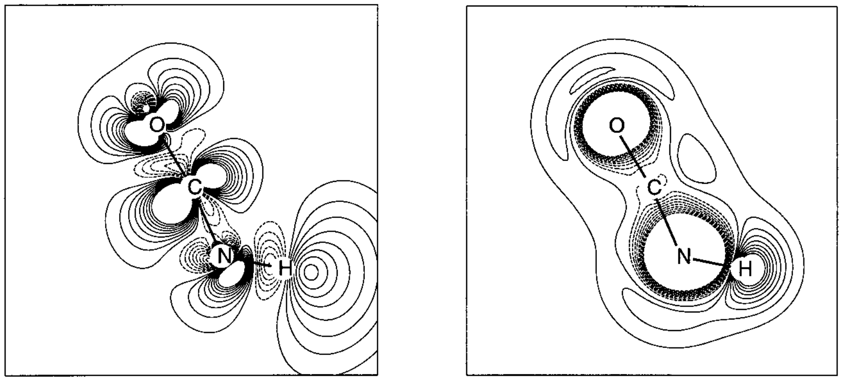
[8] Satchell, R. S.; Nymen, R. *J. Chem. Soc., Perkin Trans. 2* **1981**, 901.

[9] Schwetlick, K.; Noack, R.; Stebner, F. *J. Chem. Soc., Perkin Trans. 2* **1994**, 599.

[10] Lee, I.; Bon-Su, L.; Jae, Y. C. *J. Comput. Chem.* **1985**, *2*, 79.

[11] D'Silva, T. D. J.; Lopes, A.; Jones, R. L.; Singhawang, S.; Chan, J. K. *J. Org. Chem.* **1986**, *51*, 3781.

[12] Hegarty, A. F.; Ahern, E. P.; Frost, L. N.; Hegarty, C. N. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1935.



1 (a) 1 (b)

Figure 1. Contour map of the Fukui function f^+ (a) and f^- (b) for H−N=C=O, derived from B3PW91/cc- pVTZ calculations.

an isocyanate has been extensively reviewed over the years.[13] To rationalize a molecule's reactive behavior, Fukui functions for both nucleophilic and electrophilic attack have been calculated using the finite difference approximation introduced.[14] Hence, the Fukui function, which is given by

$$f(\vec{r}) = \left.\frac{\partial\rho(\vec{r})}{\partial N}\right|_{\nu(\vec{r})}$$

is computed as follows

$$f^+(\vec{r}) = \rho(N+1) - \rho(N)$$

$$f^-(\vec{r}) = \rho(N) - \rho(N+1)$$

where $\rho(N+1)$, $\rho(N)$, and $\rho(N-1)$ are the electron densities of the $N+1$, N, and $N-1$ electron systems, respectively, all calculated at the geometry of the N electron system. These calculations were performed using the B3PW91 functionals combined with the cc-pVTZ basis set, which has already been proven to be successful.[15] Figure 1 displays a contour map of both the Fukui function f^+ (Figure 1a) and f^- (Figure 1b) for HN=C=O. From the plot of f^+, it can be seen that nucleophilic attack is likely to happen at the central carbon. Figure 1b, on the other hand, indicates that the N position is clearly favored for electrophilic attack due to the more extended concentration of the electron density. Later in the discussion, an attempt is made to rationalize the results obtained in terms of the Fukui function.

B. Theoretical Aspects. The results obtained by theoretical methods using different models for the hydration of isocyanates are discussed in this section. Ab initio calculations were carried out with the Gaussian 94 set of programs.[16] Initial exploration of the energy surface and vibrational analysis of all stationary points were done with the dp-polarized 6-31G(d,p) basis set in the Hartree−Fock framework. Geometrical parameters of the relevant equilibrium and transition structures were subsequently refined using second-order perturbation theory. Single-point electronic energy calculations at both the MP2/6-311++G(d,p) (++ indicates a set of sp-diffuse functions on C, N, and O and s-diffuse functions on H) and the QCISD(T)/6-31G(d,p) level were performed on the MP2/6-31G(d,p) geometries. Despite the great success of density functional theory (DFT) in calculating energetic and molecular properties of equilibrium structures, it appears that this method, with the currently available functionals, encounters some serious difficulties in constructing the minimum-energy reaction paths of some specific chemical reactions, in particular for hydrogen-transfer processes.[17] On the other hand, as during the reaction paths no radical fragments occur, it is not necessary to perform MCSCF calculations. Indeed, in cases where bonds are broken and formed homolytically, a MCSCF treatment is needed to correctly describe the reaction. In this case, the electronic structure of the transition state is dominated by the HF configuration, which eliminates the need for a multireference treatment. In addition, MCSCF optimizations of transition structures in this study are also not feasible due to the lack of analytical energy Hessians in our available software.

Solvent computations were carried out by means of both the Onsager SCRF approach[18a] and the polarizable continuum method[18b] (PCM). The solvent is thereby represented by a continuum characterized by its dielectric permittivity ϵ and the solute is embedded in a cavity. As a typical example, $\epsilon = 78.3$ for water at 25 °C has been employed throughout. In nonpolar solutions with lower water concentrations, ϵ should be smaller. The value of $\epsilon = 78.3$ can be regarded as an upper bound for highly polar solvents. While the SCRF model approaches the cavity as spherical, the PCM model makes a superposition of spheres to probe the molecular shape of the solute.

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[13] For reviews, see: Saunders, J. H.; Slocombe, R. J. *Chem. Rev.* **1948**, *43*, 203. Ozaki, S. *Chem. Rev.* **1972**, *72*, 457. Satchell, D. P. N.; Satchell, R. S. *Chem. Soc. Rev.* **1975**, *4*, 231.

[14] Parr, R. G.; Yang, W. In *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.

[15] Geerlings, P.; De Proft, F.; Martin, J. M. L. In *Recent Developments and Aplications of Modern Density Functional Theory*; Elsevier Science: New York, 1996; Vol. 4.

[16] GAUSSIAN 94, Revision C.3: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowki, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. H.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Comperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; DeFrees, D. J.; Baker, J.; Stewart, J. J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian Inc., Pittsburgh, PA, 1995.

[17] (a) Baker, J.; Andzelm, J.; Muir, M.; Taylor, P. R. *Chem. Phys. Lett.* **1995**, *237*, 53. (b) Johnson, B. G.; Gonzales, C. A.; Gill, P. M. W.; Pople, J. A. *Chem. Phys. Lett.* **1994**, *221*, 100. (c) Zhang, Q.; Bell, R.; Truong, T. N. *J. Phys. Chem.* **1995**, *99*, 592. (d) Hrusak, J.; Friedrichs, H.; Schwarz, H.; Razafinjanahary, H.; Chermette, H. *J. Phys. Chem.* **1996**, *100*, 100. (e) Baker, J.; Muir, M.; Andzelm, J. *J. Chem. Phys.* **1995**, *102*, 2063.

[18] (a) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776. (b) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117.

Table 1. Calculated Total (Hartree) and Zero-Point Vibrational (ZPE, kJ·mol^{-1}) Energies for the Hydration of Isocyanic Acid (HN=C=O)

	MP2^a 6-31G**	MP2^a 6-311++G**	QCISD(T)^a 6-31G**	ZPE^b
HN=C=O (**1**)	−168.230 73	−168.311 61	−168.253 70	54
H_2O	−76.222 45	−76.274 91	−76.231 65	55
HN=C=O + H_2O	−244.450 52	−244.586 52	−244.485 35	109
TS C=O (**TS2**)	−244.379 75	−244.508 90	−244.414 76	117
HN=C(OH)$_2$ (**3**)	−244.454 40	−244.584 17	−244.492 67	133
TS 1,3-H-shift (**TS4**)	−244.401 93	−244.530 17	−244.437 09	119
NH_2COOH (**5**)	−244.487 36	−244.615 08	−244.523 53	131
TS N=C (**TS6**)	−244.396 60	−244.525 52	−244.429 36	115
HN=C=O + 2H_2O	−320.687 18	−320.861 43	−320.717 00	164
TS C=O (**TS7**)	−320.650 38	−320.829 19	−320.670 07	183
HN=C(OH)$_2$·H_2O (**8**)	−320.693 64	−320.873 55	−320.742 93	196
TS 1,3-H-shift (a) (**TS9**)	−320.647 54	−320.824 74	−320.693 72	184
TS 1,3-H-shift (b) (**TS10**)	−320.686 70	−320.864 04	−320.732 12	182
NH_2COOH·H_2O (**11**)	−320.730 97	−320.907 65	−320.778 51	196
NH_2COOH + H_2O	−320.724 45	−320.889 99	−320.755 18	186
TS N=C (**TS12**)	−320.677 61	−320.839 86	−320.704 17	182
NH_2COOH·H_2O (**13**)	−320.740 10	−320.901 58	−320.770 45	194
HN=C=O + 3H_2O	−396.898 08	−397.136 34	−396.948 65	218
TS C=O (**TS14**)	−396.895 68	−397.126 04	−396.951 39	250
HN=C(OH)$_2$·0·3H_2O (**15**)	−396.933 40	−397.164 54	−396.993 52	258
TS 1,3-H-shift (**TS16**)	−396.890 77	−397.119 79	−396.947 67	246
NH_2COOH·2H_2O (**17**)	−396.973 37	−397.202 05	−397.031 75	260
NH_2COOH + 2H_2O	−396.932 26	−397.164 90	−396.986 83	240
TS N=C (**TS18**)	−396.902 35	−397.132 95	−396.956 87	250
NH_2COOH·H_2O (**19**)	−396.960 29	−397.191 31	−397.019 02	258

[a] Based on MP2/6-31G(d,p) geometries given in Figures 2−4. [b] Zero-point energies from HF/6-31G(d,p) and scaled by 0.9.

Table 2. Calculated Relative Energies (kJ·mol^{-1}) for the Hydration of Isocyanic Acid (HN=C=O), All Corrected by Zero-Point Energies (ZPE)

	MP2^a 6-31G**	MP2^a 6-311++G**	QCISD(T)^a 6-31G**
HN=C=O + H_2O	0	0	0
TS C=O (**TS2**)	194	212	193
HN=C(OH)$_2$ (**3**)	14	30	5
TS 1,3-H-shift (**TS4**)	138	159	137
NH_2COOH (**5**)	−75	−53	−78
TS N=C (**TS6**)	148	167	154
HN=C=O + 2 H_2O	0	0	0
TS C=O (**TS7**)	116	104	143
HN=C(OH)$_2$···H_2O (**8**)	15	0	−36
TS 1,3-H-shift (a) (**TS9**)	124	117	82
TS 1,3-H-shift (b) (**TS10**)	19	11	−22
NH_2COOH···H_2O (**11**)	−82	−89	−129
NH_2COOH + H_2O	−76	−53	−78
TS N=C (**TS12**)	44	75	52
NH_2COOH···H_2O (**13**)	−108	−74	−140
HN=C=O + 3 H_2O	0	0	0
TS C=O (**TS14**)	38	59	25
HN=C(OH)$_2$···0·3H_2O (**15**)	−53	−34	−78
TS 1,3-H-shift (**TS16**)	47	71	30
NH_2COOH···2 H_2O (**17**)	−156	−131	−176
NH_2COOH + 2 H_2O	−68	−53	−78
TS N=C (**TS18**)	21	41	10
NH_2COOH···2H_2O (**19**)	−123	−104	−145

[a] Based on MP2/6-31G(d,p) geometries.

Throughout this paper, calculated bond lengths are given in Å, bond angles in degrees, total energies in hartrees, and zero point energies and relative energies in kJ·mol^{-1}.

The results in the theoretical section concern both possibilities of water attack across the C=O and N=C bonds of the isocyanate molecule. Water chain models involving different numbers of water molecules are also considered, as well as the global electrostatic influence of the surrounding bulk.

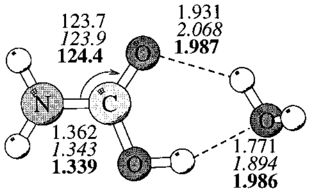
Reaction between HN=C=O and H_2O. The simplest possible model that can be used to study the hydrolysis of isocyanates is a water molecule attacking the isocyanic acid. The results obtained using this model are given in Tables 1−3 and Figure 2. However, this model leads to several unrealistic results, the activation energy being in fact unreasonably large. The values obtained at the QCISD(T) level of theory using a 6-31G(d,p) basis set are 154 via **TS2** and 193 kJ·mol^{-1} via **TS6** for both N=C and C=O additions, respectively. The transition structure for 1,3-H-shift **TS4** connecting both isomers **3** and **5** lies lower in energy than both **TS2** and **TS6**. MP2/6-311++G(d,p) calculations also suggest a comparable energy ordering. The effect of a polar solvent modeled by a large dielectric continuum is to increase both energy barriers somewhat (see Table 5). Results in solvent will be discussed later on in detail. By and large, the use of a model involving one water molecule attacking isocyanate leads to quite unsatisfactory results. This suggests the need for models using multiple water molecules. Chains with two and three water molecules were thus used, and the energetic results are also shown in Tables 1−3. The resulting structures for the reactants, transition structures (TS) and products are displayed in Figures 3 and 4. It has to be noted that, despite extensive

Table 3. Energy Barriers (kJ·mol^{-1}) for the Hydration of HN=C=O across Both C=O and N=C Bonds, Including Different Numbers of Water Molecules

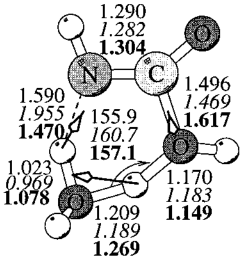
	MP2^a 6-31G**	MP2^a 6-311++G**	QCISD(T)^a 6-31G**
HN=C=O + 1H_2O			
across C=O	194	212	193
across N=C	148	167	154
HN=C=O + 2H_2O			
across C=O	116	104	143
across N=C	44	75	52
HN=C=O + 3H_2O			
across C=O	38	59	25
across N=C	21	41	10

[a] Based on MP2/6-31G(d,p) geometries.

search, we were not able to locate molecular complexes between HNCO and water chains.

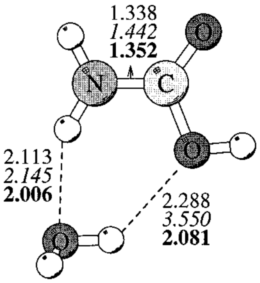


11



TS12

ν = 1316i cm^{-1}



13

Reaction between HN=C=O and Two H_2O. As shown in Table 3, energy barriers are decreased dramatically upon incorporation of a second water molecule in the reaction coordinate. At the highest level of theory, the energy barrier for attack across C=O via **TS7** is lowered by 50 kJ·mol^{-1}, whereas that across N=C via **TS12** the barrier is decreased by 102 kJ·mol^{-1}. The resulting barriers are 143 and 52 kJ·mol^{-1}, respectively. The fact that addition across N=C is favored over that across C=O can be rationalized in terms of Fukui functions. Depending on the type of attack, different sites are indicated as the most reactive site for H−N=C=O, i.e., the site for which f is largest. The distinct mechanism of hydration of isocyanate may illustrate this: the preferred attack proceeds via a nucleophilic attack of O on C (f^+ largest for C), while an electrophilic attack occurs by proton at nitrogen (f^- largest for N and not on O as can be seen from Figure 1b). This indicates that the ability of the N atom to accept and distribute positive charge is of considerable importance, in such a way that attack on N is preferred over attack on O. As addition across N=C is much preferred above the one across C=O, the discussion is continued with the former.

Calculations show that as **TS12** is approached, the two water molecules move in the form of a dimer toward the isocyanate. As in similar cases, the water dimer has a nearly linear structure. Note, however, that the form involved in a transition structure for addition does not correspond necessarily to the most stable among the possible structures of water dimer. In the course of the approach, the oxygen atom is moving toward the isocyanate carbon, while the second oxygen atom of the dimer is on the same side as the nitrogen, so that it is correctly situated to facilitate the proton transfer to nitrogen. The C−O distance of 1.617 Å (MP2 value) in the **TS12** is somewhat larger than that observed above for the reaction with one water molecule in **2** (1.586 Å). In **TS12**, there are two important nuclear motions: the deformation of the isocyanate and the closing of the OHO angle of the dimer, which changes from 179° to 157°. These movements tend to facilitate the transfer of a proton toward the nitrogen. Regarding the products, they are also markedly stabilized in the complexed forms **8**, **11**, and **13**. **TS9** linking both complexes **8** to **11** can be regarded as that of a 1,3-H-shift externally complexed by a water molecule. In contrast, **TS10** is a water-assisted transition structure for the same transfer, leading to the complex **13**. As would be expected, **TS10** is largely favored over TS9. In any case, the connection between both possible products is again much easier to achieve than the addition itself (Table 3).

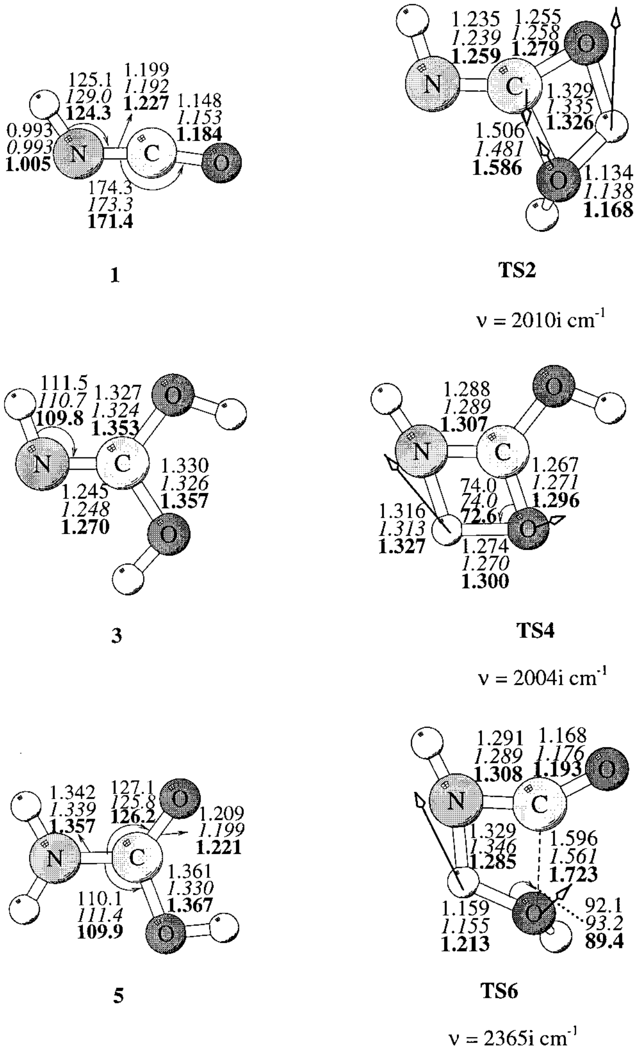
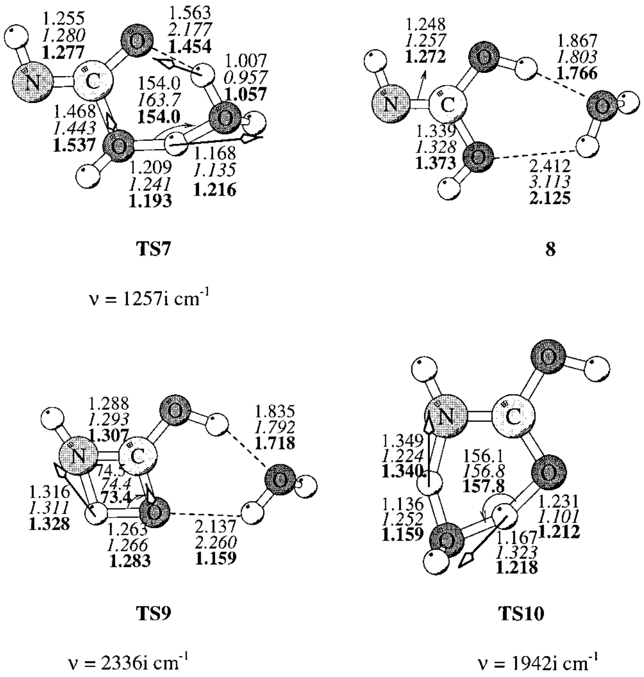


Figure 2. Optimized structures of the stationary points along the hydration path of isocyanic acid with one water molecule (HN=C=O + H_2O) across both C=O and N=C bonds.

Reaction between HN=C=O and Three H_2O. The transition structure **TS14** for attack across the C=O bond is now only 25 kJ·mol^{-1} higher than the separated reactants. This means that addition of a third water molecule in the water chain has further lowered the energy barrier by 118 kJ·mol^{-1}, from 143 kJ·mol^{-1} in the two-water-chain model down to 25 kJ·mol^{-1} for the three-water-chain model, which is a quite important result. A similar trend is observed for the attack across the N=C bond through **TS16**, yielding an energy barrier of only 10 kJ·mol^{-1}, which means a lowering of 42 kJ·mol^{-1}



TS7 ν = 1257i cm^{-1}

8

TS9 ν = 2336i cm^{-1}

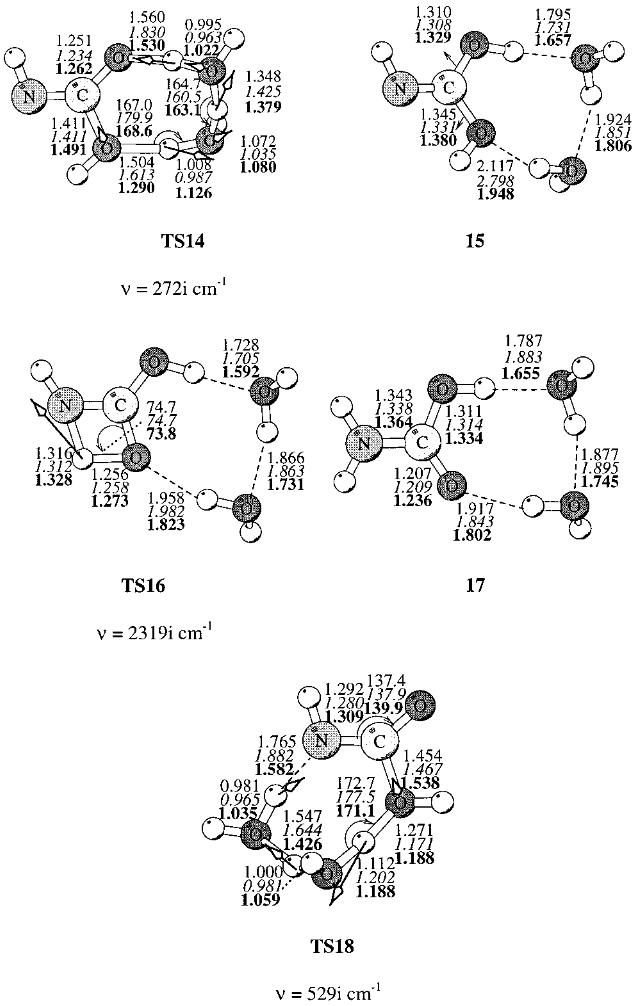
TS10 ν = 1942i cm^{-1}

Figure 3. Optimized structures of the stationary points along the hydration path of isocyanate with two water molecules ($HN{=}C{=}O + 2H_2O$) across both C=O and N=C bonds.

relative to the reaction containing two water molecules via **TS12**. There are two main reasons for this effect. First, the proton affinity of the dimer leading to $H_5O_2^+$ is much higher than that of the water monomer leading to H_3O^+. In fact, in the *three*-water chain, a nucleophilic addition leads to formation of $H_5O_2^+$. The proton affinity of the water dimer is as much as 112 kJ·mol^{-1} larger than that of the monomer. It is thus clear that the effect of a third water molecule in the water chain may be quite important.

The second main explanation for the effect of adding another water molecule in the chain is seen in Figure 4. The three-water chain seems just long enough to bridge the gap between the two points of attack to the isocyanate molecule, releasing most of the ring strain. The latter bridging effect is thus a part of the hydrolysis mechanism. From Figure 4, some special features have to be noted concerning the transition structure across the N=C bond **TS18**, which is the energetically most favored reaction route. The region around the $H_5O_2^+$ is an interesting part of the **TS18**. Within the $H_5O_2^+$ moiety, it can be noticed, when continuing to the hydroxyl end of the TS, that the hydrogen atom is not fully transferred yet. The distance between this hydrogen and the oxygen of the hydroxyl group is only 1.035 Å, which is quite short and means that the leaving hydrogen atom has not moved yet. The calculated **TS18** is reached with virtually no proton transfer from water to the adjacent N, but the supermolecule is correctly oriented for subsequent proton transfer. The product complexes **15**, **17**, and **19** are again stabilized, but at a lesser extent.

By and large, the presence of a polar continuum does not greatly modifies the conclusions discussed above for the gas-phase systems. For the water-assisted reaction, the addition across the N=C bond still remains favored over that across the C=O. Moreover, the reaction coordinate is not affected noticeably either. This fact is visible in Figures 3 and 4, which display the geometrical features of the water-assisted reactions in both gaseous state and solution.



TS14 ν = 272i cm^{-1}

15

TS16 ν = 2319i cm^{-1}

17

TS18 ν = 529i cm^{-1}

Figure 4. Optimized structures of the stationary points along the hydration path of isocyanate with three water molecules ($HN{=}C{=}O + 3H_2O$) across both C=O and N=C bonds.

Electrostatic Solvent Effects. Some additional comments on the medium effects may be useful. Chains composed of two and three water molecules perform the hydration with low barriers. The results obtained when putting these supersystems in a spherical cavity[18a] in a dielectric medium are shown in Tables 4 and 5, as well as the results with more elaborated PCM model.[18b] However, both SCRF and PCM solvation models do not modify the calculated energy barriers in a significant way. In the “three-water case”, the continuum lowers the barrier for addition across C=O by only 5 kJ·mol^{-1} (from 38 kJ·mol^{-1} in gas phase to 33 kJ·mol^{-1} with inclusion of SCRF continuum). Using the more sophisticated PCM model lowers the barrier slightly further, to about 28 kJ·mol^{-1}. Overall, these small changes do not influence qualitatively the reaction path, showing invariably the preference for the addition across N=C. The latter path appears to be even less influenced by its surroundings. The energy barrier goes from 21 kJ·mol^{-1} in the gas phase to 20 kJ·mol^{-1} in solvent, with both SCRF and PCM methods (Table 5).

In summary, calculated results emphasize again that the hydrolysis assisted by a water chain is a favored

Table 4. Total (Hartree) and Relative Energies (kJ·mol^{-1}, Including ZPE Corrections) of the Considered Stationary Points in Solvent (ϵ = 78.3), Using Both SCRF and PCM Methods

	total energies[a]			relative energies		
	MP2/SCRF 6-31G**	MP2/SCRF 6-311++G**	MP2/PCM 6-31G**	MP2/SCRF 6-31G**	MP2/SCRF 6-311++G**	MP2/PCM 6-31G**
$HN{=}C{=}O$ (**1**)	−168.232 95	−168.313 93	−168.235 54			
H_2O	−76.222 99	−76.278 39	−76.230 51			
$HN{=}C{=}O + H_2O$	−244.455 94	−244.592 32	−244.466 05	0	0	0
TS $C{=}O$ (**TS2**)	−244.381 49	−244.510 64	−244.395 85	195	214	184
$HN{=}C(OH)_2$ (**3**)	−244.455 32	−244.585 11	−244.463 95	2	22	6
TS 1,3-H-shift (**TS4**)	−244.402 85	−244.531 16	−244.413 22	139	161	139
NH_2COOH (**5**)	−244.489 39	−244.617 68	−244.503 64	−88	−67	−99
TS $N{=}C$ (**TS6**)	−244.398 35	−244.527 37	−244.406 11	151	171	163
$HN{=}C{=}O + 2H_2O$	−320.678 93	−320.870 71	−320.696 56	0	0	0
TS $C{=}O$ (**TS7**)	−320.654 47	−320.833 37	−320.674 69	83	117	76
$HN{=}C(OH)_2{\cdot}H_2O$ (**8**)	−320.695 99	−320.875 68	−320.714 20	−13	19	−14
TS 1,3-H-shift (a) (**TS9**)	−320.648 17	−320.825 33	−320.662 29	101	139	110
TS 1,3-H-shift (b) (**TS10**)	−320.687 33	−320.864 73	−320.707 85	40	34	−12
$NH_2COOH{\cdot}H_2O$ (**11**)	−320.731 82	−320.90867	−320.749 59	−107	−68	−107
$NH_2COOH + H_2O$	−320.712 38	−320.89607	−320.734 15	−66	−45	−77
TS $N{=}C$ (**TS12**)	−320.662 86	−320.84224	−320.679 43	60	93	63
$NH_2COOH{\cdot}H_2O$ (**13**)	−320.719 79	−320.90050	−320.738 82	−77	−48	−81
$HN{=}C{=}O + 3H_2O$	−396.901 92	−397.14910	−396.927 07	0	0	0
TS $C{=}O$ (**TS14**)	−396.901 35	−397.13191	−396.928 45	33	77	28
$HN{=}C(OH)_2{\cdot}3H_2O$ (**15**)	−396.934 28	−397.16531	−396.961 85	−45	−3	−51
TS 1,3-H-shift (**TS16**)	−396.890 89	−397.11986	−396.909 78	57	105	73
$NH_2COOH{\cdot}2H_2O$ (**17**)	−396.973 91	−397.20271	−396.996 33	−147	−99	−140
$NH_2COOH + 2H_2O$	−396.935 37	−397.17446	−396.964 66	−61	−45	−77
TS $N{=}C$ (**TS18**)	−396.906 54	−397.13726	−396.931 72	20	63	20
$NH_2COOH{\cdot}2H_2O$ (**19**)	−396.961 87	−397.19291	−396.989 11	−117	−75	−123

[a] Based on MP2/6-31G(d,p) geometries in the gas phase.

Table 5. Energy Barriers (kJ·mol^{-1}) in Aqueous Solvent (ϵ = 78.3) of the Considered Stationary Points along the Hydration Reaction Path of Isocyanic Acid, across Both $C{=}O$ and $N{=}C$ Bonds

	MP2/SCRF 6-31G**	MP2/SCRF 6-311++G**	MP2/PCM 6-31G**
$1H_2O$			
across $C{=}O$	195	214	184
across $N{=}C$	151	171	163
$2H_2O$			
across $C{=}O$	83	117	76
across $N{=}C$	60	93	63
$3H_2O$			
across $C{=}O$	33	77	28
across $N{=}C$	20	63	20

process. Due to practical reasons and limited computational resources, the paths with more water molecules ($n \geq 4$) cannot be examined. Additional water molecules are likely to reduce the barriers, but at a much lesser extent. The direct hydrolysis across the $N{=}C$ bond should be predominant. On the other hand, substituted isocyanates might behave somewhat differently with respect to the water chain, due to possible steric effects.

C. Experimental Aspects. In this section, experimental results concerning the hydration of isocyanates are reported. First, the hydrolysis of 1-(phenylcarbamoyl)imidazole at 30 °C is studied, and repetition of this work is done at the lower temperature of 25 °C. The latter is an adduct of phenyl isocyanate. This is followed by an examination of the competing reaction of morpholine for the isocyanate, liberated from the urea as a result of the hydrolysis reaction. Finally, the hydrolysis of pure phenyl isocyanate was studied at various water concentrations and a method developed for measuring the rates of hydrolysis at low water concentrations.

Hydrolysis of 1-(Phenylcarbamoyl)imidazole 20. Few direct studies on isocyanates have been carried out in aqueous solutions due to their rapid reaction with water over the entire pH range. One method is to use a urea in the presence of an excess of its constituent amine, thus generating a steady concentration of the corresponding isocyanate that can react with the aqueous media. This enables the measurement of the reactivity of certain isocyanates in an almost purely aqueous environment. This technique uses the idea that in neutral solution the main route to the hydrolysis of the urea is via its zwitterion with initial formation of the isocyanate and the amine. Rates of hydrolysis of ureas by acids and bases have been studied;[19] the half-life of such reactions is generally very large. Hegarty et al.[20] have found that by incorporating an extra heteroatom, such as nitrogen, into the urea system, e.g., an imidazole group, the hydrolysis rates for these reactions are enhanced enormously. The imidazole group is strongly electron withdrawing; the involvement of the lone pair of electrons on the nitrogen in the aromatic sextet of the heterocycle is responsible for this. Hydrolysis of ureas has been shown, in certain circumstances, to involve general acid−general base catalysis consistent with an E1cB mechanism. Previous studies[20] show that when the various species are in equilibrium with each other and at high buffer concentration a bell-shaped pH profile is observed, while at low buffer concentration two maxima are observed. These observations may be understood by considering the reverse reaction, i.e., the synthesis of urea from isocyanate and amine, whereby the decomposition of the zwitterion intermediate involves diffusion-limiting proton transfers. Buffer catalysis approaches zero as the

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(19) Hegarty, A. F.; Frost, L. N. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1249.

(20) (a) Hegarty, A. F.; Hegarty, C. N.; Scott, F. L. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1258. (b) Hegarty, A. F.; Hegarty, C. N.; Scott, F. L. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1166.

Table 6. Observed Rate Constants and Their Reciprocals for the Hydrolysis of 1-(Phenylcarbamoyl)imidazole in Imidazole Buffer at 30 °C in Water and $\mu = 1.0$ with KCl

[imidazole] ($\times 10^{-2}$ M)	k_{obs} ($\times 10^{2}$) (s^{-1})	$1/k_{obs}$ (s)
0.50	1.96	51.11
0.80	1.58	63.38
2.70	0.70	141.97
5.40	0.38	265.40
8.10	0.24	415.92
10.90	0.18	562.04

Table 7. Observed Rate Constants and Their Reciprocals for the Hydrolysis of 1-(Phenylcarbamoyl)imidazole in Imidazole Buffer at 25 °C in Water and $\mu = 1.0$ with KCl

[imidazole] ($\times 10^{-2}$ M)	k_{obs} ($\times 10^{3}$) (s^{-1})	$1/k_{obs}$ (s)
0.50	10.09	106.10
0.80	5.40	185.15
2.70	1.60	627.07
5.40	0.88	1136.90
8.10	0.58	1734.10
10.90	0.43	2316.40

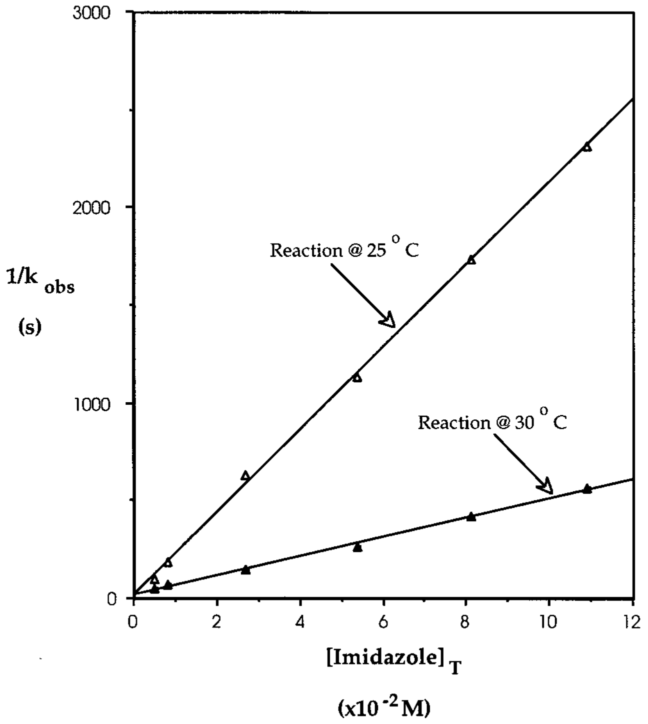

Figure 5. Plot of the reciprocal of the observed rate for the hydrolysis of 1-(phenylcarbamoyl)imidazole against total imidazole buffer concentration at 25 °C and 30 °C and pH 7.20 and 7.35, respectively, and $\mu = 1.0$ with KCl.

buffer concentration increases, consistent with a change in the rate-controlling step. At high buffer concentration, the proton-transfer step is not rate determining and the decomposition of the zwitterion becomes rate limiting. At low buffer concentration, the proton-transfer steps are rate determining. When there are sufficient general acids and general bases present the urea and zwitterion are in equilibrium.

Greatest solvolytic reactivity is observed when the major species present is the neutral urea. A decrease in reactivity is seen under acidic and basic conditions when the ionic species are in the majority. The enhanced reactivity observed at near neutral conditions is due to the reactive zwitterion, rather than the neutral urea, with which it is in equilibrium.[21] Zwitterionic species are the reactive species over the entire pH range,[20a] except at very high pH where the conjugate base of the urea reacts. The rate of decomposition of the urea, to give phenyl isocyanate and imidazole, is so rapid that the diffusion-controlled proton transfers involved in the formation of the zwitterion become rate limiting at pH 4–10. When there is enough general acid–general base present there is a change in the rate-determining step to that of decomposition of the zwitterion in this region.

This present work involved a study on the hydrolysis of 1-(phenylcarbamoyl)imidazole **20**. Williams and Jencks[21] have confirmed that the hydrolysis of urea occurs through a stepwise mechanism involving the formation of an intermediate zwitterion **21**. When the hydrolysis of **20** is carried out in the presence of excess imidazole at equilibrium, a steady concentration of phenyl isocyanate **22** is produced, and the reactivity of the isocyanate under these conditions can be measured by monitoring the change in absorbance due to the urea at a suitable wavelength. During this study, optical density measurements were carried out at $\lambda = 250$ nm and at 25 and 30 °C. The ionic strength was kept constant at $\mu = 1.0$ throughout this series of experiments using potassium chloride. Since previous studies on the hydrolysis of **20** show enhanced reactivity in the pH region ca.4–10, these hydrolysis studies were carried out at neutral pHs, corresponding to the pK_a of imidazole at the different temperatures. The results obtained are shown in Tables 6 and 7. There are two consequences of carrying out these reactions in the presence of excess imidazole: the imidazole can behave as a general acid–general base, thus creating a true equilibrium, or it can react again with the isocyanate generated, reforming the zwitterion, which in turn may undergo proton transfer to the urea.

Previous investigations[20a] have shown that at very low concentrations of imidazole, i.e., lower than 10^{-4}M, the observed rate actually increased. This was attributed to the fact that at low imidazole concentrations imidazole itself acts as a general acid–general base pair rather than as a reactant. These present studies were carried out at imidazole concentrations greater than this. At high imidazole concentrations, the observed rate is retarded since the imidazole is acting as a trap for the phenyl isocyanate intermediate, thus regenerating the urea and giving the impression of an overall reduction in the rate. Since imidazole is one of the products of the initial reaction, its increasing concentration in solution as the reaction proceeds affects the rate of reaction of the remaining substrate. Results show, in fact, that the observed rate for the reaction decreases markedly as the total imidazole concentration is increased. This may be seen from the positive slope in the graph of the reciprocal of the observed rate against the total imidazole concentration (Figure 5).

The phenyl isocyanate **22** may react in one of two ways under these conditions at neutral pH; it may react with the added imidazole reforming the urea or alternatively

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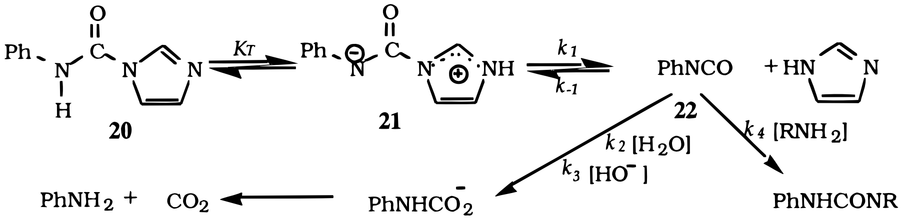
(21) (a) Williams, A.; Jencks, W. P. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1753. (b) Williams, A.; Jencks, W. P. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1760.

Scheme 4



with a molecule of water, thus forming the carbamic acid, which decomposes to aniline and carbon dioxide, which accounts for the observed decrease in k_{obs} with increasing [imidazole]; see Scheme 4. Hegarty et al.[20] found the free imidazole to be 3.5×10^4-fold more reactive toward the isocyanate than the water.

If other nucleophiles are present, the phenyl isocyanate may be similarly trapped by such nucleophiles, and their reactivity toward the isocyanate changes the overall reaction pathway and products; see the following section. If it is assumed that all the ionic species are in equilibrium and there is a steady-state concentration of phenyl isocyanate, eq 1 can be derived. This relates the rate of disappearance of the urea to the imidazole concentration. Since the reaction is carried out at neutral pH, it is assumed that there is negligible contribution by species such as hydroxide on the rate, and thus, they do not appear in the rate equation.

$$k_{obs} = \frac{k_5 K_T k_7[H_2O]}{k_{-5}[Im] + k_7[H_2O]} \qquad (1)$$

From this equation, it is implied that $1/k_{obs}$ should also be proportional to the imidazole concentration at constant pH. The equation also implies that when the plot of $1/k_{obs}$ is extrapolated to $[imidazole]_T = 0$ the intercept is equal to $1/k_5K_T$. The constant k_5 was previously approximated to be 10^4 s^{-1}, and since $k_5K_T = 5.3 \times 10^{-2}$ s^{-1} and 5.7×10^{-2} s^{-1} at 25 and 30 °C, respectively, then K_T can correspondingly be estimated at 5.3×10^{-6} s^{-1} and 5.7×10^{-6} s^{-1}, respectively. Assuming that the concentration of water during the reaction remained more or less constant at 55.5 M a value for k_{-5}/k_7, a measure of the relative reactivities of imidazole to water may be estimated at 6.68×10^4 and 1.55×10^4 for the reactions at 25 and 30 °C, respectively. Thus, the value for the hydrolysis of the isocyanate is 6.68×10^4- and 1.55×10^4-fold slower than reaction with imidazole for the above conditions.

Reaction of Morpholine with 1-(Phenylcarbamoyl)imidazole 20. The rate of hydrolysis of **20** was examined in the presence of morpholine hydrochloride and a constant concentration of imidazole hydrochloride, which had the function of acting as a buffer and maintaining the pH. When the reaction is carried out at a large constant concentration of imidazole buffer, a small equilibrium concentration of phenyl isocyanate is continually generated. As discussed before, this may either react with the imidazole reforming the urea or with water, since the reaction is carried out in an aqueous environment, to ultimately form aniline and carbon dioxide. The addition of another nucleophile introduces the possibility of another reaction, i.e., attack of the phenyl isocyanate with that nucleophile (Scheme 4). The reactivity of the nucleophile toward the isocyanate affects the overall reaction. A good nucleophile competes effectively for the isocyanate with imidazole or water. The overall rate of disappearance of the urea increases with addition of such a nucleophile. The observed rate increased nonlinearly as the total amine concentration was increased. At low morpholine concentration, the observed rate increases rapidly; however, at higher concentrations the rate decelerates and appears to become independent of the amine concentration; the results of these are detailed in Table 8. On examination of Scheme 4, it can be seen that the actual rate due to the morpholine may be determined by subtracting the rate due to the imidazole from the observed rate constants, see eq 2. Since these studies were all carried out at a constant imidazole concentration, the reaction rate due to the imidazole is a constant and could be determined from the previous work. Performing these reactions at a relatively high concentration of imidazole had the advantage of retarding the hydrolysis reaction.

Table 8. 1-(Phenylcarbamoyl)imidazole in the Presence of Morpholine Measured at a Constant [Imidazole] = 0.05 M at 30 °C in Water and $\mu = 1.0$ with KCl

[morpholine] ($\times 10^{-3}$ M)	1/ [morpholine] (M^{-1})	k_{obs} ($\times 10^4$) (s^{-1})	$k_{obs} - k_0$ ($\times 10^4$) (s^{-1})	$1/(k_{obs} - k_0)$ (s)
1.00	1000.00	6.029	1.659	6026.2
2.50	400.00	8.409	4.039	2475.9
5.00	200.00	12.593	8.224	1216.0
7.50	133.33	17.017	12.647	790.7
9.00	111.11	19.104	14.734	678.7
10.00	100.00	20.314	15.944	627.2

Table 9. Observed Rate Constants for Phenyl Isocyanate Hydrolysis at 25 °C

[H$_2$O] (M)	k_{obs} ($\times 10^3$) (s^{-1})	k_{obs}/[H$_2$O] ($\times 10^3$) (s^{-1} M^{-1})
0.60	0.014	0.023
0.80	0.032	0.040
1.00	0.051	0.051
1.25	0.139	0.111
1.50	0.279	0.186
2.00	0.547	0.274
2.50	1.010	0.404
5.00	4.510	0.902
6.00	6.684	1.114
7.00	9.268	1.324
8.00	12.536	1.567
9.00	15.732	1.748
10.00	19.210	1.921
15.00	42.211	2.814
20.00	79.423	3.971
25.00	125.675	5.027
30.00	179.338	5.978
35.00	248.567	7.102
40.00	328.962	8.224
45.00	407.205	9.049
50.00	498.802	9.976
55.50	621.700	11.202

The maximum rate of hydrolysis can be determined by extrapolating the linear plot of $1/k_{obs}$ against $1/[morpholine]_T$ to infinite total morpholine concentration,

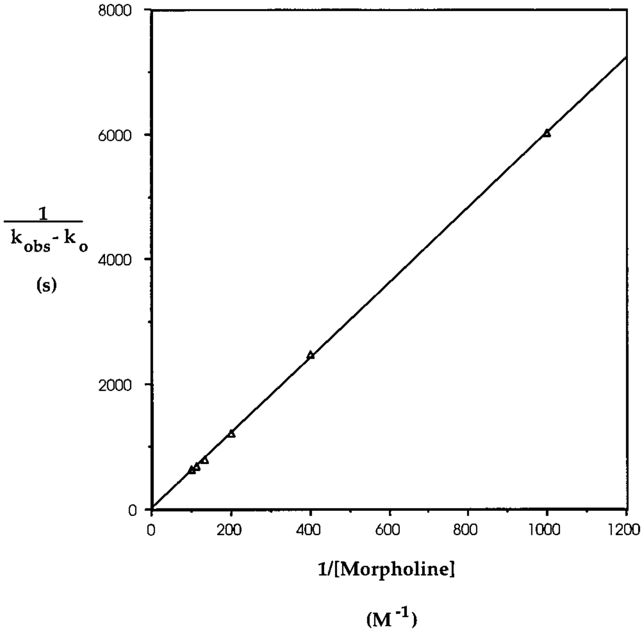


Figure 6. Plot of the reciprocal of the observed rate for the hydrolysis of 1-phenylcarbamoylimidazole against the reciprocal morpholine concentration measured at a constant [Imid] = 0.05 M at 30 °C in water, $\mu = 1.0$ with KCl.

$$k_{Nu} = k_{obs} - k_o = \frac{k_1K_Tk_4[\text{morpholine}]}{k_{-1}[\text{Im}] + k_4[\text{morpholine}]} \quad (2)$$

$$\frac{1}{k_{Nu}} = \frac{k_{-1}[\text{Im}]}{k_1K_Tk_2}\frac{1}{[\text{morpholine}]} + \frac{1}{k_1K_T} \quad (3)$$

regardless of how much amine is present; see Figure 6. This value worked out at approximately 5.9×10^{-2} s^{-1} for morpholine in agreement with the value found for k_5K_T previously from eq 1.

From eq 3, the slope of the plot is equal to k_{-1}[Imid]/$k_1K_Tk_4$. Since k_1K_T has been determined from the intercept to be 5.9×10^{-2} s^{-1} and the imidazole is a known constant concentration of 0.05 M, the ratio for the relative reactivities of morpholine to imidazole on reaction with phenyl isocyanate, k_4/k_{-1}, was found to be 7.1, implying that morpholine is approximately seven times more reactive toward phenyl isocyanate than is imidazole.

Hydrolysis of Phenyl Isocyanate 22. The hydrolysis of **22** has been shown to be subject to general base catalysis by tertiary amines. Brønsted plots for such reactions show the point for water itself to be on these plots. It was suggested from this result that water is acting both as a nucleophile and as a base catalyst for the reaction.[7b] Castro et al.[7b] found no evidence, in unbuffered water solutions, for the preequilibrium formation of the hydrated isocyanate intermediate, previously believed to be the route taken. Our theoretical results discussed above provide a support for the view that water attack at the electrophilic carbon center is the rate-limiting transition-state structure involves at least a dimer of water. These earlier experimental studies also revealed, in agreement with our findings, that the environment has little or no effect on the transition-state structure.[20] The present work investigates the hydrolysis reaction over the complete water concentration range. The various concentrations of water were accomplished using acetonitrile as the cosolvent. The reaction was monitored by observing the increase in optical density, due to the formation of the carbamate, at wavelength λ = 282 nm and at 25 °C. Problems arose in the measurement of the hydrolysis reaction at low water concentrations, since the reaction half-life is very slow under these conditions. A technique was developed to remedy this. This method uses the idea that at high water concentrations the reaction with a small fixed amount of phenyl isocyanate is complete in a relatively short time and the total absorbance range for the reaction may be determined. Thus, a scale could be set up linking unit absorbance to phenyl isocyanate concentration. A consequence of performing the low water concentration reactions in the presence of a relatively high concentration of phenyl isocyanate is that the initial reaction is relatively fast and the initial reaction appears as a linear plot. The absorbance difference over a particular range can be correlated to concentration for the particular time interval, thus giving a value for $dC/dt(= x \cdot dA/dt)$. This slope is related to the amount of isocyanate added at the start of the reaction. From eq 4 it is now possible to determine the rate of hydrolysis at that water concentration. Determination of the observed rate, when this procedure is used, at high water and phenyl isocyanate concentrations indicates that the results obtained using the above method are quite consistent and accurate.

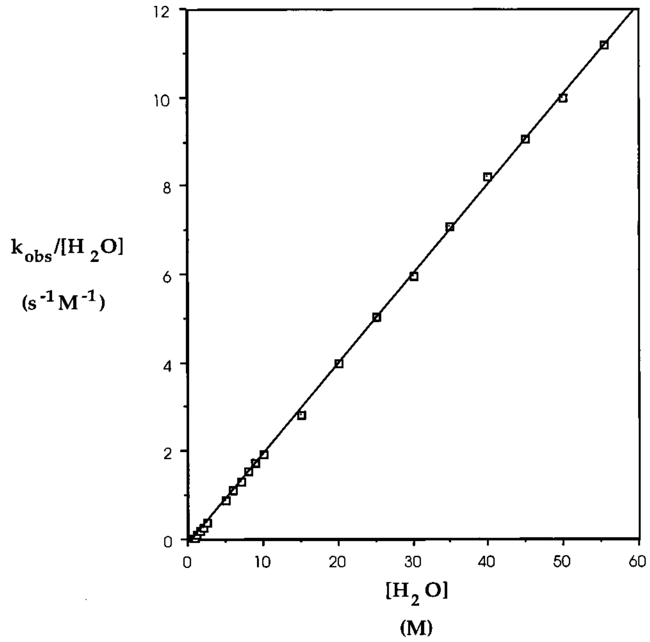


Figure 7. Plot of the observed rate over water concentration against water concentration for hydrolysis of phenyl isocyanate at 25 °C.

$$x\frac{dA}{dt} = \frac{dC}{dt} = k_{obs}[\text{PhNCO}]_{\text{In}} \quad (4)$$

A full account of the results is given in Table 9. A plot of the observed rate against water concentration shows a second-order dependence on water. The results confirm that two molecules of water are involved in the rate-determining step over the entire concentration range. This conclusion is corroborated from the positive slope in the plot of $k_{obs}/[H_2O]$ against $[H_2O]$, Figure 7. Since the plots both pass through or very close to the origin, this indicates that a monomer plays no significant role in the hydrolysis reaction. Also, since the plot of $k_{obs}/[H_2O]$ against $[H_2O]$ is a straight line with no noticeable upward curvature, over the entire concentration range, this suggests that higher polymers than the dimer of water make no appreciable contribution to the rate either. The analogous reaction involving the ketene also occurs through water dimers.[22]

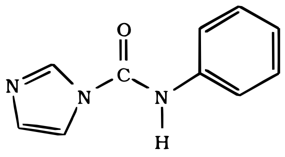
Concluding Remarks

In the present paper, a kinetic and mechanistic investigation of the solvent-catalyzed hydration of isocyanates has been undertaken. Both experimental and theoretical results show that the hydrolysis reaction should be understood by a chain of water molecules ($HN{=}C{=}O + n(H_2O) \rightarrow H_2NCOOH + (n-1)H_2O$, $n = 1-3$). For the simplest model isocyanate, two water molecules in the form of a water dimer seem to play the key role in neutral hydration, while a third water molecule may be needed to bridge the gap from the point of attack on the isocyanate to the water dimer. Water trimer has also recently been shown to be the preferred pathway in neutral hydration of carbon dioxide.[23] The role of catalyst is played by a dimer/trimer as such rather than by hydronium or hydroxide ions. Experimental results also imply a second-order dependence on water during its nucleophilic addition to phenyl isocyanate, over a wide concentration range. In this specific case, water oligomers higher than the dimer seem to make no appreciable contribution to the rate of the hydrolysis reaction. The nucleophilic addition occurs in a concerted way across the N═C bond of the isocyanate rather than across the C═O bond. Such a preferential reaction mechanism could be rationalized in terms of Fukui functions for both nucleophilic and electrophilic attack. Even though a charge separation occurs in the transition state, electrostatic effects of a highly polar solvent do not reduce substantially the energy barriers.

Experimental Details

General Methods. ^{1}H NMR spectra were recorded at 60 MHz. The solvent used was deuterated chloroform. Tetramethylsilane was used as internal reference in all cases. pH values were found using a combined pH glass electrode. Combustion analyses of compounds were carried out in the Microanalytical Laboratory, University College Dublin. Inorganic materials used for kinetic measurements were of AnalaR grade, where possible, and recrystallized if necessary. Solvents were HPLC grade and were dried, where required, using standard procedures. Acetonitrile was distilled from phosphorus pentoxide initially and then freshly distilled from calcium hydride as required. Diethyl ether was dried over and distilled from sodium, under dry nitrogen. AnalaR grades of the alcohols were dried and freshly distilled before use, by standard techniques.[24] Commercially available amines were purified: imidazole by recrystallization from dichloromethane and morpholine by distillation from calcium hydride. Phenyl isocyanate was purified every 2−3 days by refluxing over phosphorus pentoxide and then distilling under vacuum to free it from any of the hydrolyzed product.

Substrates. Imidazole (6.8 g, 0.1mol), in dry diethyl ether (150 mL), was added to a solution of phenyl isocyanate (11.9 g, 0.1mol), which was dissolved in dry diethyl ether (50 mL) with stirring. A white solid precipitated and was removed by filtration under dry nitrogen. The urea (15.5 g, 82.7%), **a**, was washed with dry diethyl ether and was used without further purification. A melting point of 111−112 °C was recorded for the urea, which is in agreement with literature values:[25] δ_H (60 MHz, $CDCl_3$) 7.02−7.64 (7H, m, aryl), 8.36 (1H, s, N═CH), 9.76 (1H, bs, NH). Anal. Calcd for $C_{10}H_9N_3O$: C, 64.15; H, 4.86; N, 22.44. Found: C, 64.08; H, 4.81; N, 22.56.



1-Phenylcarbamoylimidazole **(20)**

The urea could be stored over P_2O_5 in vacuo for a number of weeks without formation of the diphenylurea. After this time, however, some decomposition took place, and so a fresh sample of the substrate was prepared every 2−3 weeks for use in kinetic studies.

Kinetic Method. Repetitive scans were performed to determine suitable wavelengths for rate measurements. Rates were measured at 25 ± 0.1 °C, unless otherwise stated.

Urea Hydrolysis Experiments. A number of 50% ionized imidazole buffer solutions were prepared from a stock 0.2 M imidazole solution (1.36 g, 0.02 mol of imidazole, 1 mL of 1 M HCl, and 7.455 g, 0.1 mol of KCl made up to 100 mL with water). Usually, a further dilution of this solution, to 2×10^{-2} M, was made using a 1 M KCl solution. Typical solutions prepared from this dilution were as follows: 5×10^{-4}, 8×10^{-4}, 2.7×10^{-3} M, 5.4×10^{-3}, 8.1×10^{-3}, 10.9×10^{-3}. A morpholine stock solution was similarly prepared. Dilutions of this were as follows: 2.5×10^{-3}, 5.0×10^{-3}, 7.5×10^{-3}, 1.0×10^{-2}, 1.25×10^{-2} M. A 0.1 M solution of 1-(phenylcarbamoyl)imidazole was prepared by dissolving 9.36×10^{-2} g of the urea in dry acetonitrile to a volume of 5 mL. Aliquots (2 mL) of the imidazole-buffered solution, in a 1 cm quartz cell, were left to equilibrate at 30 °C in the cell compartment of the spectrometer for 15 min. Runs were performed at 250 nm by injecting 3 μL of the 0.1 M solution of the urea into the various imidazole solutions and monitoring the change in absorbance. These experiments were also carried out at 25 °C. To a low concentration imidazole buffer solution were added a 20 μL sample of a morpholine solution and 3 μL of the urea solution, again while the buffer solution was equilibrated at 30 °C and at 250 nm. This was repeated for all the morpholine solutions.

Phenyl Isocyanate Solvolysis Reactions. High-concentration water solutions were prepared by diluting pure water with acetonitrile. More dilute solutions were prepared by making dilutions of these with acetonitrile. A 0.1 M solution of phenyl isocyanate was prepared by dissolving approximately 0.119 g of the isocyanate in dry acetonitrile to a volume of 10 mL. A fresh solution was prepared daily. The different water solutions (2 mL) were again kept at 25 °C for 15 min. At a wavelength of 282 nm, the reaction was initiated with addition of phenyl isocyanate. Normally, 10 μL of the 0.1 M isocyanate solution or either a 1 or 2 μL aliquot of the pure isocyanate were added to the more concentrated water solutions, and a 2 or 15 μL sample of the pure isocyanate was added to the dilute water solutions. A similar procedure was followed for the alcohols, 2-propanol and cyclohexanol.

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[22] (a) Allen, B. M.; Hegarty, A. F.; O'Neill, P.; Nguyen, M. T. *J. Chem. Soc., Perkin Trans. 2* **1992**, 927. (b) Nguyen, M. T.; Hegarty, A. F. *J. Am. Chem. Soc.* **1984**, *106*, 1552.

[23] Nguyen, M. T.; Raspoet, G.; Vanquickenborne, L. G.; Van Duijnen, Ph. T. *J. Phys. Chem.* **1997**, *101*, 1, 7379.

[24] Vogel, A. I. *Textbook on Practical Organic Chemistry*, 4th ed.; (reviewed by Furniss, B. S.); Langman: London, 1978.

[25] Gopalakrishnan, G.; Hogg, J. L. *J. Org. Chem.* **1983**, *48*, 2038.