Synergism of Catalysis and Reaction Center Rehybridization in Nucleophilic Additions to Cumulenes: The One-, Two- and Three-Water Hydrolyses of Carbodiimide and Methyleneimine**

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Abstract: The results of a theoretical study of the one-, two- and three-water hydrolyses of carbodiimide and the one- and two-water hydrolyses of methyleneimine are presented. All structures were optimized and characterized at the MP2(full)/6-31G* level of theory. Energies for the one-water hydrolysis of carbodiimide were determined at numerous higher levels of theory, up to the QCISD(T)(fc)/6-311+G(3df,2p)//MP2-(full)/6-31G* level. The $\Delta E_0(\Delta G_{298})$ activation barriers for the rate-determining steps of the one-, two- and three-water hydrolyses of carbodiimide, respectively, are 44.8 (46.3), 29.3 (32.3) and 22.9 (26.2) kcal mol^{-1} at the MP2(full)/6-31G* level. The consideration of a second water molecule catalyzes the hydrolysis by 15.5 kcal mol^{-1} on the E_0 surface and by 14.0 kcal mol^{-1} on the G_{298} surface with respect to the one-water hydrolysis. Placement of a third water molecule opposite the site of proton transfer catalyzes the reaction by an additional 6.4 kcal mol^{-1} on the E_0 surface and by 6.1 kcal mol^{-1} on the G_{298} surface. The catalytic effect of the third water molecule results from the synergistic effects of rehybridization and charge relaxation in the transition state. The charge relaxation in the transition state is illustrated through natural population analysis calculations on the precoordination complexes and the transition state structures. We also consider the placement of the third water molecule in the proton transfer chain and we show this to be of little catalytic relevance. The activation barriers determined for the one- and two-water hydrolyses of methyleneimine are $\Delta G_{298} = 51.9$ and $\Delta G_{298} = 35.5$ kcal mol^{-1}, respectively, and they are larger than for carbodiimide. The results are compared with the hydrolyses of carbon dioxide and formaldehyde.

Keywords: ab initio calculations · carbodiimide · hydrolysis · population analyses · reaction mechanisms

Introduction

Addition reactions to alkenes[1] and various heteroderivatives of the type $R_2C{=}X$ (X = O, S, NR, PR)[2–5] were studied in great detail in the past. In contrast, much less attention has been given to the associated cumulenes where the methylene fragment is replaced by a =C= unit. Among the cumulenes that contain only N and O as the heteroatom (see below), the studies have focused on the hydrolysis of carbon dioxide,[6, 7] the hydrolysis and nucleophilic additions to ketenes[8] and keteneimines,[9] and the molecular and electronic properties of carbodiimide.[10–12]

HN=C=NH Carbodiimide	HN=C=O Isocyanate
O=C=O Carbon dioxide	$H_2C{=}C{=}O$ Ketene
$H_2C{=}C{=}CH_2$ Allene	$H_2C{=}C{=}NH$ Keteneimine

Over the past forty years the chemistry of carbodiimides has proliferated from reagents for peptide and nucleotide syntheses[13, 14] to include many important roles in a wide array of chemical applications.[15] Carbodiimides are used in the formation of heterocycles through cycloaddition reactions, they have broad utility in biochemical processes, and they are important in polymer chemistry.[15] The most important reactions of carbodiimides all involve nucleophilic attack across one of the imine bonds and the nucleophilic addition of water to dicyclohexylcarbodiimide is widely used for dehydration.[16] We are particularly interested in the hydrolysis of carbodiimides for their potential role as reactive intermediates in guanine deamination.[17]

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In spite of the widespread interest in carbodiimides, there have been surprisingly few mechanistic studies on its addition chemistry. There have been a few experimental studies of the addition of carboxylic acids to dicyclohexylcarbodiimide,[18] but, to our knowledge, there have not been any studies of the addition of water to carbodiimide. An even more astonishing fact is that, until recently, theoreticians have overlooked the subject. Computational studies were performed on the parent carbodiimide, HN=C=NH, but they focused on the geometry and spectroscopic properties of the equilibrium structure,[10] the electronics of the N-inversion,[11] the torsional–rotational dynamics,[12] and the electric dipole polarizability.[19]

Theoretical studies of the hydration of CO_2,[6] $H_2C{=}C{=}O$,[8] and $H_2C{=}C{=}NH$,[9] showed that consideration of a second water molecule resulted in catalysis with respect to the single water hydration. Similar results also were obtained for the hydrolyses of SO_3[20] and SO_2.[21] 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. Here, we report the results of an ab initio molecular orbital study of the one-, two- and three-water hydrolyses of carbodiimide. These studies led us to discover the synergistic effect of the third water molecule placed away from the site of proton transfer and we communicated on the catalytic effect of the third water in the rate-determing step.[22] In the present article, we report the results of our theoretical study of the kinetics and the thermodynamics of both reaction steps of the hydrolysis of the parent carbodiimide; the addition reaction to form isourea and its tautomerization to urea. The kinetics of the isourea formation is contrasted to results of a recent study by Nguyen and co-workers[23] and also is compared to the carbonic acid formation. We have also calculated the kinetics for the water addition to methyleneimine to ascertain the effects of conjugation in the hydrolysis of cumulenes and we will draw comparisons to the hydrolyses of carbon dioxide and formaldehyde.

Computational Methods

All molecules, precoordination complexes and transition states were optimized with the inclusion of electron correlation using the MP2 method in conjunction with the 6-31G* basis set. All electrons, including the core, were considered in the correlation treatment. Each structure was characterized by analytical frequency calculations. Minima on the potential energy surface were characterized by the presence of no imaginary frequencies and transition states had one imaginary frequency.[24]

A better estimation of the relative energies was obtained by calculating energies with the G1 and G2 methods for the one-water hydrolysis of carbodiimide. The G1 and G2 methods were devised by Pople to approximate QCISD(T)(fc)/6-311+G(2df,p) and QCISD(T)(fc)/6-311+G(3df,2p) energies[25] at relatively moderate time and computational cost. We also explicitly calculated energies at the QCISD(T)/6-311+G(2df,p)//MP2(full)/6-31G* and QCISD(T)/6-311+G(3df,2p)//MP2(full)/6-31G* levels for the one-water hydrolysis of carbodiimide as a means of evaluating how the G1 and G2 methods performed in predicting these values.

We report both E_0 and G_{298} energy surfaces. The G_{298} values were determined by the methods outlined by Forseman and Frisch.[26] All thermodynamic data were obtained at the MP2(full)/6-31G* level. The ΔG_{298} values for the G1, G2, QCISD(T)/6-311+G(2df,p)//MP2(full)/6-31G* and QCISD(T)/6-311+G(3df,2p)//MP2(full)/6-31G* levels used the thermodynamic MP2(full)6-31G* data as well.

The catalytic effect described in this paper is explained by the charge relaxation in proceeding from the pre-coordination complexes to the transition states. The atomic charges for the pre-coordination complexes and the transition states of the one-, two-, and three-water hydrolyses of carbodiimide were calculated using the natural bond orbital method developed by Weinhold and Glendening.[27]

Calculations were performed on the University of Missouri's Silicon Graphics Power Challenge L cluster using Gaussian 94.[28]

Results and Disscusion

One-water hydrolysis of carbodiimide

The MP2(full)/6-31G* optimized structures for the single water hydrolysis of carbodiimide are shown in Figure 1. The most stable van der Waals complex between water and carbodiimide is structure **1a** where the O-atom of water is engaged in a hydrogen bond with carbodiimide. Nucleophilic attack of the water molecule on the carbodiimide C-atom leads to the four-membered transition state structure **2**. The first step of the addition of H_2O to $C(NH)_2$ is complete upon full proton transfer from O to N to form isourea *E*-**3**. Tautomerization of *E*-**3**, via transition state structure **4**, leads to urea **5**.

An exhaustive search for all of the pre-coordination structure between H_2O and $C(NH)_2$ (Figure 2) showed two minima, **1a** and **1b**. Structure **1a** is the more stable of the two by $\Delta E_0 = 1.0\,\text{kcal mol}^{-1}$ at the highest level of theory, QCISD(T)(fc)/6-311+G(3df,2p)//MP2(full)/6-31G*. On the G_{298} surface **1a** is more stable by $1.3\,\text{kcal mol}^{-1}$. If the van der Waals complex of water and carbodiimide is constrained to have C_2 symmetry (**1c**, Figure 2), as is the case for water and CO_2,[6a] a structure with two imaginary frequencies is obtained and it is $4.2\,\text{kcal mol}^{-1}$ less stable at MP2/6-31G*.

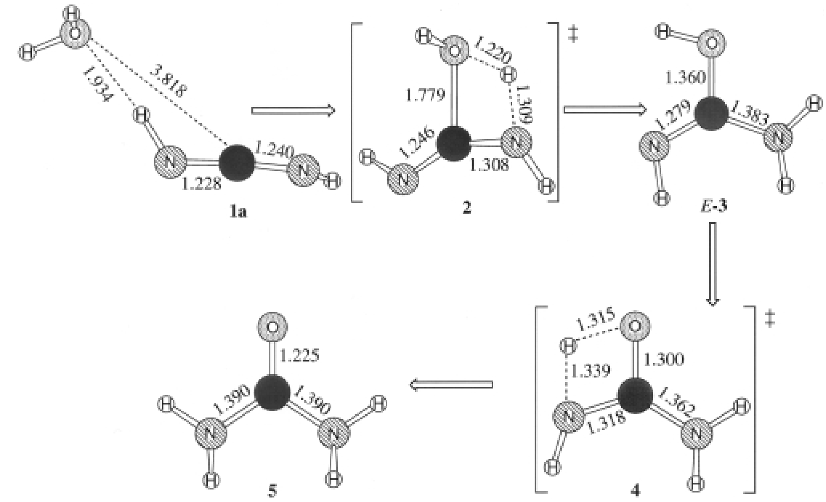

Figure 1. MP2(full)/6-31G* optimized structures for the one-water hydrolysis of carbodiimide.

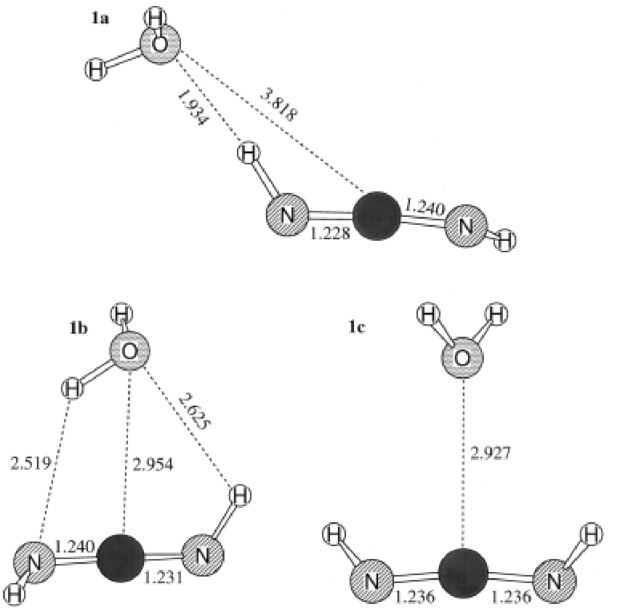

Figure 2. MP2(full)/6-31G* optimized structures for three possible van der Waals complexes between carbodiimide and water.

There are two minima for isourea **3**, one with an *E*-stereochemistry and the other with *Z*-stereochemistry (Figure 3). Isourea *E*-**3** is more stable than the *Z*-isomer by $\Delta E_0 =$ 3.2 kcal mol^{-1} and $\Delta G_{298} = 3.27$ kcal mol^{-1} at the highest level of theory. Besides being the more stable minimum, we show structure *E*-**3** in Figure 1 because it has the geometry that naturally follows the water addition via transition state **2**. One may also envision the existence of two more isomers of **3**, where the imine-H atoms in the *E*- and *Z*-isomers are rotated 180°. A search for these two structures, however, led to *E*-**3** and *Z*-**3**.

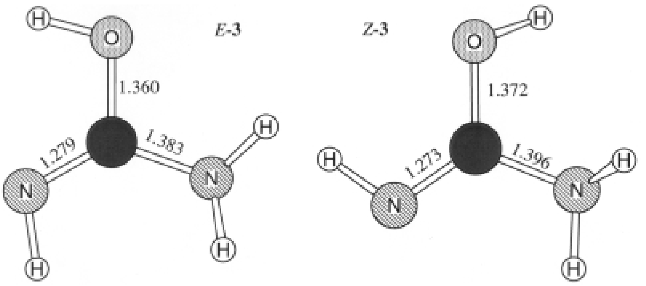

Figure 3. MP2(full)/6-31G* optimized structures of the two C=N geometrical isomers of the isourea intermediate in the one-water hydrolysis of carbodiimide.

The total energies, thermodynamic data, and ΔE_0 and ΔG_{298} values for structures **1**–**5** are collected in Table 1. The E_0 and G_{298} surfaces for the single water hydrolysis of carbodiimide are illustrated in Figure 4 at the MP2(full)/6-31G* and QCISD(T)(fc)/6-311+G(3df,2p) levels of theory.

The ΔE_0 activation barrier for the first step in the hydrolysis of carbodiimide is 46.0 kcal mol^{-1} at the best level of theory. At the same level, the activation barrier for the second step is 33.0 kcal mol^{-1} and the overall reaction energy is −33.5 kcal mol^{-1}. The inclusion of thermal motion and entropy increases the first activation barrier to $\Delta G_{298} =$ 47.5 kcal mol^{-1} at the QCISD(T)(fc)/6-311+G(3df,2p) level of theory. The second activation barrier and the overall reaction energy on the G_{298} surface, however, are both reduced to 29.6 and −25.3 kcal mol^{-1}, respectively.

Two-water hydrolysis of carbodiimide

The two-water hydrolysis of carbodiimide has a main advantage over the single-water hydrolysis because of the energetic stability gained from being able to assume a six-membered

Table 1. Total energies, thermodynamic data and ΔE_0 and ΔG_{298} relative energies for the single-water hydrolysis of carbodiimide (structures **1**–**5**).[a]

Theory	**1a**	**1b**	**2**	*E*-**3**	*Z*-**3**	**4**	**5**
MP2(full)/6-31 G*							
E_{total}	−224.562026	−224.559555	−224.490657	−224.592558	−224.587389	−224.541671	−224.622066
E_{therm}	40.27	40.20	37.71	43.07	43.08	39.62	43.58
S	81.12	79.81	67.52	66.07	65.98	66.20	64.71
ΔE_0	0.00	1.55	44.79	−19.16	−15.92	12.77	−37.68
ΔG_{298}	0.00	1.87	46.27	−11.87	−8.60	16.56	−29.48
G1							
E_{total}	−224.889331	−224.887713	−224.817182	−224.910439	−224.904893	−224.864676	−224.934618
ΔE_0	0.00	1.02	45.27	−13.25	−9.77	15.47	−28.42
ΔG_{298}	0.00	1.33	46.76	−5.96	−2.45	19.26	−20.22
QCISD(T)(fc)/6-311+G(2 df,p)							
E_{total}	−224.865531	−224.863691	−224.792582	−224.893662	−224.888436	−224.841839	−224.918263
ΔE_0	0.00	1.15	45.78	−17.65	−14.37	14.87	−33.09
ΔG_{298}	0.00	1.47	47.26	−10.37	−7.05	18.66	−24.89
G2							
E_{total}	−224.893083	−224.891533	−224.820673	−224.914692	−224.909414	−224.868011	−224.938917
ΔE_0	0.00	0.97	45.44	−13.56	−10.25	15.73	−28.76
ΔG_{298}	0.00	1.29	46.93	−6.27	−2.93	19.52	−20.56
QCISD(T)(fc)/6-311+G(3 df,2 p)							
E_{total}	−224.884987	−224.883391	−224.811665	−224.913819	−224.908665	−224.861168	−224.938346
ΔE_0	0.00	1.00	46.01	−18.09	−14.86	14.95	−33.48
ΔG_{298}	0.00	1.32	47.50	−10.81	−7.54	18.74	−25.28

[a] Total energies in hartrees; thermal energy (E_{therm}), ΔE_0 and ΔG_{298} relative energies in kcal mol^{-1}; entropy (S) in cal mol^{-1} K^{-1}. All ΔG_{298} values use the MP2(full)/6-31G* thermodynamic data. Relative energies with respect to **1a**.

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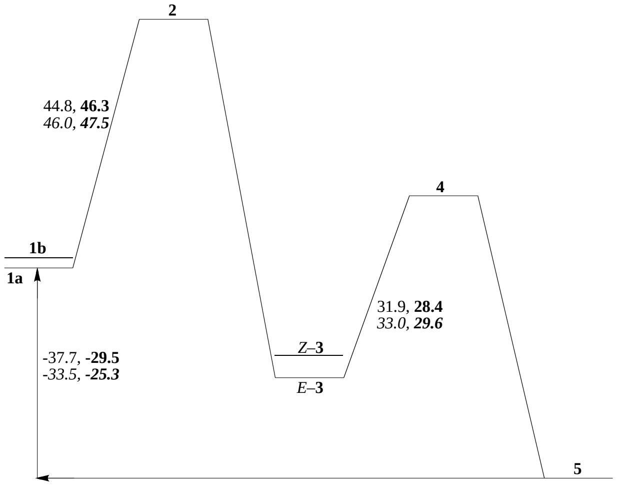
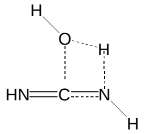
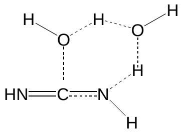


Figure 4. Potential energy surface diagram for the one-water hydrolysis of carbodiimide. MP2(full)/6-31G* values on top, QCISD(T)(fc)/6-311+G(3df,2p) values on bottom and italicized. ΔE_0 values in plain text, ΔG_{298} values in bold text.

ring proton-transfer transition state. This is illustrated below where the transition states for the one- (structure **A**) and two-water (structure **B**) hydrolyses of carbodiimide are shown. The MP2(full)/6-31G* optimized structures for the two-water



A



B

hydrolysis of carbodiimide are pictured in Figure 5. There is only one pre-coordination complex, **6**, for the two-water hydrolysis. Nucleophilic attack leads to transition state structure *E*-**7**. Structure *E*-**7** has an isomer *Z*-**7** (Figure 6) that is less stable by $\Delta E_0 = 4.0$ kcal mol^{-1} and $\Delta G_{298} = 2.2$ kcal mol^{-1}. The product of the first step in the two-water hydrolysis of carbodiimide is a water-solvated isourea.

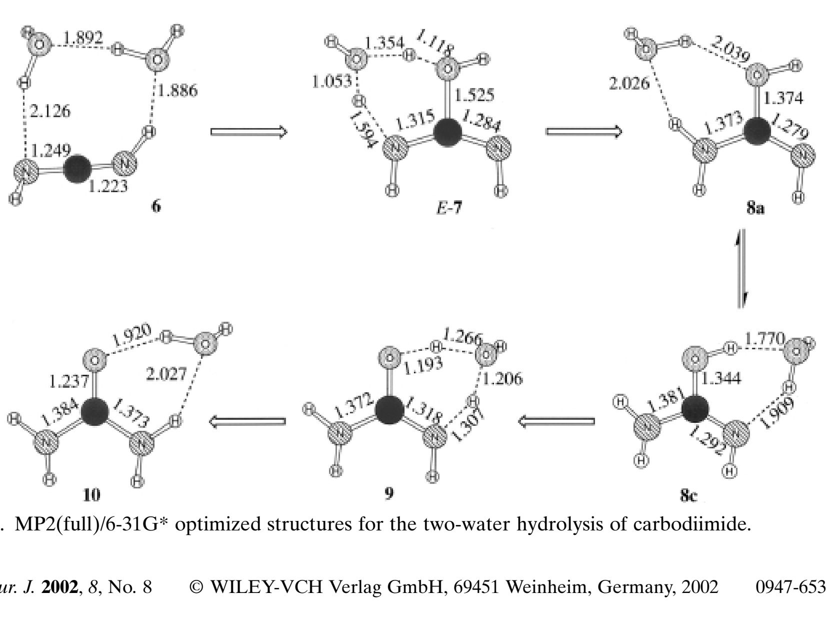


Figure 5. MP2(full)/6-31G* optimized structures for the two-water hydrolysis of carbodiimide.

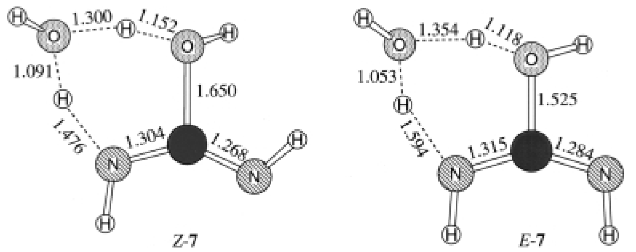


Figure 6. MP2(full)/6-31G* optimized structures for the two possible transition state structures in the two-water hydrolysis of carbodiimide.

Given the two possible transition state structures *E*-**7** and *Z*-**7**, one may be tempted to only consider the two intermediates **8a** and **8b** (Figure 7). The structure that naturally follows from *E*-**7** is **8a**, and the structure that follows *Z*-**7** is **8b**. However, structure **8c** is the most pertinent structure of the solvated isourea with a view to the six-membered tautomerization transition state **9**. The final product of the two-water hydrolysis of carbodiimide is a mono-hydrated urea, **10**.

The MP2(full)/6-31G* energies for the two-water hydrolysis of carbodiimide are collected in Table 2 and schematic E_0 and G_{298} surfaces are shown in Figure 8. The ΔE_0 activation barrier for the first step of the reaction is 29.3 kcal mol^{-1} and the ΔG_{298} barrier is 32.3 kcal mol^{-1}. This constitutes a catalytic effect of 15.5 kcal mol^{-1} on the E_0 surface and of 14.0 kcal mol^{-1} on the G_{298} surface with respect to the one-water hydrolysis. The activation barrier for the second step of the two-water hydrolysis of carbodiimide is very small, only $\Delta E_0 = 0.3$ kcal mol^{-1}. On the G_{298} surface the second transition state does not even exist and there is no activation barrier with respect to **8c**. The inclusion of thermal motion and entropy makes transition state **9** 2.9 kcal mol^{-1} more stable than **8c**. The magnitude of the activation energy of the second step depends on the reference point, as was the case for the activation barrier of the first step. Structure **8c** is the least stable of the three calculated isourea intermediates. If we calculated the activation barrier of the second step with **8a**, the most stable intermediate, the ΔE_0 value would be 4.8 kcal mol^{-1} and the ΔG_{298} value would be 2.9 kcal mol^{-1}. Regardless of the intermediate we choose as a reference, the consideration of a second water molecule in the hydrolysis of carbodiimide results in a large catalytic effect on the second step, up to 31.7 kcal mol^{-1} on the E_0 surface with **8c** as the reference. The overall reaction energy for the two-water hydrolysis of carbodiimide is -23.5 kcal mol^{-1} on the E_0 surface and -17.5 kcal mol^{-1} on the G_{298} surface.

The reaction energy and the kinetics of the hydrolysis of carbon dioxide are markedly different than for carbodiimide. The hydrolysis of carbon dioxide is a one-step process and the

Table 2. Total energies, thermodynamic data and ΔE_0 and ΔG_{298} relative energies for the two-water hydrolysis of carbodiimide (structures **6**–**10**).[a]

Molecule	**6**	*Z*-**7**	*E*-**7**	**8a**
E_{total}	– 300.783856	– 300.730902	– 300.737202	– 300.808141
E_{therm}	58.26	55.24	56.59	60.78
S	89.55	75.52	73.99	81.82
ΔE_0	0.00	33.23	29.28	– 15.24
ΔG_{298}	0.00	34.40	32.25	– 10.42
	8b	**8c**	**9**	**10**
E_{total}	– 300.802687	– 300.800986	– 300.800540	– 300.821310
E_{therm}	60.57	60.99	56.39	61.43
S	82.77	78.29	73.43	80.16
ΔE_0	– 11.82	– 10.75	– 10.47	– 23.50
ΔG_{298}	– 7.48	– 4.66	– 7.53	– 17.53

[a] Total energies in hartrees; thermal energy (E_{therm}), ΔE_0 and ΔG_{298} relative energies in kcal mol^{-1}; entropy (S) in cal mol^{-1}K^{-1}. Relative energies with respect to **6**.

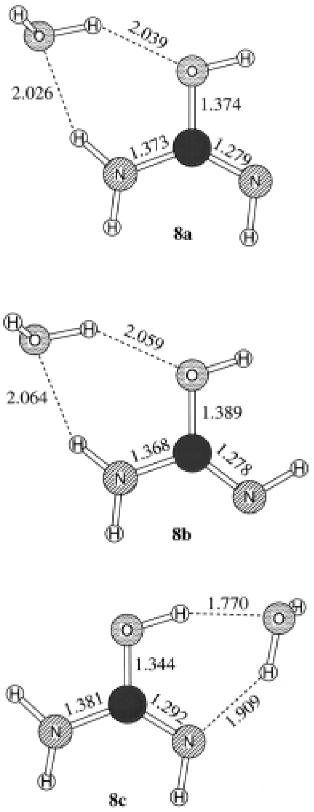


Figure 7. MP2(full)/6-31G* optimized structures for the three possible hydrated isourea intermediates in the two-water hydrolysis of carbodiimide. Structures **8a** and **8c** are *E*-configured about the C=N bond and structure **8b** is *Z*-configured.

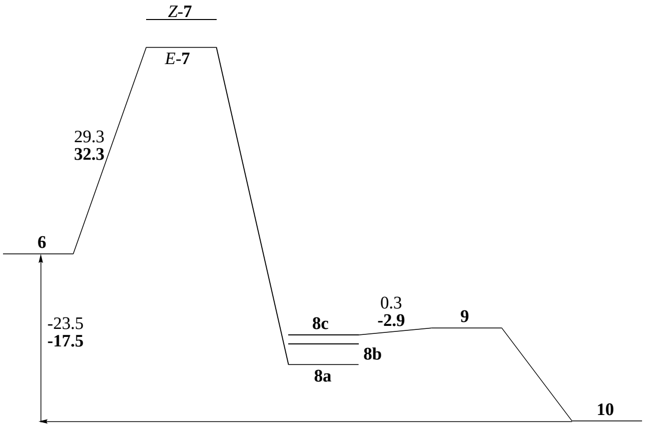
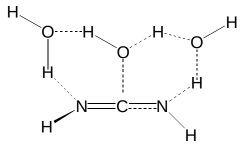


Figure 8. MP2(full)/6-31G* Potential energy surface diagram for the two-water hydrolysis of carbodiimide. ΔE_0 values in plain text, ΔG_{298} values in bold text.

overall reaction energy is endothermic by 6.4 kcal mol^{-1} at the MP4/6-31G**//HF/6-31G** level.[6b] The activation barrier for the one-water hydrolysis of carbon dioxide is $\Delta H_0 =$ 51.2 kcal mol^{-1} at the QCISD(T)/6-31G**//MP2/6-31G** level of theory[6a] and this is slightly larger than the activation barrier for the one-water hydrolysis of carbodiimide. The activation barrier for the two-water hydrolysis of carbon dioxide is $\Delta H_0 = 32.5$ kcal mol^{-1} at the QCISD(T)/6-31G**// MP2/6-31G** level[6a] and this too is slightly larger than the respective value for carbodiimide. The catalytic effect of the second water in the hydrolysis of carbon dioxide is $\Delta H_0 =$ 18.7 kcal mol^{-1} at the QCISD(T)/6-31G**//MP2/6-31G** level[6a] and this effect is about 7 kcal mol^{-1} greater than for the first step of the hydrolysis of carbon dioxide than for carbodiimide.

Three-water hydrolysis of carbodiimide

Rehybridization and the placement of the third water molecule: The consideration of the effect of a third water molecule on the hydrolysis of the parent carbodiimide is the next logical step. The placement of a third water molecule, however, is not a trivial matter. There are two possible positions for the placement of the third water molecule and they are labeled **C** and **D**. As we pointed out in our earlier communication,[22] hydbridization effects on the charge relaxation associated with the transition states led us to consider the placement of the third water molecule as shown in structure **C**, and we will revisit our arguments for this placement shortly. The more obvious placement of the third water molecule would be at the site of proton transfer (**D**) thus expanding the proton transfer ring to eight atoms. The arrangement depicted by structure **D** was studied by Nguyen and co-workers.[23] The paper by Nguyen et al. might lead one to believe that structure **D** is significant, however, this conclusion is the result of serious flaws in their analysis. We will show that structure **D** is, in fact, insignificant.



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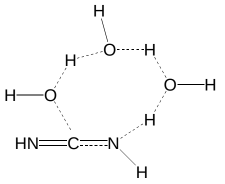


D

The optimized structures of the three-water hydrolysis of carbodiimide with the third water molecule placed as shown in **C** are given in Figure 9 and the energetic data is given in Table 3. Pre-coordination structure **11a** represents one of two

Table 3. Total energies, thermodynamic data and ΔE_0 and ΔG_{298} relative energies for the three-water hydrolysis of carbodiimide (structures **11**–**15**).[a]

Molecule	**11a**	**11b**	*E*-**12**	*Z*-**12**
E_{total}	– 377.007444	– 376.998706	– 376.971036	– 376.956136
E_{therm}	76.12	76.05	73.92	73.66
S	103.04	103.94	84.42	86.44
ΔE_0	0.00	5.48	22.85	32.20
ΔG_{298}	0.00	5.14	26.19	34.68
	E-**13**	*Z*-**13**	**14**	**15**
E_{total}	– 377.034912	– 377.020621	– 377.019572	– 377.061010
E_{therm}	78.75	78.42	74.19	79.17
S	93.47	101.39	88.12	94.63
ΔE_0	– 17.24	– 8.27	– 7.61	– 33.61
ΔG_{298}	– 11.76	– 5.48	– 5.10	– 28.06

[a] Total energies in hartrees; thermal energy (E_{therm}), ΔE_0 and ΔG_{298} relative energies in kcal mol^{-1}; entropy (S) in cal mol^{-1}K^{-1}. Relative energies with respect to **11a**.

van der Waals complexes between carbodiimide and three water molecules, the other being **11b** (Figure 10a). Structure **11a** is given in Figure 9 because it is more stable than **11b** by $\Delta E_0 = 5.5$ kcal mol^{-1} and by $\Delta G_{298} = 5.1$ kcal mol^{-1}. Nucleophilic attack of the central water molecule in **11a** leads to transition state structure *E*-**12**. There are two isomeric transition state structures with the other having *Z*-stereochemistry (*Z*-**12**, Figure 10b). Structure *E*-**12** is more stable than *Z*-**12** by $\Delta E_0 = 9.35$ kcal mol^{-1} and $\Delta G_{298} = 8.49$ kcal mol^{-1}. Transition state structure *E*-**12** leads to dihydrated isourea *E*-**13**, which then proceeds through tautomerization transition state **14** to the solvated urea complex **15**. Isourea *E*-**13** also has a possible structure with *Z*-stereochemistry (*Z*-**1**, Figure 10c). Structure *E*-**13** is more stable than *Z*-**13** by $\Delta E_0 = 9.0$ kcal mol^{-1} and by $\Delta G_{298} = 6.28$ kcal mol^{-1}. Note that the imine bond in *E*-**13** (Figure 9) is in the proper orientation to undergo proton-transfer to urea.

Structural inspection alone would suggest that pre-coordination complexes **11a** and **11b** lead to transition state structure *Z*-**12** because these three structures have the carbodiimide hydrogen atoms in a *gauche* conformation. Structural inspection would also suggest that structure **11b** leads to *E*-**12** because they have the same H-bonded motif, with the spectator water molecule acting as an H-bond donor and the carbodiimide nitrogen as the H-bond acceptor. However, it is difficult to envision complex **11a** proceeding through transition state *E*-**12** because a rotation about the C=N bond is necessary. Moreover, the process **11a** → *E*-**12** requires a reorganization of the H-bonded network because the spectator water molecule in **11a** is an H-bond acceptor and in *E*-**12** the water molecule is an H-bond donor with respect to the imine NH group. Therefore, we calculated the four reaction paths that connect **11a** and **11b**, respectively, with *E*-**12** and *Z*-**12**, respectively, and the results are provided as Supporting Information online for easy visualization. These extensive potential energy surface explorations clearly establish the validity of our discussions of the connectivity of pre-coordination complex **11a** and transition state structure *E*-**12** on the potential energy surface.

The E_0 and G_{298} surfaces for the three-water hydrolysis of carbodiimide is shown schematically in Figure 11. The activation barrier for the first step of the reaction is $\Delta E_0 = 22.9$ kcal mol^{-1} and $\Delta G_{298} = 26.2$ kcal mol^{-1}. On the E_0 surface this represents a catalytic effect of 21.9 kcal mol^{-1} with respect to the one-water hydrolysis and a catalytic effect of 6.4 kcal mol^{-1} with respect to the two-water hydrolysis. On the G_{298} surface the catalytic effect is 20.1 and 6.1 kcal mol^{-1} with respect to the one- and two-water hydrolyses, respectively. The activation barrier for the second step in the three-water hydrolysis of carbodiimide is $\Delta E_0 = 9.6$ kcal mol^{-1} and $\Delta G_{298} = 6.66$ kcal mol^{-1}. Thus, unlike for the two-water hydrolysis, there is a significant barrier for the second step of the three-water hydrolysis of carbodiimide. However, the barrier is small and the rate determining step remains the first step. The overall reaction energy for the three-water hydrolysis is $\Delta E_0 = -33.6$ kcal mol^{-1} and $\Delta G_{298} = -28.06$ kcal mol^{-1}.

Reaction center rehybridization and catalysis: The choice of structure **C** for the first transition state in the three-water hydrolysis of carbodiimide was the result of a thorough charge analysis of the van der Waals complexes **1a** and **6** and the transition state structures **2** and *E*-**7**. A structural comparison of **2** and *E*-**7** (Figure 1 and 5) 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 while the H-transfer (H^T) has slowed. The C-O^A distance decreases by 0.254 Å and the O^A-H^T distance decreases by 0.102 Å. Note also that the rehybridization of the C-atom has progressed more in *E*-**7** than in **2** and this is illustrated by the ∡(N-C-N) angles of 147.7° for **2** and 145.9° for *E*-**7** as well by the lengthening of the C=NH bond that remains an imine from 1.246 Å in **2** to 1.284 Å in *E*-**7**. These *structural* differences have important *electronic* consequences during

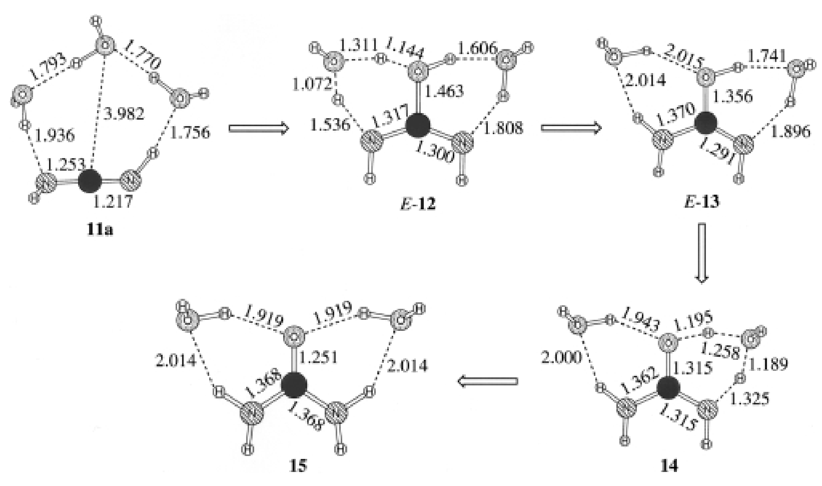
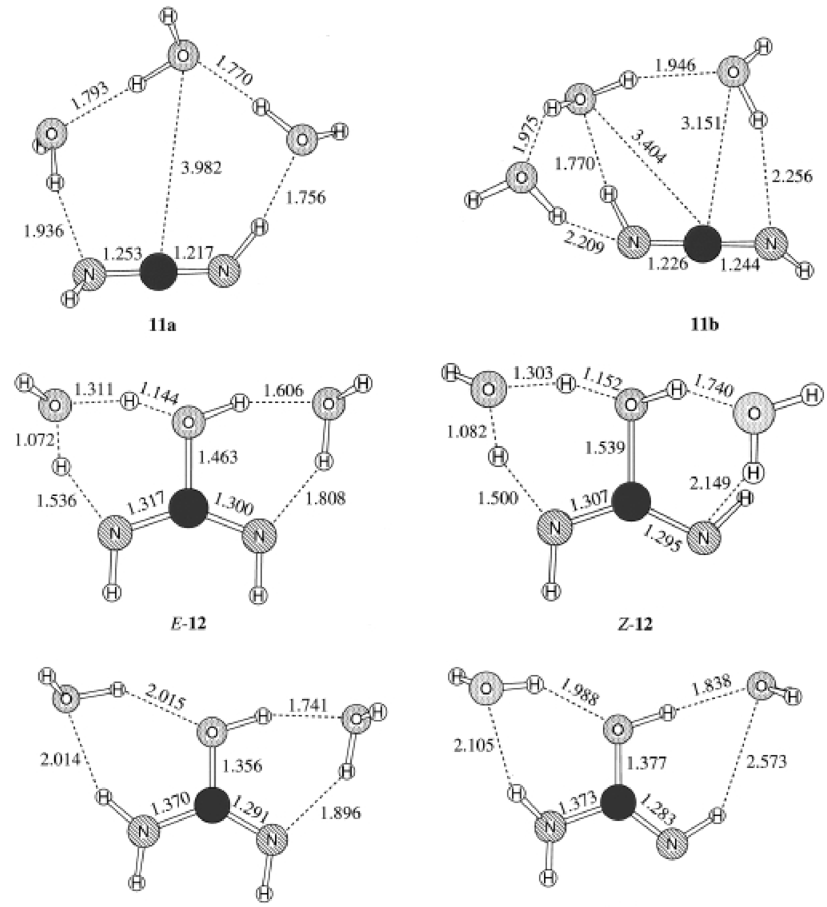


Figure 9. MP2(full)/6-31G* optimized structures for the three-water hydrolysis of carbodiimide.



11a **11b** *E*-**12** *Z*-**12** *E*-**13** *Z*-**13**

Figure 10. a) MP2(full)/6-31G* optimized structures for the two possible van der Waals complexes in the three-water hydrolysis of carbodiimide, b) for the two possible transition state structures in the three-water hydrolysis of carbodiimide, c) for the two possible dihydrated isourea intermediates in the three-water hydrolysis of carbodiimide.

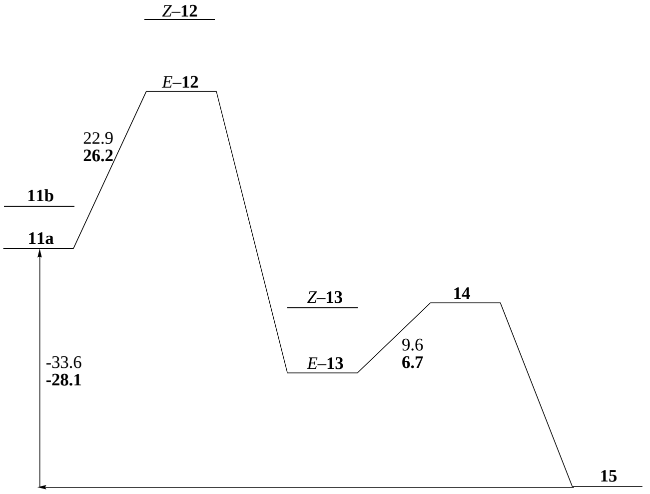


Figure 11. MP2(full)/6-31G* potential energy surface diagram for the three-water hydrolysis of carbodiimide. ΔE_0 values in plain text, ΔG_{298} values in bold text.

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}. Simple hybridization concepts would suggest that an =NH group in a diimide will be less negative than in an imine.[29a] Therefore we would predict that the change in the charge of the (NH)^{R} group would be more negative for the process **6** → *E*-**7** than for **1a** → **2**. This prediction was confirmed by Natural Population Analysis (NPA) of these four molecules which revealed Δq(NH^{R}) values of +0.01 for **1a** → **2** and −0.24 for **6** → *E*-**7** (Table 4). Similarly, in the course of the addition 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.[29b] This electronic relaxation should be manifested more in the process **6** → *E*-**7** than for **1a** → **2** and the NPA analyses (Table 4) indeed show a greater 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 (Δq +0.00 for **1a** → **2** and +0.18 for **6** → *E*-**7**) and for the H^{R}-atom (Δq +0.01 for **1a** → **2** and +0.07 for **6** → *E*-**7**).

The electronic relaxations during the activation processes **1a** → **2** and **6** → *E*-**7** 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. Note that the C–O^{A} bond in *E*-**12** is even shorter than in *E*-**7** and, in fact, all parameters indicate that all the structural and electronic changes associated with the processes **1a** → **2** and **6** → *E*-**7** clearly are enforced for **11a** → *E*-**12**. The catalytic effects of the second and third water molecules truly are synergetic. The consideration of the

Table 4. Change in atomic charges.[a]

Reaction	O^{A}	(O^{A})H^{R}	(NH)^{R}	(NH)^{A}	C	H^{T}
1a → **2**	0.00	+0.01	+0.01	−0.22	+0.12	+0.08
6 → *E*-**7**	+0.18	+0.07	−0.24	−0.18	+0.09	+0.07, +0.05
6 → *Z*-**7**	+0.11	+0.04	−0.19	−0.14	+0.11	+0.07, +0.05
11a → *E*-**12**	+0.16	+0.10	−0.32	−0.14	+0.11	+0.06, +0.04
11b → *E*-**12**	+0.17	+0.07	−0.17	−0.28	+0.10	+0.08, +0.06

[a] O^{A} is the adding O-atom, the (O^{A})H^{R}-atom remains bonded to O^{A} during the addition, the (NH)^{R} is the imine group in carbodiimide which remains an imine and (NH)^{A} is the imine group that is beeing added to, and H^{T} is (are) the H-atom(s) that are being transferred.

reaction $6 \rightarrow Z$-**7** instead of $6 \rightarrow E$-**7** leads to the same conclusions.

The effects of the kind of microsolvation described above 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 (structure **C**).

Catalysis via the eight-membered ring transition state structure? The more obvious site to place a third water molecule is in the proton transfer ring (structure **D**), as was studied by Nguyen et al.[23] In our initial study[22] we deemed this structure to be of minor relevance since it is well known that there is little energetic gain in going from a six- to an eight-membered cyclic transition state. In fact, in a recent study on the hydrolysis of carbon dioxide, Nguyen et al. showed that the catalytic effect of adding a third water molecule to the proton transfer ring was merely 0.9 kcal mol^{-1} with respect to the two-water hydrolysis.[6a] Despite their work on the hydrolysis of carbon dioxide, these workers suggested a significant catalytic effect from structure **D** for the hydrolysis of carbodiimide.[23] They report a catalysis of 32.3 kcal mol^{-1} with respect to the one-water hydrolysis of carbodiimide and 10.0 kcal mol^{-1} with respect to the two-water hydrolysis on the E_0(MP2/6-31G**) surface. A closer inspection of Nguyen's work, however, reveals serious flaws. Nguyen and co-workers report all activation barriers with respect to the *isolated* carbodiimide and *isolated* water molecules and *not* with respect to the pre-coordination complexes. In fact, they do not even calculate the pre-coordination complexes. The inherent flaw in their approach is underscored by the fact that their **D**-type transition state is *more* stable than the sum of the energies of carbodiimide and three water molecules at the MP2/6-31G** level. On the E_0(MP2/6-31G**) potential energy surface, Nguyen's analysis thus leads to a *negative* activation barrier for the three-water hydrolysis with transition state **D**. A positive activation barrier is only "obtained" after the inclusion of zero-point energies.

The analysis by Nguyen describes a *tetramolecular* gas-phase reaction based on energy alone! The inclusion of zero-point vibrational energies does not improve the analysis in any significant manner; still only part of the enthalpy is considered while the all-important entropy effect remains entirely neglected. In any case, it is not the purpose of these studies to model the gas-phase reaction. Instead, it is the goal of these studies to better understand the solution reaction. In solution, entropy is less of an issue because all molecules are aggregated at all times and in solution this reaction is basically a "unimolecular" reaction of an aggregate. Therefore, the pre-coordination complexes represent the smallest meaningful aggregates that allow one to model the situation in solution.

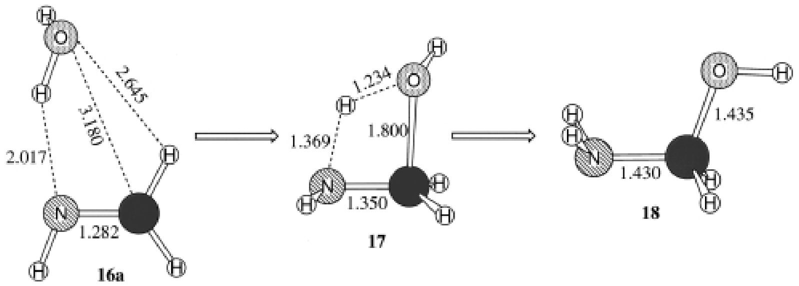


Figure 12. MP2(full)/6-31G* optimized structures for the one-water hydrolysis of methyleneimine.

Table 5. Catalytic effect of transition state structure **D**.[a]

Molecule	MP2/6-31G**	Nguyen activation energies[b]		True activation energies	
		ΔE_0	ΔE_0+ZPE	ΔE_0	ΔG_{298}
CDI+1 H_2O[b]	– 224.57812				
1a	– 224.58969				
2[b]	– 224.51972	36.6	37.8	43.9	45.4
CDI+2 H_2O[b]	– 300.79791				
6	– 300.83098				
Z-**7**[b]	– 300.77978	11.4	15.5	32.1	33.3
CDI+3 H_2O[b]	– 377.01770				
11b	– 377.06576				
D type TS[b]	– 377.02167	– 2.5	5.5	27.7	30.4

[a] MP2/6-31G** total energies in hartrees. Relative energies in kcal mol^{-1}. ΔG_{298} values in use frequencies calculated at the MP2/6-31G* level of theory. For transition state **D**, the ΔG_{298} value was calculated using the MP2/6-31G* frequency for *Z*-12. [b] Value calculated by Nguyen et al.

We recalculated our pre-coordination complexes **1a**, **6**, and **11b** at the level used by Nguyen to determine the *true* catalytic effect of transition state **D** and the data is collected in Table 5. The activation barrier for the first step in the three-water hydrolysis of carbodiimide using transition state **D** is $\Delta E_0 = 27.7$ kcal mol^{-1} and $\Delta G_{298} = 30.4$ kcal mol^{-1}. This represents a small catalytic effect of 4.4 kcal mol^{-1} on the E_0 surface and of 2.9 kcal mol^{-1} on the G_{298} surface with respect to the two-water hydrolysis of carbodiimide.[30] It is important to note that we calculated the activation barrier for the three-water hydrolysis of carbodiimide with respect to pre-coordination complex **11b**, and not with respect to the more stable **11a**. We did this because structure **11b** appears to have the water molecules better situated to give transition state structure **D**. However, it is possible that a reaction path exists between **11a** and transition state structure **D**. Considering that structure **11a** is about 2 kcal mol^{-1} more stable than **11b**, this would *decrease* the catalytic effect of transition state **D** to less than 1 kcal mol^{-1} on the G_{298} surface, as was the case for carbon dioxide.[6a] When one examines transition state structure **D** properly it becomes abundantly apparent that it has no catalytic significance in the hydrolysis of carbodiimide.

Comparison between methyleneimine and carbodiimide

One- and two-water hydrolysis of methyleneimine: Theoretical studies on the reactivity of methyleneimine, or methanimine, have concentrated on its [2 + 2]-cycloaddition chemistry with ketenes,[31] ketenimines,[32] and thioketenes[33] and its addition chemistry with hydrogen cyanide.[34] Methyleneimine has also been studied in the context of the rearrangement of methylnitrene.[35] The MP2(full)/6-31G* optimized structures for the one-water hydrolysis of methyleneimine are shown in Figure 12. We found two pre-coordination complexes between water and methyleneimine (Figure 13). The first has the

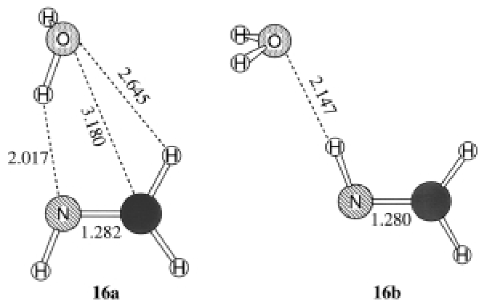


Figure 13. MP2(full)/6-31G* optimized structures for the two possible van der Waals complexes in the one-water hydrolysis of methyleneimine.

water molecule engaged in two H-bonds, **16a**, and the other has the water O-atom engaged in an H-bond with the imine hydrogen to give a C_2 symmetric geometry, **16b**. Complex **16a** is $\Delta E_0 = 3.1$ kcal mol^{-1} and $\Delta G_{298} = 0.6$ kcal mol^{-1} more stable than **16b** and, thus, we show **16a** in Figure 12. Nucleophilic attack of the water molecule on methyleneimine leads to the four-membered transition state structure **17** before giving hydroxymethylamine, **18**.

The MP2(full)/6-31G* optimized structures for the two-water hydrolysis of methyleneimine are shown in Figure 14. One van der Waals complex was located, **19**, and it contains a seven-membered ring with three hydrogen bonds. Nucleophilic attack of the water molecule that is H-bonded to the methylene hydrogen gives the six-membered transition state structure **20**. The product of the reaction is a hydrated hydroxymethylamine, **21**.

The MP2(full)/6-31G* thermodynamic data and relative energies for the one- and two-water hydrolyses of methyleneimine are collected in Tables 6 and 7 and the ΔE_0 and ΔG_{298} surfaces for the one- and two-water hydrolyses are shown in Figure 15. The hydration of methyleneimine is a one step process. The activation energy of the single-water hydrolysis is $\Delta E_0 = 52.0$ kcal mol^{-1} and $\Delta G_{298} = 51.9$ kcal mol^{-1}. The consideration of a second water molecule lowers the activation barrier to $\Delta E_0 = 35.0$ kcal mol^{-1} and $\Delta G_{298} = 35.5$ kcal mol^{-1}. Thus, the catalytic effect of the second water molecule is $\Delta E_0 = 17.0$ kcal mol^{-1} and $\Delta G_{298} = 16.4$ kcal mol^{-1}. The reaction energy for the single-water hydrolysis of carbodiimide is -10.1 and -5.4 kcal mol^{-1} on the E_0 and G_{298} surfaces. The reaction energy is slightly diminished for the two-water hydrolysis to -7.0 and -3.0 kcal mol^{-1} on the E_0 and G_{298} surfaces.

Table 6. Total energies, thermodynamic data and ΔE_0 and ΔG_{298} relative energies for the single-water hydrolysis of methyleneimine (structures **16**–**18**).[a]

Molecule	**16a**	**16b**	**17**	**18**
E_{total}	−170.535425	−170.530444	−170.452624	−170.551558
E_{therm}	45.07	44.76	42.17	47.17
S	72.08	79.54	62.45	63.37
ΔE_0	0.00	3.13	51.96	−10.12
ΔG_{298}	0.00	0.59	51.93	−5.43

[a] Total energies in hartrees; thermal energy (E_{therm}), ΔE_0 and ΔG_{298} relative energies in kcal mol^{-1}; entropy (S) in cal mol^{-1}K^{-1}. Relative energies with respect to **16a**.

Table 7. Total energies, thermodynamic data and ΔE_0 and ΔG_{298} relative energies for the two-water hydrolysis of methyleneimine (structures **19**–**21**).[a]

Molecule	**19**	**20**	**21**
E_{total}	−246.755382	−246.699608	−246.766551
E_{therm}	62.97	59.05	64.94
S	86.09	71.23	79.23
ΔE_0	0.00	35.00	−7.01
ΔG_{298}	0.00	35.51	−3.00

[a] Total energies in hartrees; thermal energy (E_{therm}), ΔE_0 and ΔG_{298} relative energies in kcal mol^{-1}; entropy (S) in cal mol^{-1}K^{-1}. Relative energies with respect to **19**.

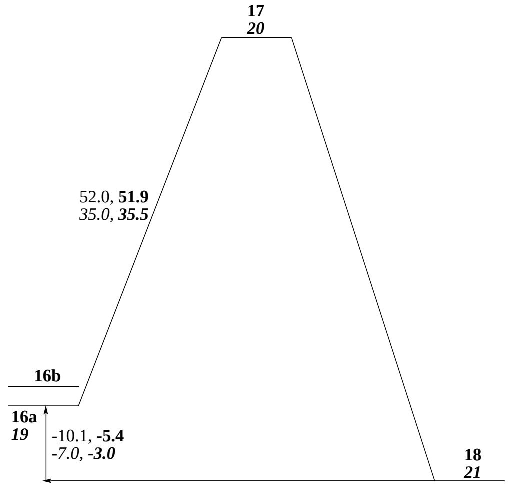


Figure 15. MP2(full)/6-31G* ΔE_0 (plain text) and ΔG_{298} (bold text) potential energy surface diagrams for the one-water (top values) and two-water (bottom values, italicized) hydrolyses of methyleneimine.

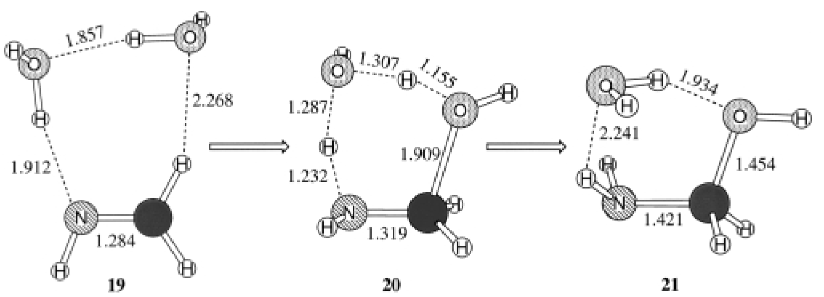


Figure 14. MP2(full)/6-31G* optimized structures for the two-water hydrolysis of methyleneimine.

Effect of conjugation of the hydrolysis of heterocumulenes: The activation energy of the rate determining step for the one-water hydrolysis of carbodiimide is 7.2 kcal mol^{-1} less than for the hydrolysis of methyleneimine on the E_0(MP2(full)/6-31G*) surface. On the G_{298} surface the difference is 5.7 kcal mol^{-1}. For the two-water hydrolyses of carbodiimide and methyleneimine the difference in activation energies is only 1.8 and 1.1 kcal mol^{-1} on the E_0 and G_{298} surfaces, with the activation energy of the hydrolysis of carbodiimide being the smaller.

The activation energies for the one- and two-water hydrolyses of carbon dioxide[6a] and formaldehyde[2a] have been calculated at the MP2/6-31G** and MP2(full)/6-31G* levels of theory, respectively. The ΔE_0 activation barrier of the rate determining step for the one-water hydrolysis of carbon dioxide is 8.9 kcal mol^{-1} greater that for the hydrolysis of formaldehyde. For the two-water hydrolyses, the difference between the two activation barriers is 7.0 kcal mol^{-1}, with the activation energy of the hydrolysis of carbon dioxide being the greater. Thus, the trend for carbon dioxide and formaldehyde is opposite to the trend for carbodiimide and methyleneimine. The hydrolysis of carbodiimide is catalyzed by the conjugative effects of the second imine bond while the hydrolysis of carbon dioxide is inhibited by the conjugative effects of the second =O bond.

Conclusion

The ΔG_{298} activation barriers for the rate-determining steps of the one-, two- and three-water hydrolyses of carbodiimide, respectively, are 46.3, 32.3, and 26.2 kcal mol^{-1} at the highest common level employed. The activation barrier for the one-water hydrolysis of carbodiimide is about 5 kcal mol^{-1} smaller than for carbon dioxide while the activation barriers for the two-water hydrolyses of both heterocumulenes are almost the same. The activation barriers determined for the one- and two-water hydrolyses of methyleneimine are $\Delta G_{298} = 51.9$ and $\Delta G_{298} = 35.5$ kcal mol^{-1}, respectively. While the kinetic barrier for hydrolysis of formaldehyde is smaller than for carbon dioxide, the opposite is found for the N-analogues. Throughout the discussion we provided both the activation parameters ΔE_0 and ΔG_{298} and we have shown that they are very similar. We have argued above that entropy effects should be modest for the solution reaction because the hydrolysis in solution is basically a “unimolecular” reaction of an aggregate. The precoordination complexes represent the smallest meaningful aggregates and the similarity of the ΔE_0 and ΔG_{298} parameters computed corroborate the argument.

The three-water hydrolysis of carbodiimide with the lowest activation barrier involves a transition state structure (**C**) in which only *two* water molecules are involved in the six-membered proton transfer ring. The third water molecule engages in H-bonding to the alcohol H-atom and to the imine-N of the forming isourea. We have shown that the consideration of the transition state structure (**D**) in which all *three* water molecules are employed to form an eight-membered proton-transfer ring offers little additional catalysis as compared to the respective six-membered cyclic transition state. This conclusion corrects a previously made claim.[23] The consequence of expanding the ring size of the proton transfer ring is thus entirely the same for carbodiimide and for carbon dioxide[6a] and there is nothing special about carbodiimide in this regard.

The catalytic effect exhibited by the third water in the transition state structure **C** has been explained based on the charge relaxation in the transition state. The structural and electronic relaxation associated with the formation of the transition state can greatly effect the properties of groups that are not directly involved in the bond-breaking and forming region. The kind of synergism described here between the catalysis and the reaction center hybridization could have implications for numerous other systems. The environmental stabilization of localized charges in the transition state via micro-solvation can lead to great catalytic effects.

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[29] a) NPA calculations on MP2(full)/6-31G* optimized structures show that the population of an =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.

[30] The ΔG_{298} value for transition state **D** was calculated using the thermodynamic data for *Z*-**12** since Nguyen and co-workers did not report the values for **D** in their paper. The thermodynamic data for *Z*-**12** and *E*-**12**, as well as for all other conformational isomers (see Tables 1–3), are almost identical and thus this is a reasonable approximation.

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