Synergism of Catalysis and Reaction Center Rehybridization. An ab Initio Study of the Hydrolysis of the Parent Carbodiimide

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Over the past forty years, the chemistry of carbodiimides has proliferated from reagents for peptide and nucleotide syntheses[1,2] to include compounds with important roles in a wide array of chemical applications.[3] The most important reactions of carbodiimides all involve nucleophilic attack, and the nucleophilic addition of water to dicyclohexylcarbodiimide is widely used for dehydration.[4] We are particularly interested in the hydrolysis of carbodiimides for their potential role as reactive intermediates in guanine deamination.[5] There have been a few experimental studies of the addition of carboxylic acids to dicyclohexylcarbodiimide,[6] but to our knowledge, there have not been any studies of the addition of water to carbodiimide. Computational studies were performed on the parent carbodiimide, $HN=C=NH$, but they focused on the equilibrium structure,[7,8] the N-inversion,[9] and the torsional–rotational dynamics.[10] We report here the results of an ab initio molecular orbital study into the kinetics of the hydrolysis of the parent carbodiimide. The study shows that the catalysis by a second water molecule causes electronic relaxation that facilitates further catalysis due to H-bonding with the environment.

All geometries were optimized and vibrational analyses were performed at the MP2(full)/6-31G* level.[11,13] Populations were determined using the natural bond orbital (NBO) method.[12] The relative energies include vibrational zero-point energy corrections which were scaled by the empirical value 0.9646.[14] Higher level G2 and QCISD(T)(fc)/6-311+G(3df,2p) energies were computed for the single water hydrolysis of carbodiimide, and they gave approximately the same relative energy values for the activation barriers as the MP2(full)/6-31G* calculations. For example, the ΔE_0 activation energies computed at the MP2(full)/6-31G*, G2, and QCISD(T)(fc)/6-311+G(3df,2p) levels are 44.8, 45.4, and 46.0 kcal/mol, respectively.

The hydrolysis of the parent carbodiimide, $HN=C=NH$, should be similar to the hydrolyses of carbon dioxide,[15] ketene,[16] and keteneimine[17] since these heterocumulenes are isoelectronic. Theoretical studies into the hydration of CO_2, $H_2C=C=O$, and $H_2C=C=NH$ showed that consideration of a second water molecule resulted in catalysis. Similar results were also obtained for the hydrolysis of SO_3.[18] Obviously, the catalysis arises in all of these cases from alleviation of steric strain in going from a four-membered to a six-membered cyclic transition-state structure. Our calculations of the van der Waals complexes and transition states for the one- and two-water hydrolyses of the parent carbodiimide (Figure 1, **1**–**4**) resulted in activation energies of 43.7 and 32.1 kcal/mol, respectively (Figure 2). Thus, the inclusion of a second water molecule results in a catalysis of 11.6 kcal/mol, and this result can be rationalized just as in the case of the other heterocumulenes and SO_3.[15–18]

The consideration of the effect of a third water molecule was the next logical step. The placement of a third water molecule is not a trivial matter, and we initially considered two possibilities. The first option involved placement of the water at the site of proton transfer (Scheme 1, **A**). We quickly judged **A** to be catalytically of little relevance because it is well-known that there is little energy gain in going from a six- to an eight-membered cyclic transition state. In fact, this was recently illustrated for the hydrolysis of carbon dioxide,[19] where the addition of a third water molecule to the site of proton transfer reduced the activation energy merely by another 2.6 kcal/mol. The second option, and the less intuitive yet the more interesting one, involved the placement of the third water molecule as shown in **B**[20] (Scheme 1). In this scenario, the transition-state structure still involves proton transfer through a six-membered ring (thick dashed lines in **B**), but the C–O bond forming O-atom is H-bonded to another water molecule (boxed and with thin dashed lines in **B**) which is not taking part in the proton transfer.

The logic behind recognizing the importance of structure **B** relates to hybridization effects on charge relaxation associated with the activation barriers. Comparison of **2** and **4** shows that the consideration of a second water molecule results in a transition-state structure in which bond formation between the adding water (H_2O^A) and the C-atom ($C-O^A$) has progressed more quickly while the H-transfer (H^T) has slowed; the $C-O^A$ distance decreases by 0.129 Å, and the O^A-H^T distance decreases by 0.068 Å. Note also that the rehybridization of the C-atom has progressed more in **4** than in **2** and this is illustrated by the $\angle(N-C-N)$ angles of 147.7° for **2** and 139.9° for **4**.

These *structural* differences between **2** and **4** have important *electronic* consequences during activation for the $=NH$ group that remains an imine during the reaction (NH^R) and the O^A-H group where the H-atom remains bonded to O^A during the reaction (O^A-H^R). Hybridization concepts suggest that an $=NH$ group in a diimide will be less negative than in an imine.[21a] Therefore, we would predict that the change in the charge of the NH^R group would be more negative for the process **3 → 4** than for **1 → 2**. This prediction was confirmed by natural population analysis of **1**–**4** which revealed $\Delta q(NH^R)$ values of +0.01 for **1 → 2** and −0.19 for **3 → 4** (Table 1). Similarly, in the course of the addition

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(13) We examined the hydrolysis of CO_2 involving two water molecules at the MP2(full)/6-31G* and MP2(full)/6-311G** levels and determined activation enthalpies at 0 K of 31.8 and 34.3 kcal/mol, respectively. There is close agreement between these levels, and the magnitude of the effect we are discussing greatly exceeds the theoretical model dependency.

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(20) The imine is Z-configured in **A**, but it is E-configured in **B** to take advantage of the H-bonding interaction with water. The intrinisic Z-preference energy is very small.

(21) (a) NBO calculations on MP2(full)/6-31G* optimized structures show that the population of the $=NH$ group in carbodiimide is −0.40, while it is −0.52 in isourea. (b) Similar calculations show that the charge of an −OH group is −0.48 in water, while it is −0.27 in isourea.
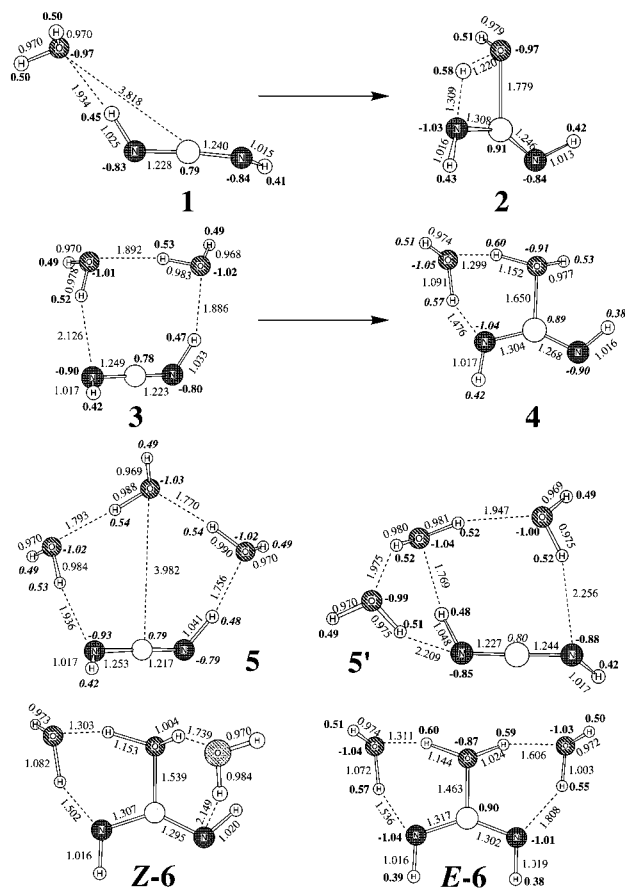
Figure 1. Precoordination complexes and transition-state structures for the one-, two-, and three-water hydrolyses of carbodiimide. Distances are in angstroms, and charges are given in boldface.
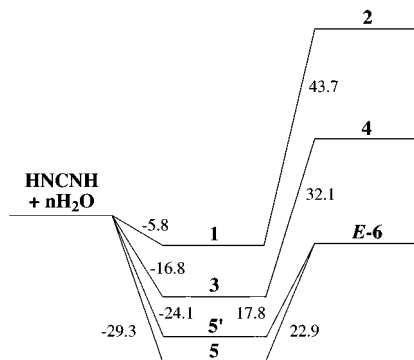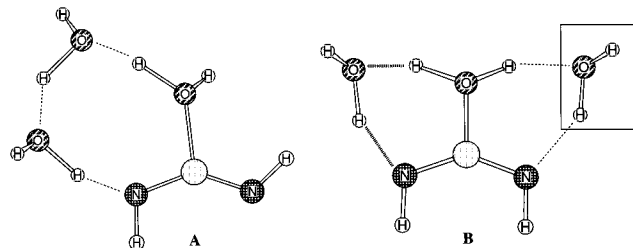

Figure 2. Potential energy surface diagrams for the activation barriers of the hydrolyses of carbodiimide ($n = 1-3$). All energies are given in kcal/mol as computed at the MP2(full)/6-31G*//MP2(full)/6-31G* level with inclusion of corrected[14] VZPE values.

Scheme 1

reaction, a water molecule H−OH is converted into an alcohol R−OH, and one can expect that the OH-group in the alcohol will be overall less negative than in water.[21b] This electronic relaxation should be manifested more in the process **3 → 4** than for **1 → 2**, and the NBO analyses (Table 1) indeed show a greater

Table 1.   Change in Atomic Charges

	O^A	H^R	NH^R	NH^A	C	H^T
1 → 2	+0.00	+0.01	+0.01	−0.22	+0.12	+0.08
3 → 4	+0.11	+0.04	−0.19	−0.14	+0.11	+0.07, +0.05
5 → E-6	+0.16	+0.10	−0.32	−0.14	+0.11	+0.06, +0.04
5′ → E-6	+0.17	+0.07	−0.17	−0.28	+0.10	+0.08, +0.06

loss of electron density in O^A-H^R for the former reaction. Moreover, this decrease of electron density occurs both for the O^A-atom ($\Delta q = +0.00$ for **1 → 2** and +0.11 for **3 → 4**) and for the H^R-atom ($\Delta q = +0.01$ for **1 → 2** and +0.04 for **3 → 4**).

The electronic relaxations during the activation processes **1 → 2** and **3 → 4** clearly demonstrate an increased propensity for H-bonding interactions of both the $O^A H^R$- and the NH^R-groups in the latter case. The $O^A H^R$-group is a better H-bond donor because the negative O-charge is reduced and because the positive charge on H is increased. The NH^R-group is a better H-bond acceptor because it is more negatively charged. These effects should be felt in any H-bonding environment, and the three-water hydrolysis can be seen as the special case in which the H-bonding to both sites is accomplished by one water molecule (**B**).

The optimized van der Waals complexes, **5** and **5′**, and the transition-state structures, **Z-6** and **E-6**, for the three-water hydrolysis are shown in Figure 1. **Z-6** and **E-6** lead to geometric isomers about the evolving imine bond, and it is this stereochemical attribute that is considered in naming these structures. **Z-6** and **E-6** show the same H-bonding pattern, **Z-6** is 8.8 kcal/mol less stable than **E-6**, and, therefore, it is the transition state **E-6** that we are primarily concerned with here. Complex **5** is the more stable of the two van der Waals complexes, but **5′** is probably an intermediate between **5** and **6** since the H-bonding motif in **6** is like that in **5′**. Figure 2 shows that the addition of the third water molecule, as described by **B**, does lead to a lower energy of activation for the hydrolysis; the activation barrier dropped to 22.9 kcal/mol (Figure 2), and this is a catalysis of 9.2 or 20.8 kcal/mol with respect to the two- or single-water hydrolyses, respectively. We also computed the activation free energies for standard conditions and obtained barriers of 44.3, 34.4, and 26.2 kcal/mol, respectively, for the one-, two- and three-water hydrolyses which result in catalytic effects of 8.2 and 18.1 kcal/mol. This result illustrates that alleviation of steric strain in the transition state is not the only process involved in the catalysis of the hydration of HN=C=NH. It is equally important to consider the effects of the charge relaxation along the activation path of groups that are not "directly" involved in catalysis. Note that the $C-O^A$ bond in **E-6** is even shorter than that in **4** and, in fact, all parameters indicate that all the structural and electronic changes associated with the processes **1 → 2** and **3 → 4** clearly are enforced for **5 → E-6**. The catalytic effects of the second and third water molecules truly are synergetic.

This kind of synergism between the catalysis and the reaction center rehybridization may also play a key role in the electronic relaxations along the activation paths in the hydrolyses of the previously studied heterocumulenes. Considering the biological importance of the hydrolysis of CO_2 with respect to human carbonic anhydrase[22] the environmental significance of the hydrolyses of SO_3 with regard to acid rain,[23] and the modeling of proton transfers in enzymes,[24] reinvestigations of the hydrolyses of these molecules seem warranted.

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