

Diazetines (9) might not open as easily, but are expected to be highly reactive.

Conclusions

The lack of aromaticity of four-membered-ring 6π -heterocycles can be attributed to two main factors, viz., the strongly 1,2- and/or 1,3-antibonding character of the higher occupied π -orbitals and the electronegativity difference between C and O or C and N. Both factors favor localization of π -electrons and ring-opening reactions. Presumably, 6π -aromaticity requires at least a five-

membered-ring system, where the nonbonded repulsions are much less severe.

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Registry No. 1, 287-50-3; 3, 110175-39-8; 4, 110175-40-1; 6, 107-22-2; 8, 287-35-4; 9, 5663-08-1; 12, 74726-45-7; 13, 27670-35-5; 21, 40079-19-4; 29, 13473-83-1; 32, 157-33-5; 34, 106-99-0; 36, 822-35-5; (C-H₃)₂NH, 124-40-3; CH₂=CHNH₂, 593-67-9; CH₂CH₂NH, 151-56-4; CH=CHNH, 157-17-5; CH₂=NH, 2053-29-4.

Supplementary Material Available: Complete specifications (Z matrices and Cartesian coordinates) of the geometries of 1-36 (10 pages). Ordering information is given on any current masthead page.

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Theoretical Modelling of Specific Solvation Effects upon Carbonyl Addition

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Abstract: Geometries have been fully optimized at the HF/3-21G and AM1 levels of theory for reagent, activated, and product complexes for ammonia addition to formaldehyde catalyzed by 0, 1, or 2 molecules of water. One water molecule reduces the 3-21G reaction barrier by 113 kJ mol⁻¹ by virtue of increased hydrogen bonding with the zwitterion-like ammonia-formaldehyde moiety in the cyclic six-membered activated complex. The second water molecule reduces the barrier by a further 33 kJ mol⁻¹ in 3-21G by permitting less-bent hydrogen bonds in the cyclic eight-membered activated complex. Hydrogen bond strengths are overestimated at the 3-21G and MP2/6-31G**//3-21G levels but are underestimated by AM1, particularly for hydrogen bonds involving charged species; AM1 consistently prefers bifurcated to linear hydrogen bonds. Relative Gibbs free energies of activation estimated for the addition reactions predict the two-water-catalyzed process to be preferred over the one-water-catalyzed process by ~10 kJ mol⁻¹ in the gaseous and aqueous phases and by ~25 kJ mol⁻¹ in dioxan. The reaction-coordinate vibrational modes are dominated by motions of the transferring protons; proton donation is more advanced than proton abstraction in the activated complexes.

The zwitterionic species H₂O⁺CH₂O⁻, which would be the expected intermediate in a stepwise mechanism for nucleophilic addition of a water molecule to formaldehyde, was predicted by ab initio self-consistent-field molecular-orbital (SCFMO) calculations at the STO-3G and 4-31G level to be unbound in the gas phase.^{1,2} As the neutral reagents approach along the minimum-energy Bürgi-Dunitz trajectory,^{3,4} their interaction is wholly repulsive for all separations less than ~2.4 Å.² Uncatalyzed formation of the product diol is enforced to proceed by a concerted mechanism involving a four-center activated complex **1** (Figure 1, curve U). A single ancillary water molecule may interact favorably with the reacting system by serving monofunctionally either as a hydrogen bond donor to the carbonyl oxygen (simulating general acid catalysis) or as a hydrogen bond acceptor from the nucleophilic water (simulating general base catalysis). The energy of all points along the uncatalyzed addition path is lowered

by these interactions (Figure 1, curves A and B), which therefore provide for catalysis which may be described as *passive*: facilitation without significant alteration of the reaction coordinate.¹ However, the ancillary water molecule may also serve bifunctionally as both donor and acceptor of hydrogen bonds in a cyclic fashion **2**. Now the intervention of the extra molecule effects not only an energetic reduction but also profound change in the nature of the reaction coordinate for the addition (Figure 1, curve C). This catalysis may be described as *active*: facilitation by alteration of the reaction coordinate.¹

Bifunctional participation of a single ancillary water molecule in a six-membered, cyclic activated complex for nucleophilic addition to carbonyl was first suggested by Syrkin⁵ in connection with ester hydrolysis. (An earlier discussion of mechanisms for acid and base catalyzed ester hydrolyses by Laidler⁶ had postulated cyclic activated complexes involving hydrogen bonding of a catalytic molecule to both nucleophile and nucleofuge but not to the carbonyl group.) Eigen⁷ mentioned the possibility of cooperative mechanisms for proton transfer in aqueous solution involving bifunctional participation of *several* water molecules in

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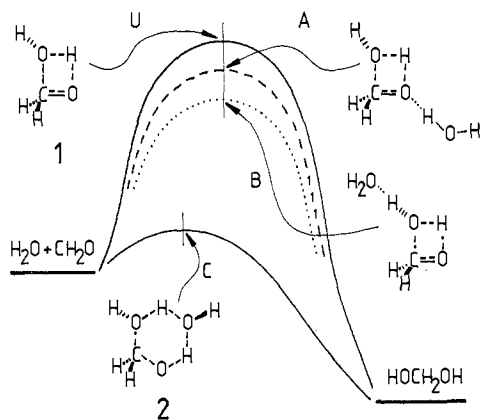


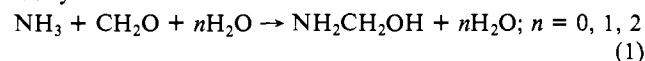
Figure 1. Active and passive catalysis of formaldehyde hydration by a single ancillary water molecule.

a ring, and Bell's⁸ discussion of mechanisms for *gem*-diol dehydration (or its reverse, carbonyl hydration) was illustrated by diagrams suggesting at least *two* ancillary water molecules in a cyclic activated complex. Ab initio STO-3G SCFMO calculations for formaldehyde hydration proceeding via activated complexes **1** and **2** predicted gas-phase entropies from which estimated activation entropies of -96 and $-195 \text{ J mol}^{-1} \text{ K}^{-1}$ (25°C , 1 M) were obtained for reactions in dioxan solution involving one and two water molecules (i.e., zero and one ancillary water molecules), respectively.⁹ An extrapolated estimate of $-294 \text{ J mol}^{-1} \text{ K}^{-1}$ for a concerted mechanism involving three water molecules was in accord with the experimental activation entropy of $-290 \text{ J mol}^{-1} \text{ K}^{-1}$ for hydration of 1,3-dichloroacetone in dioxan.¹⁰ Kinetic isotope effects for this reaction with $\text{H}_2\text{O}/\text{D}_2\text{O}$ -mixtures in dioxan¹¹ provided evidence for an activated complex containing at least six exchangeable protons, i.e., three water molecules, in agreement with the conclusion based on the observation of a kinetic order of 3 with respect to water.^{11,12} Although preliminary STO-3G calculations were made for cyclic structures containing formaldehyde and three water molecules,¹³ the activated complex for concerted hydration of formaldehyde catalyzed by two ancillary water molecules was never determined in these earlier theoretical studies.

A more recent semiempirical theoretical study¹⁴ of the mechanism of amine addition to formaldehyde appears to be deficient on two accounts. First, the influence of solvation was explicitly neglected whereas the earlier ab initio theoretical studies^{1,9} had suggested that the role of solvent molecules was of crucial importance. Second, the MINDO/3 SCFMO method employed is not reliable for these reactions.² The zwitterionic species $\text{NH}_3^+\text{CH}_2\text{O}^-$ was predicted to lie in an energy minimum 13 kJ mol^{-1} above the isolated ammonia and formaldehyde reagents with an activation barrier of 40 kJ mol^{-1} to its formation, whereas the ab initio results showed that the interaction of these neutral molecules was entirely repulsive in this region.² The energies and geometries of the zwitterion and of its preceding activated complex reported by Shokhen et al.¹⁴ agree entirely with those obtained with the MINDO/3 method by Hogan et al.¹⁵ (cf. ref 16).

Shokhen et al.¹⁴ concluded that formation of the zwitterion was the rate-determining step in carbinolamine formation, the neutral product being formed in a subsequent fast isomerization step. This conclusion may be correct under certain conditions, but for the wrong reasons. In the gas phase, or in aprotic solution, concerted mechanisms are more likely, which avoid charge-separated species.^{2,9} In aqueous solution the zwitterion is stabilized^{9,17} and its formation may indeed be rate-determining,¹⁷ but the (solvent-mediated) intramolecular proton transfer leading to the neutral carbinolamine may also be kinetically significant,¹⁸ and the lifetime of the zwitterion may be so short as to enforce a concerted mechanism.¹⁹

The present paper describes an ab initio SCFMO theoretical study of nucleophilic addition of ammonia to formaldehyde (reaction 1) catalyzed by 0, 1, or 2 ancillary water molecules participating bifunctionally in cyclic hydrogen-bonded structures. The reported results should permit some more meaningful discussion regarding the mechanisms of carbonyl addition in condensed media, and their analysis provides insight into the nature of active catalysis.



Methodological Considerations

Any method proposed for use in a theoretical modelling study of a reaction occurring in a protic medium must satisfy two minimal criteria. First, it must afford at least a qualitatively correct description of the intrinsic, gas-phase reactivity of the system in the absence of solvation effects. Second, it must be capable of describing solute-solvent and solvent-solvent hydrogen bonding in a general and consistent manner. The MINDO/3 semiempirical SCFMO method^{14,20} meets neither requirement: it incorrectly predicts the existence of the zwitterion **4** in the gas phase and it fails to predict ammonia-water,²¹ carbonyl-water,²² and water-water^{21,22} hydrogen bonds. The MNDO semiempirical method²³ reproduces the qualitative features of the gas-phase addition of ammonia to formaldehyde as determined by ab initio methods, but it shares with MINDO/3 the inability to describe hydrogen bonding.^{24,25} A modified version of the MNDO method has been reported,^{24a} in which extra terms are included for pairs of atoms known to be forming a hydrogen bond, but this ad hoc procedure lacks the desired quality of generality.^{24b} The recently published "third generation" semiempirical method AM1²⁵ appears to correct these deficiencies; it predicts genuine (if somewhat weak) hydrogen bonds for ammonia-water, formaldehyde-water, and water-water.²⁵

There are at least two distinct philosophies of theoretical modelling of solvation effects upon chemical reactivity. One approach is exemplified by an important recent study by Madura and Jorgensen²⁶ of the effect of aqueous solvation upon nucleophilic addition of hydroxide anion to formaldehyde. These authors have performed ab initio SCFMO calculations for the gas-phase hydroxide-formaldehyde addition path and for the interaction between the reacting system and a water molecule both with frozen intramolecular geometries (i.e., only intermolecular variables were optimized) and have fitted analytical potential functions to these data. Monte Carlo simulations in the NPT ensemble were then

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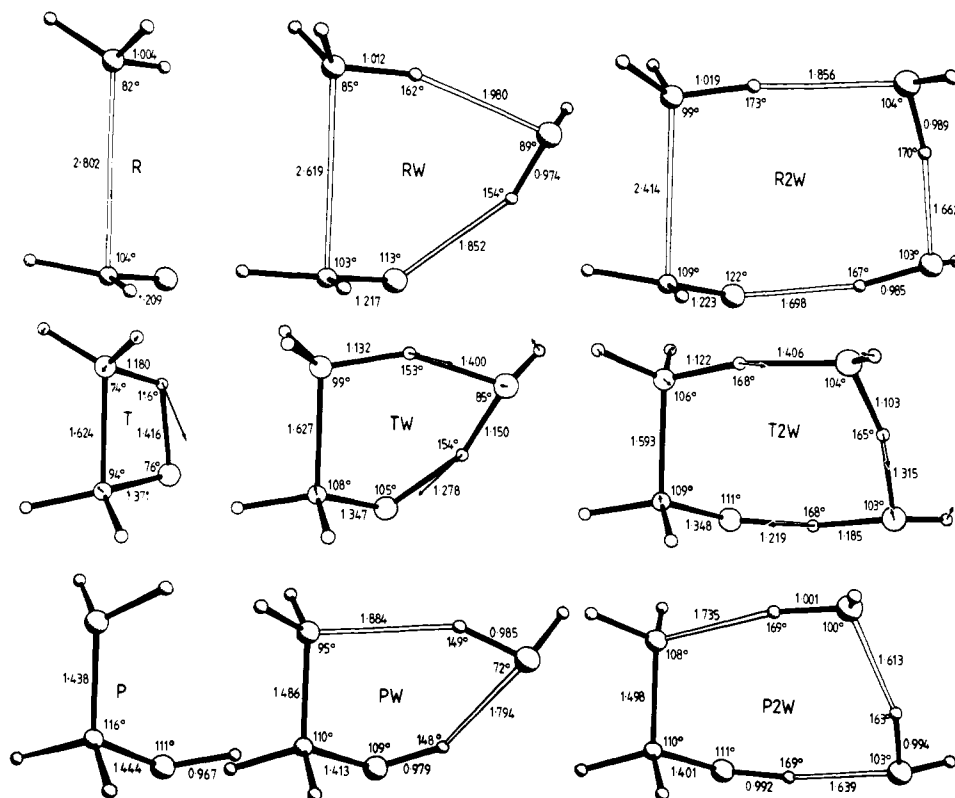


Figure 2. 3-21G optimized geometries for reactant, activated, and product complexes for ammonia addition to formaldehyde catalyzed by 0, 1, or 2 water molecules (bond lengths in Å).

run for a box containing hydroxide anion, formaldehyde, and 269 TIP4P²⁷ water molecules in order to compute the potential of mean force as a function of the value of the reaction coordinate. The advantage of this procedure is that the effects of thermal and configurational averaging are properly accounted for by the statistical mechanical calculations. Its limitation is that the results "correspond to the effects of solvating the gas-phase reaction. To detect a change in mechanism in solution would require the construction of multidimensional potentials of mean force".²⁶ In other words, as currently implemented and as computational resources presently allow, this approach is capable of realistic simulation of the *passive* effects of solvation upon reactivity but cannot reveal any *active* role for specific solvent molecules.

An alternative approach is that adopted in the present work. The reagent molecules and small numbers of solvent molecules are together considered as a supermolecule, and *all* internal degrees of freedom are subjected to geometry optimization. The disadvantage of this method is that no statistical averaging is performed, except in so far as entropies and Gibbs free energies may be estimated by using standard expressions for molecular partition functions. Only the effects of specific solvation in vacuo may be investigated; bulk solvation effects are omitted from consideration. On the other hand, the advantage is that this approach is capable of exploring the possibility of mechanistic change involving the active participation of solvent molecules. Thus while the detailed energetics may be quantitatively in error, the overall features of a reaction mechanism in solution may be predicted correctly and most usefully.

Computational Methods and Results

The CADPAC²⁸ and GAMESS²⁹ program packages, as implemented on the Cray 1 S at the University of London Computer Centre,

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have been employed throughout for ab initio quantum-chemical calculations. Geometry optimizations were performed at the level of SCFMO theory with the 3-21G basis set³⁰ (denoted HF/3-21G) by using standard quasi-Newton methods employing analytical gradients, except that the activated complexes (transition structures) for the solvated reactions were determined by using the modified algorithm of Bell et al.³¹ as available in GAMESS. Residual forces were less than 6×10^{-4} au ($3 \text{ kJ mol}^{-1} \text{ \AA}^{-1}$) on each atom, with a root-mean-square force of 3×10^{-5} au ($0.15 \text{ kJ mol}^{-1} \text{ \AA}^{-1}$); the residual errors in the optimized geometries were in all cases less than 0.002 Å for bond lengths, 0.2° for bond angles, and 0.8° for dihedral angles. CADPAC was employed for single-point energy calculations at the level of second-order Møller-Plesset perturbation theory, with frozen core orbitals, using the 6-31G* basis³² for structures optimized at the HF/3-21G level (denoted MP2/6-31G*/HF/3-21G). Harmonic force constants were computed at the HF/3-21G level by analytical second differentiation of the energy using CADPAC. Normal modes and vibrational frequencies were obtained by diagonalization of the matrix of mass-weighted Cartesian force constants, from which residual translational and rotational contributions had been projected out,³³ and which was uniformly scaled by a factor of 0.835 chosen to minimize the error between vibrational frequencies calculated and observed for ammonia, formaldehyde, and water.

Semiempirical quantum-chemical calculations have been performed with the AMPAC program,³⁴ as implemented locally on a Systeim 8750A under VMS, using the AM1 hamiltonian with standard parameters.²⁵ Saddle points were located with use of a combination of the SADDLE³⁵ and SIGMA³⁶ algorithms.

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Table I. Total Energies, Enthalpic Contributions, and Molar Entropies (298 K, 1 atm) for Structures Optimized at the HF/3-21G Level and Heats of Formation for AM1 Optimized Structures

species	total energy (hartrees)			$H - E$ (kJ mol ⁻¹)	S° (J K ⁻¹ mol ⁻¹)	AM1 ΔH_f° (kJ mol ⁻¹)
	HF/3-21G	HF/6-31G*	MP2/6-31G*			
NH ₃	-55.87220	-56.18250	-56.35623	96.6	192.5	-30.5
CH ₂ O	-113.22182	-113.86528	-114.16681	79.5	218.1	-131.8
H ₂ O	-75.58596	-76.00976	-76.19648	62.1	188.5	-247.9
R	-169.10167	-169.99916	-170.47162	182.2	323.2	-174.6
T	-169.04323	-169.97498	-170.46874	178.4	259.1	-1.8
P	-169.12536	-170.06497	-170.53853	190.0	266.8	-239.4
RW	-244.71316	-246.07319	-246.73892	255.5	359.8	-451.8
TW	-244.69802	-246.02390	-246.71290	248.8	296.6	-266.7
PW	-244.73650	-246.08623	-246.75519	263.0	316.5	-496.7
R2W	-320.33019	-322.09312	-322.95335	328.2	410.1	-731.8
T2W	-320.32755	-322.05058	-322.93503	315.9	344.4	-497.7
P2W	-320.35607	-322.10760	-322.97172	333.8	370.6	-773.9
H ₂ O...CH ₂ O	-188.81626	-189.87950	-190.36935	148.3	317.0	-395.0
HOH...OCH ₂	-188.82230	-189.88239	-190.37376	149.8	296.8	-396.3 ^b
HOH...OH ₂	-151.18940	-152.02757	-152.40386	132.9	284.3	-516.6 ^b
HOH...NH ₃	-131.47508	-132.20255	-132.56226	167.3	297.7	-290.5 ^b
H ₂ NH...OH ₂	-131.46948 ^a	-132.19626	-132.55525	163.9	282.2	-291.8 ^b
NH ₄ ⁺	-56.23386	-56.53056	-56.70013	136.0	185.6	630.0
CH ₃ O ⁻	-113.72480	-114.38301	-114.70174	100.6	220.6	-161.1
NH ₄ ⁺ ...OH ₂	-131.87388	-132.57149	-132.93365	203.1	270.1	318.2 ^b
CH ₃ O ⁻ ...HOH	-189.37002	-190.43121	-190.94551	171.3	300.7	-476.9 ^b
R' ^c	-169.10039					-173.7
T'	-169.04326					-10.0
R''	-169.09769					-173.3
T''	-169.04110					-50.9

^aSaddle point on HF/3-21G//HF/3-21G surface. ^bBifurcated hydrogen bonding. ^cSingle-point calculation for unoptimized structure; see subsection on Origins of Catalytic power.

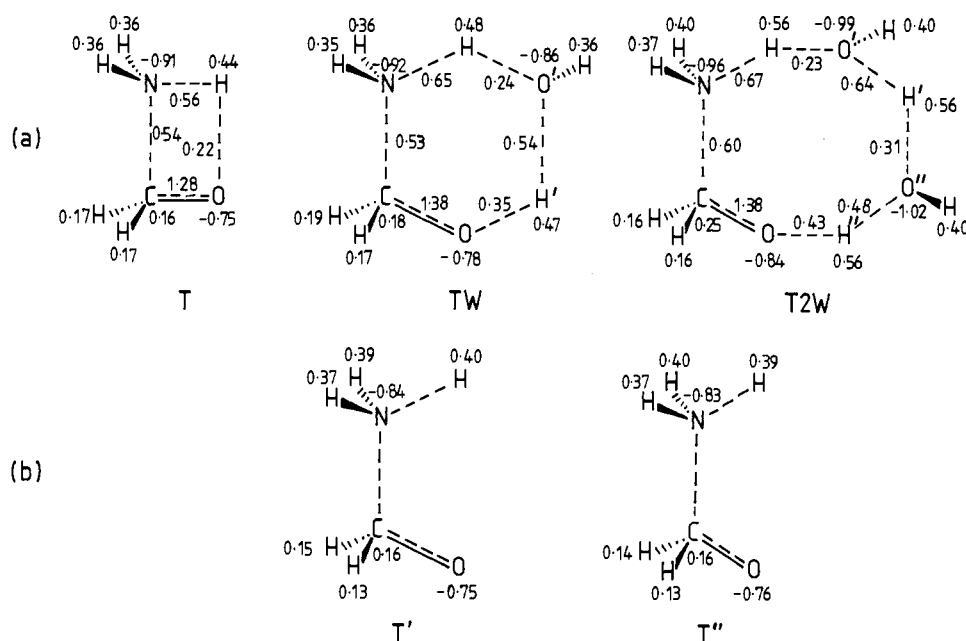


Figure 3. (a) Pauling bond orders (inside rings) for endocyclic bonds and net atomic charges for 3-21G optimized activated complexes T, TW, and T2W; (b) net atomic charges for T' and T'' in 3-21G.

The optimized structures for the reactant complex, activated complex, and product complex for each of the three reactions are shown in Figure 2: R, T, and P (left column) for the unsolvated process ($n = 0$); RW, TW, and PW (center column) for the process solvated by a single water molecule ($n = 1$); R2W, T2W, and P2W (right column) for the process solvated by two water molecules ($n = 2$). Also shown are the lengths (in Å) of the making and breaking bonds and the angles (in degrees) between these bonds. Although all internal degrees of freedom were optimized, the values of the remaining geometrical parameters are

not reported here for brevity's sake. Table I contains total energies for species optimized at the HF/3-21G level and heats of formation for species optimized with AM1. Also included are the enthalpic contribution $H - E$ and the molar entropy S° calculated for each species at 298.15 K with use of the 3-21G scaled vibrational frequencies and geometries (cf. ref 9).

Figure 3a shows Pauling bond orders³⁷ for making and breaking bonds of the activated complexes: these are calculated from the data of Figure 2 according to

$$B = \exp\{|R(1) - R(B)|/0.3\}$$

where R is the length of a bond of order B and values of $R(1)$, for bonds with orders assumed to be unity, are taken from NH in R and from CN, CO, and OH in P. Figure 3a also shows net

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Table II. Comparison of Calculated and Experimental Hydrogen Bond Strengths (Energies in kJ mol⁻¹)

equilibrium	$\Delta H(\text{exptl})$	$\Delta(H-E)^a$	$\Delta E(\text{exptl})$	$\Delta E(\text{calcd})$		$\Delta H(\text{AM1})$	
				HF/3-21G	MP2/6-31G* ^b	bifurcated	linear
$2\text{H}_2\text{O} \rightleftharpoons (\text{H}_2\text{O})_2$	$-15.0 \pm 2^{c,d}$	9.2^c	-24.2 ± 2	-45.9	-28.6	-20.9	-13.0
$\text{NH}_4^+ + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{NH}^+\cdots\text{OH}_2$	$-72.4 \pm 2^{e,f}$	4.9^e	-77.3 ± 2	-141.8	-97.2	-63.9	-58.9
$\text{CH}_3\text{O}^- + \text{H}_2\text{O} \rightleftharpoons \text{CH}_3\text{O}^-\cdots\text{HOH}$	$-83.3 \pm 7^{e,g}$	8.6^e	-91.9 ± 7	-155.6	-124.2	-67.9	-50.0

^a Calculated from 3-21G scaled vibrational frequencies. ^b Geometries optimized at the HF/3-21G level. ^c 373 K. ^d Curtiss, L. A.; Frurip, D. J.; Blander, M. J. *J. Chem. Phys.* **1979**, *71*, 2703. ^e 298 K. ^f Payzant, J. D.; Cunningham, A. J.; Kebarle, P. *Can. J. Chem.* **1973**, *51*, 3242. ^g Caldwell, G.; Rozeboom, M. D.; Kiplinger, J. P.; Bartmess, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 4660.

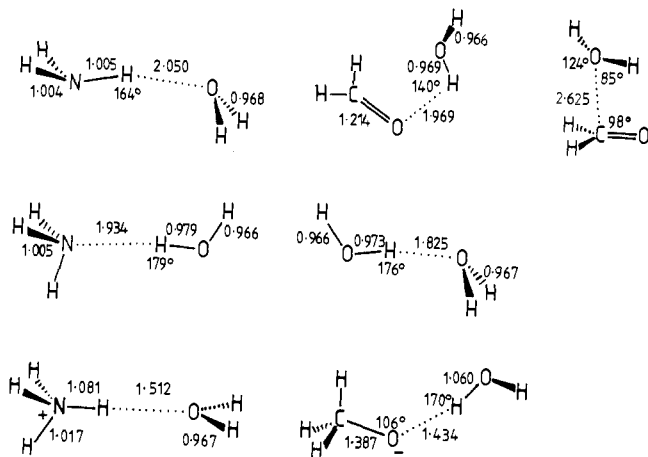


Figure 4. 3-21G optimized geometries for some hydrogen-bonded and dipole-dipole complexes (bond lengths in Å).

atomic charges from Mulliken population analyses at the HF/3-21G level for the optimized structures T, TW, and T2W. Figure 3b shows net atomic charges for distorted ammonia and formaldehyde moieties fixed in the same geometries as in TW and T2W. Figure 4 shows 3-21G optimized geometries for hydrogen-bonded complexes $\text{H}_2\text{NH}\cdots\text{OH}_2$, $\text{H}_3\text{N}\cdots\text{HOH}$, $\text{CH}_2\text{O}\cdots\text{HOH}$, $\text{H}_2\text{O}\cdots\text{HOH}$, $\text{H}_3\text{NH}^+\cdots\text{OH}_2$, and $\text{CH}_3\text{O}^-\cdots\text{HOH}$ and the dipole-dipole complex $\text{H}_2\text{O}\cdots\text{CH}_2\text{O}$.

Discussion

Hydrogen Bonding. Before considering the structural and energetic consequences of specific solvation, it is first necessary to assess the reliability of the component hydrogen-bonding interactions as presently calculated. The 3-21G basis, in common with other split-valence bases, is known to exaggerate bond dipole moments³⁸ and thus to overestimate the electrostatic contribution to hydrogen bonding; being a small basis it also predicts artificially large intermolecular interactions owing to the superposition error.³⁹ The water dimer is predicted to have the correct geometry at the HF/3-21G level (Figure 4) with a nearly linear hydrogen bond. To compare the calculated hydrogen bond strength with the experimental enthalpy of dimerization it is necessary to include the zero-point and thermal energy change $\Delta(H-E)$; this yields $\Delta H_{373} = -37$ kJ mol⁻¹ (HF/3-21G) vs. -15 ± 2 kJ mol⁻¹ (experimental⁴⁰). Since the error is in the potential energy change ΔE , rather than in $\Delta(H-E)$, it is better to compare $\Delta E(\text{HF/3-21G}) = -46$ kJ mol⁻¹ with $\Delta E(\text{experimental}) = -24 \pm 2$ kJ mol⁻¹ (Table II). Thus the strength of the hydrogen-bonding interaction in the water dimer is overestimated by about 90% at this level. The error is substantially reduced at the MP2/6-31G*/HF/3-21G level to about 20%. As the data in Table II reveal, the hydrogen bonding in ionic species $\text{H}_3\text{NH}^+\cdots\text{OH}_2$ and $\text{CH}_3\text{O}^-\cdots\text{HOH}$ is also overestimated by ~70–85% at the HF/3-21G level and by ~25–30% at the MP2/6-31G* level.

The AM1 method consistently predicts bifurcated hydrogens in contrast to most experimental findings. The value of $\Delta H = -13$ kJ mol⁻¹ calculated for a linearly constrained hydrogen-bonded water dimer is rather close to the experimental value, but the fully optimized structure contains a bifurcated hydrogen bond whose strength is overestimated by 40%. The preferred bifurcated hydrogen bonds in $\text{H}_3\text{NH}^+\cdots\text{OH}_2$ and $\text{CH}_3\text{O}^-\cdots\text{HOH}$ are underestimated by 12 and 18%, respectively, and the linearly constrained hydrogen bonds in these ion-molecule complexes are underestimated by 30 and 45%, respectively.

Structural Consequences of Specific Solvation. The water molecule in RW acts as a proton acceptor in a hydrogen bond with ammonia and as a proton donor in a hydrogen bond to formaldehyde. The resulting singly solvated reactant complex has a cyclic structure. The atoms N-H...O'-H...O are nearly coplanar whereas the carbon atom lies ~35° out of this plane; in contrast the carbon atom is coplanar with the N-H...O atoms in the symmetrical unsolvated complex R. The N...O' distance is shorter (2.960 Å) in RW than in $\text{H}_2\text{NH}\cdots\text{OH}_2$ (3.029 Å), but the N-H distance is longer (1.012 Å vs. 1.005 Å). Similarly the O'...O distance is slightly shorter (2.763 Å) than in $\text{CH}_2\text{O}\cdots\text{HOH}$ (2.771 Å) despite a longer O'-H' bond (0.974 Å vs. 0.969 Å). The nucleophilicity of ammonia and the electrophilicity of formaldehyde are each enhanced by hydrogen bonding to the water: the N...C distance is shorter (2.619 Å vs. 2.802 Å) and the C=O bond is longer (1.217 Å vs. 1.209 Å) in RW than in R.

Incorporation of a second water molecule in the hydrogen-bonded chain leads to further enhancement of nucleophilicity and electrophilicity and the N...C distance decreases to 2.414 Å and the carbonyl bond stretches to 1.223 Å. The progressive extension and loosening of the C=O bond in the series CH_2O , R, RW, and R2W is manifest in the respective calculated carbonyl stretching frequencies: 1751, 1750, 1720, and 1693 cm⁻¹. The hydrogen bond lengths N...O' = 2.871 Å and O'...O = 2.668 Å are shorter still in R2W than in RW or in $\text{H}_2\text{NH}\cdots\text{OH}_2$ and $\text{CH}_2\text{O}\cdots\text{HOH}$, respectively, and the O'...O' hydrogen bond is also shorter (2.642 Å) than in $\text{HOH}\cdots\text{OH}_2$ (2.797 Å), but the N-H and O-H bond lengths in the hydrogen-bonded chain are longer than in RW. The eight-membered ring in R2W permits more nearly linear hydrogen bonds than does the six-membered ring of RW; the average angle at an endocyclic hydrogen in R2W is 170° whereas in RW it is 158°. The atoms of the hydrogen-bonded chain are again approximately coplanar in R2W, with the carbon atom tilted out of the plane. The N...C=O angle of 109° is almost the same as in the product complex P2W.

Whereas the effect of specific solvation of the reagent complexes is to shift their structures in the direction of carbonyl addition, the reverse effect is seen in the product complexes. Incorporation of 1 or 2 water molecules in cyclic hydrogen-bonded complexes PW and P2W leads to a longer C-N bond and a shorter C-O bond.

Specific solvation of the activated complex for carbonyl addition causes a general increase in the bond orders of the endocyclic bonds: breaking bonds are less broken and making bonds are generally more made in TW and T2W than in T (Figure 3a). The bond angles in TW and T2W are more product-like than in T. The $\text{NH}_3\text{-CH}_2\text{O}$ fragment in both TW and T2W appears to be less distorted than in T: the interior angles at nitrogen and at carbon are larger and the breaking N-H and C=O bonds are shorter. The degree of tetrahedrality about carbon is also more product-like for the specifically solvated activated complexes, and the angles at the transferring protons are much larger than the

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Table III. Calculated Energy Changes (kJ mol⁻¹) for Hydrogen Bonding and Dipole-Dipole Equilibria

equilibrium	HF/3-21G			MP2/6-31G*	AM1 ΔH
	ΔE	$\Delta(H-E)$	ΔH		
NH ₃ + H ₂ O \rightleftharpoons HOH...NH ₃	-44.4	8.6	-35.8	-25.1	-12.1
NH ₃ + H ₂ O \rightleftharpoons H ₂ NH...OH ₂	-29.7	5.2	-24.5	-6.7	-13.4
2H ₂ O \rightleftharpoons HOH...OH ₂	-45.9	8.6	-37.3	-28.6	-20.9
CH ₂ O + H ₂ O \rightleftharpoons CH ₂ O...HOH	-38.1	8.2	-29.9	-27.5	-16.6
CH ₂ O + H ₂ O \rightleftharpoons H ₂ O...CH ₂ O	-22.3	6.7	-15.6	-15.9	-15.3
CH ₂ O + NH ₃ \rightleftharpoons R	-20.1	5.4	-14.7	135.0 ^a	-12.3
CH ₂ O + NH ₃ + H ₂ O \rightleftharpoons RW	-87.1	17.4	-69.8	-50.9	-41.6
CH ₂ O + NH ₃ + 2H ₂ O \rightleftharpoons R2W	-168.7	27.9	-140.8	-98.1	-73.7

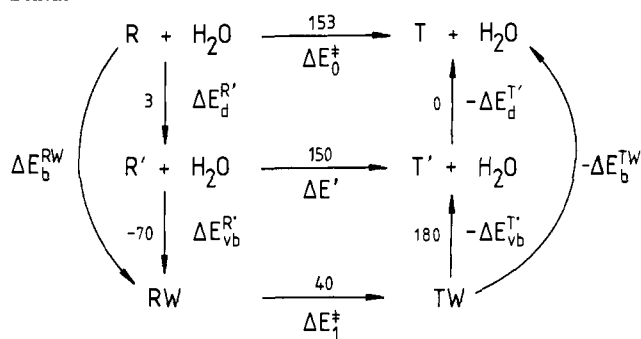
^aThe complex R is very unstable in 6-31G*: the MP2/6-31G**//HF/6-31G* value is $\Delta E = 125$ kJ mol⁻¹; the solvated complexes RW and R2W are normal in this basis.

116° value in *T*. The average angle at an endocyclic hydrogen in TW is 153° whereas in T2W it is 167°; these values are slightly lower than the corresponding angles in RW and R2W, but nonetheless they manifest the same tendency to more nearly linear endocyclic hydrogen bonds with increasing ring size.

The AM1 optimized geometry for RW displays the predilection of this method toward bifurcated hydrogen bonds: the ammonia serves as a double donor toward the water which in turn serves as a double donor toward formaldehyde. Similarly the AM1 structure for R2W contains a chain of three bifurcated hydrogen bonds. The activated complex TW has a similar structure in AM1 as in 3-21G but is somewhat more product-like. The AM1 Pauling bond order for making the N-C bond is 0.75 as compared with the 3-21G value of 0.53, whereas the breaking N-H bond order is 0.46 vs. 0.65. The endocyclic hydrogen bonds are, at 149° and 140°, rather more bent in the AM1 structure than in the 3-21G optimized TW structure, but they are nonetheless "linear" rather than bifurcated. The AM1 activated complex T2W also contains "linear" endocyclic hydrogen bonds, bent by 155°, 161°, and 149°, but resembles an ion pair NH₃⁺CH₂OH·HOHOH⁻: Pauling bond orders of 0.75 for the making N-C and H'-O bonds and 0.80 for the breaking N-H bond are predicted.

Energetic Consequences of Specific Solvation. Potential Energies. Association of 1 water molecule with the reagent complex R to form RW is exoergic by -67 kJ mol⁻¹ (Table III). This value may be compared with the sum of the individual hydrogen bond strengths in H₂NH...OH₂ and HOH...OCH₂ which is -68 kJ mol⁻¹. The hydrogen bonding in RW, in which water serves bifunctionally, is as effective as the component interactions taken together, in which a water molecule serves monofunctionally, despite the fact that the hydrogen bonds in RW are bent. The association of R with two water molecules to form R2W, in which the hydrogen bonds are more nearly linear, is exoergic by -149 kJ mol⁻¹ as compared with a value of -114 kJ mol⁻¹ for the sum of the component hydrogen-bond strengths (H₂NH...OH₂, HOH...OH₂, and HOH...OCH₂). The increased effectiveness of the hydrogen bonding in the cyclic complexes is in part a cooperative phenomenon, and in part it arises from the increased polarity of the NH₃-CH₂O moiety relative to the isolated fragments. Similar considerations apply to hydrogen bonding in the product complexes.

The potential energy of reaction ΔE (Table IV) for addition of ammonia to formaldehyde within an encounter complex is not much affected by specific solvation, but the potential energy of activation ΔE^* is dramatically reduced as water molecules are involved catalytically in the activated complexes TW and T2W. The first water molecule effects a massive 113 kJ mol⁻¹ reduction in the activation energy, and the second water molecule brings about a further lowering of 33 kJ mol⁻¹ such that the poten-

Scheme I

tial-energy barrier to reaction via T2W is only 7 kJ mol⁻¹. If the activated-complex energies are taken relative to the isolated reagents ammonia, formaldehyde, and water (Table V) then the catalytic effect of the first water molecule is 181 kJ mol⁻¹, which may be compared with 173 kJ mol⁻¹ calculated in STO-3G for the catalytic effect of a single ancillary water molecule on hydration of formaldehyde.⁹

Similarly dramatic energy-barrier reductions effected by a single ancillary water molecule have been reported in other theoretical studies of additions to double bonds. The energy barrier (with respect to isolated reagents) for hydration of the C=C bond of ketenimine is lowered by 177 kJ mol⁻¹ in STO-3G or 187 kJ mol⁻¹ at the HF/4-31G//HF/STO-3G level.⁴² The barrier reduction for hydration of the carbonyl bond is somewhat lower (~152 kJ mol⁻¹ in STO-3G) for ketene⁴³ but somewhat higher (209 kJ mol⁻¹ in 3-21G) for carbon dioxide.⁴⁴ Ruelle et al.⁴⁵ studied a water-catalyzed decarboxylation of formic acid at various levels of theory: the barrier for the reverse reaction, hydrogenation of carbon dioxide, is lowered by participation of the water molecule to the extent of 231 kJ mol⁻¹ in STO-3G, 215 kJ mol⁻¹ in 3-21G, or by rather less (121 kJ mol⁻¹) at the MP2/6-31G**//HF/6-31G** level. Oie et al.⁴⁶ found that an ancillary molecule of ammonia catalyzed the addition of ammonia to formic acid by 170 kJ mol⁻¹ at the HF/3-21G//HF/STO-3G level but only by 105 kJ mol⁻¹ at the MP2/6-31G**//HF/3-21G level.

The present calculations at the MP2/6-31G**//HF/3-21G level also predict a reduction in barrier height (relative to isolated reagents) of only 126 kJ mol⁻¹ for catalysis by a single water molecule as compared with 181 kJ mol⁻¹ at the HF/3-21G//HF/3-21G level (Table V), consistent with the lower hydrogen bond strengths predicted by the higher level of theory as discussed above. This finding accords with the results of other authors for the effects of inclusion of electron correlation, and the use of a larger basis, upon barrier-height reductions.

Origins of Catalytic Power. The source of the catalytic effect of the water molecule(s) may be analyzed most directly in terms of potential energies rather than free energies, since the latter contain contributions, such as entropies of association, which are not instructive in this context (cf. ref 9). The potential energy barrier ΔE_1^* , for the reaction catalyzed by 1 water molecule may be expressed as

$$\Delta E_1^* = \Delta E_0^* - \Delta E_b^{RW} + \Delta E_b^{TW} \quad (2)$$

where ΔE_0^* is the barrier height for the uncatalyzed addition and ΔE_b^{RW} and ΔE_b^{TW} are the respective binding energies of R and T with a single water molecule (Scheme I). Rearrangement of

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Table IV. Calculated Energy Changes for Ammonia Addition to Formaldehyde at 298 K within an Encounter Complex

reaction	activation energies (kJ mol ⁻¹)				reaction energies (kJ mol ⁻¹)			
	ΔE^*_{3-21G}	ΔH^*_{3-21G}	ΔG^*_{3-21G}	ΔH^*_{AM1}	ΔE_{3-21G}	ΔH_{3-21G}	ΔG_{3-21G}	ΔH_{AM1}
R → [T] ⁺ → P	153	149	168	173	-62	-55	-38	-65
RW → [TW] ⁺ → PW	40	33	52	185	-61	-54	-41	-45
R2W → [T2W] ⁺ → P2W	7	-5	14	234	-68	-62	-51	-41

Table V. Calculated Activation Energies (kJ mol⁻¹) for Ammonia Addition to Formaldehyde at 298 K Relative to Isolated Reagents

reaction	ΔE^*		ΔH^*	
	HF/ 3-21G	MP2/ 6-31G* ^a	3-21G	AM1
NH ₃ + CH ₂ O	133	143	135	161
H ₂ O + NH ₃ + CH ₂ O	-47	17	-36	144
2H ₂ O + NH ₃ + CH ₂ O	-162	-50	-146	161

^a Geometries optimized at the HF/3-21G level.

eq 2 allows the potential energetic contribution ΔE_1^{cat} to catalysis by 1 water molecule to be determined.

$$\begin{aligned}\Delta E_1^{\text{cat}} &= \Delta E_0^* - \Delta E_1^* \\ &= \Delta E_b^{\text{RW}} - \Delta E_b^{\text{TW}} \\ &= (-67) - (-180) = 113 \text{ kJ mol}^{-1}\end{aligned}\quad (3)$$

Similarly the contribution ΔE_2^{cat} to catalysis by two water molecules may be found as eq 4. These contributions to catalysis reflect the differential binding of the activated complex vs. the reactant complex to the solvating water molecule(s). The larger binding energy of the activated complex with the catalyst, water, causes a reduction in the barrier height (cf. ref 9 and 47).

$$\begin{aligned}\Delta E_2^{\text{cat}} &= \Delta E_0^* - \Delta E_2^* \\ &= \Delta E_b^{\text{R2W}} - \Delta E_b^{\text{T2W}} \\ &= (-149) - (-295) = 144 \text{ kJ mol}^{-1}\end{aligned}\quad (4)$$

Further insight may be gained by a formal dissection of the binding energies into (i) distortion and (ii) "vertical binding" components. Scheme I illustrates these conceptual steps for catalysis by a single water molecule. Distortion of R yields a structure R', with the same geometry as the NH₃...CH₂O fragment in RW, at the cost of $\Delta E_d^{\text{R'}}$. Interaction of a water molecule with R' to form RW thus involves a vertical binding energy $\Delta E_{vb}^{\text{R'}}$ which differs from ΔE_b^{RW} by $\Delta E_d^{\text{R'}}$. Similarly, distortion of T yields a structure T', with the same geometry as the NH₃-CH₂O fragment in TW, and the binding energy $\Delta E_b^{\text{T'W}}$ is the sum of $\Delta E_{vb}^{\text{T'}}$ and $\Delta E_d^{\text{T'}}$. The distortion and vertical binding energies may be obtained as potential energy changes calculated by consideration of the structures R' and T' (and of R'' and T'' for the 2-water reaction, for which a similar relation is also simply derived). These structures do not correspond to critical points on the potential energy surfaces and thus are not amenable to evaluation of their free energies.

The energy barriers ΔE_1^* and ΔE_2^* may therefore be expressed as eq 5 and 6. The barrier ΔE_0^* and the distortion energies involve only the ammonia and formaldehyde (solute) moieties whereas the vertical binding energies involve only the (solvent) water molecules. The components of each of eq 5 and 6 may therefore

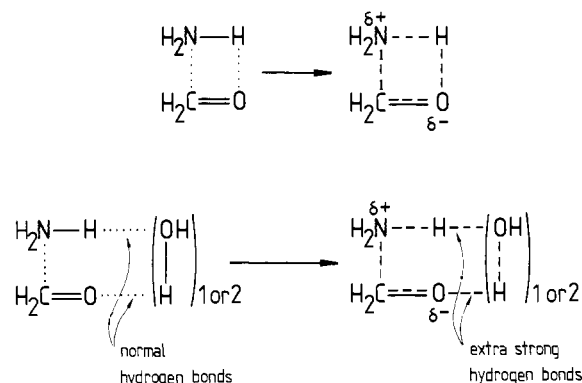
$$\begin{aligned}\Delta E_1^* &= \Delta E_0^* - (\Delta E_{vb}^{\text{R'}} + \Delta E_d^{\text{R'}}) + (\Delta E_{vb}^{\text{T'}} + \Delta E_d^{\text{T'}}) \\ &= 153 - (-70 + 3) + (-180 + 0) \text{ kJ mol}^{-1}\end{aligned}\quad (5)$$

$$\begin{aligned}\Delta E_2^* &= \Delta E_0^* - (\Delta E_{vb}^{\text{R''}} + \Delta E_d^{\text{R''}}) + (\Delta E_{vb}^{\text{T''}} + \Delta E_d^{\text{T''}}) \\ &= 153 - (-159 + 10) + (-301 + 6) \text{ kJ mol}^{-1}\end{aligned}\quad (6)$$

be grouped into a "solute reorganization" term and a "solvent reorganization" term. The values of these terms, as summarized in Table VI, reveal an almost constant positive solute reorganization energy and an increasingly negative solvent reorganization energy, which is almost solely responsible for the reduction in the

Table VI. 3-21G and AM1 Calculated Contributions to Energies of Activation (kJ mol⁻¹) for Ammonia Addition to Formaldehyde, within an Encounter Complex, Catalyzed by 0, 1, or 2 Water Molecules

method	no. of water molecules	solute reorganization	solvent reorganization	total activation energy
3-21G	0	153		153
	1	150	-110	40
	2	149	-142	7
AM1	0	173		173
	1	164	21	185
	2	122	112	234

Scheme II

total energy barrier as the number of catalyzing water molecules is increased.

The high barrier to the uncatalyzed, gas-phase addition of ammonia to formaldehyde may be attributed to the unfavorable charge separation which accompanies approach of the reagents. The activated complex T and the nonexistent zwitterionic intermediate NH₃⁺CH₂O⁻ are similar in this regard; they differ in that T is unbound not only toward reagents but also toward products, by virtue of the disposition of the transferring proton. The Mulliken population analysis for T (Figure 3a) suggests overall partial positive and negative charges on the ammonia and formaldehyde moieties of magnitude ~|0.25e|. As these partial charges develop, so the strength of hydrogen bonding of a water molecule to either the nucleophile or the electrophile increases. The advantage for a single water molecule is maximized when it serves not just monofunctionally, as a hydrogen bond donor or acceptor, but bifunctionally, as both donor and acceptor.

The solvent reorganization energy (Table VI) represents that increases in overall hydrogen bonding which is due to the charge separation. The consequence of a unit charge separation may be modelled by considering the difference between the sum of the hydrogen bond strengths in H₂NH...OH₂ and CH₂O...HOH and the sum of the hydrogen bond strengths in NH₄⁺...OH₂ and CH₃O...HOH; this may be calculated as -230 kJ mol⁻¹ in 3-21G. The solvent reorganization energy of -110 kJ mol⁻¹ for catalysis by a single water molecule is clearly consistent with less-than-unit charge separation in the activated complex TW. The Mulliken analyses for TW and T' suggest ~|0.3e|.

A second ancillary water molecule aids the catalysis, not so much through additional strong hydrogen bonding to a partially charged moiety but rather by allowing more of the hydrogen bonding potential to be expressed. The Mulliken analysis for T2W suggests a slightly greater degree of charge separation than in TW. The more nearly linear hydrogen bonds in the eight-membered

Table VII. 3-21G Calculated Contributions to Gibbs Free-Energy Changes, Relative to Isolated Reagents, for Addition of Ammonia to Formaldehyde at 298 K Catalyzed by *n* Water Molecules^d

phase	<i>n</i>	association			activation			total		
		ΔE	$\Delta(H-E)$	ΔS	ΔE^*	$\Delta(H-E)^*$	ΔS^*	ΔE^*	$\Delta(G-E)^*$	G^*
gaseous ^a	0	-20	7	-87	153	-4	-64	133	48	181
	1	-87	17	-239	40	-7	-63	-47	101	53
	2	-169	28	-378	7	-12	-66	-162	148	-14
dioxan ^b	0	-20	7	-52	153	-4	-64	133	37	170
	1	-87	17	-153	40	-7	-63	-47	75	28
	2	-169	28	-244	7	-12	-66	-162	108	-54
aqueous ^c	0	1	-1	-48	153	-4	-64	154	29	183
	1	26	-7	-98	40	-7	-63	65	34	99
	2	36	-13	-140	7	-12	-66	43	36	79

^aStandard state 1 atm. ^bStandard state 1 M. ^cStandard state 1 M for NH₃ and CH₂O and 55.5 M for H₂O. ^dEnergies in kJ mol⁻¹, entropies in J K⁻¹ mol⁻¹.

ring of T2W are presumably somewhat less strained than the more-bent hydrogen bonds in the six-membered ring of TW (cf. ref 48).

The number of hydrogen bonds remains unchanged within the encounter complex for each of the catalyzed reactions; the catalysis arises from the increased strength of the hydrogen bonds at the transition state. Interestingly, a similar result emerges from the Monte Carlo simulations of Madura and Jorgensen²⁶ for hydroxide addition to formaldehyde in aqueous solution; here the solvation-induced barrier is attributed to "reduction in hydrogen-bond strengths rather than in numbers of hydrogen bonds".²⁶ There is essentially no barrier to gas-phase addition of hydroxide anion to formaldehyde, a process characterized by charge dispersal;² solvation by molecules of water is more effective for the charge-localized reagents than for the charge-delocalized activated complex, and hence a barrier is introduced. Gas-phase addition of a neutral nucleophile, ammonia, to neutral formaldehyde does involve a barrier since the process is characterized by net charge separation or polarization;² solvation by molecules of water is more effective for the activated complex than for the reagents, and hence the barrier is reduced.

The AM1 method surprisingly fails to predict any catalysis by water of nucleophilic addition: the heats of activation for reactions within the encounter complexes (Table IV) actually *increase* with water participation. The catalytic terms ΔE_1^{cat} and ΔE_2^{cat} are given by eq 7 and 8; their negative values imply anticatalysis. The

$$\Delta E_1^{\text{cat}} = \Delta E_b^{\text{RW}} - \Delta E_b^{\text{TW}} = (-29) - (-17) = -12 \text{ kJ mol}^{-1} \quad (7)$$

$$\Delta E_2^{\text{cat}} = \Delta E_b^{\text{R2W}} - \Delta E_b^{\text{T2W}} = (-61) - (0) = -61 \text{ kJ mol}^{-1} \quad (8)$$

contributions ΔE_b^{RW} and ΔE_b^{R2W} are roughly equal to the sums of the pairwise component interactions (Table III) introduced by binding of 1 and 2 water molecules respectively to R, and as such they are well behaved. The small or zero contributions ΔE_b^{TW} and ΔE_b^{T2W} correspond to negligible binding energies of the zwitterion-like activated complex T with 1 or 2 water molecules. Just as AM1 underestimates the strength of bifurcated and (particularly) linear hydrogen bonds between water and the ammonium and methoxide ions (Table II), so also it appears that AM1 seriously underestimates the strength of hydrogen bonding between water and the partially charged ammonia and formaldehyde moieties in the cyclic activated complexes TW and T2W. Alternatively, the solute reorganization energy (Table VI) decreases as the number of water molecules increases whereas the solvent reorganization energy is unfavorable—quite contrary to the HF/3-21G results.

Reaction-Coordinate Motions and Catalytic Water Acidity. The arrows in Figure 2 indicate the atomic displacements occurring in the normal modes corresponding to the 3-21G (unscaled) reaction-coordinate frequencies of 1611i, 985i, and 773i cm⁻¹ respectively for the activated complexes T, TW, and T2W. In each case the reaction-coordinate mode is dominated by proton transfer along the hydrogen bonds. The 0.7:1 ratio of the magnitudes of the displacement vectors for transferring protons H and H' concurs with the evidence of the Pauling bond orders for the endocyclic making and breaking bonds (Figure 3a) to suggest that N-H-O'

transfer is more advanced than O'-H'-O transfer in the activated complex TW. Similarly, the 0.5:0.7:1 ratio of the magnitudes of the displacement vectors for transferring protons H, H', and H'', along with the Pauling bond orders, suggests relative degrees of proton transfer N-H-O' < O'-H'-O'' < O''-H''-O in the activated complex T2W. Thus it appears that each catalytic water molecule, although bifunctional, shows a tendency to be acidic.

These results accord with those of a recent HF/3-21G theoretical study of formamide formation (from 1,1-addition of NH₃ to HNC) catalyzed by water: Nguyen and Hegarty⁴⁹ report that a water molecule acts as an acid catalyst in a cyclic activated complex comprising also the ammonia nucleophile and the isocyanide molecule. On the basis of relative bond lengths in the activated complex, these authors describe the proton transfers as "highly asynchronous". Two comments are in order. First, it is safer to use bond orders (e.g., Pauling bond orders, as above) than bond lengths in discussions of relative degrees of bond making and breaking. Second, it would seem that the term "synchronous" (or its converse "asynchronous") may be used to describe multiple proton transfer in two different senses. The proton transfer occurring in TW (or T2W) may properly be described as synchronous in that the protonic displacements each contribute to the reaction-coordinate normal mode of vibration. However, two (or more) proton transfers are often also described as synchronous if they have proceeded to the same extent in the activated complex, even if they do not each contribute to the reaction-coordinate mode. An activated complex is conceivable in which two protons have been transferred to unequal extents but whose displacements contribute equally to motion along the reaction coordinate!

Consideration of Pauling bond orders for the making and breaking bonds in the cyclic HF/3-21G activated complex for ammonia catalyzed addition of ammonia to carbon dioxide⁵⁰ suggests that the catalyst acts as a base: proton abstraction from the nucleophile is more advanced than proton donation to the electrophile in the activated complex. This agrees with Nguyen and Hegarty's finding that ammonia acts as a basic catalyst in the cyclic activated complex for ammonia addition to isocyanide⁴⁹ and contrasts with the apparent tendency of water to act as an acidic catalyst.

Relative Gibbs Free Energies. The preceding discussion of the energetics of catalysis, besides being based upon potential-energy changes, was also mainly confined to changes occurring within the encounter complex for the reaction, i.e., to the activation process. To establish which of the reaction pathways would be preferred under particular conditions, it is necessary also to consider the association process leading to formation of the encounter complex from the reagents. Table VII contains the enthalpic and entropic contributions to the association and activation processes for the reactions catalyzed by 0, 1, and 2 water molecules in the ideal gas phase at 298 K (standard state 1 atm). As expected, the 1- and 2-water reactions involve large negative entropies of association. However, the entropy of activation within

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the encounter complex is almost the same for all three reaction pathways. The entropic disadvantage of specific solvation is countered by favorable enthalpies of association, so that the overall free energy of activation ΔG^* for the 1-water reaction via TW is virtually the same as its value for the activation process only. The value of ΔG^* is increased for the uncatalyzed reaction, and that for the two-water reaction is decreased, relative to the values of ΔG^* within the respective encounter complexes.

The energetics of reaction in an aprotic solvent of low dielectric constant, such as dioxan, may be estimated by using three assumptions. First, it is assumed that the enthalpic contributions are the same as in the gas phase. Second, it is assumed that the entropy of any solute in dioxan is simply related to its gas-phase molar entropy (cf. ref 51) as previously discussed.⁹ At 298 K and a standard state of 1 M, the entropy of any species is given by

$$S_d^+ = 0.77S^\circ - 15.7 \text{ J K}^{-1} \text{ mol}^{-1}$$

Third, it is assumed that the reagents are unassociated in their initial state. The resulting entropic contributions to the free-energy changes of ammonia addition to formaldehyde in dioxan are also given in Table VII. The adverse entropies of association are mitigated so that the overall activation energies ΔG^* are less than in the gas phase.

To estimate the energetics of reaction in aqueous solution it is necessary also to consider the initial desolvation of the reagents. This may be done in an unsophisticated but simple manner as follows. In order to form the reagent complex R, one $\text{HOH}\cdots\text{NH}_3$ hydrogen bond and one $\text{H}_2\text{O}\cdots\text{CH}_2\text{O}$ interaction must be broken. The penalty for so doing is offset by the $\text{H}_3\text{N}\cdots\text{CH}_2\text{O}$ interaction and by formation of a new hydrogen bond between the immediately desolvated water molecules. To form the reagent complexes RW and R2W the same terms are involved plus the extra energy to desolvate 1 and 2 water molecules, respectively, at a cost of two $\text{HOH}\cdots\text{OH}_2$ hydrogen bonds per water molecule released. The enthalpic terms ΔE and $\Delta(H - E)$ contributing to the desolvation + association process may be estimated from the values given in Table III for the individual equilibria, and the resulting sums are presented in Table VII. The entropy of any solute in aqueous solution at 298 K and standard state 1 M is assumed to be given by (cf. ref 9 and 51)

$$S_{\text{aq}}^+ = 0.54S^\circ + 1.0 \text{ J K}^{-1} \text{ mol}^{-1}$$

and the entropy of water in aqueous solution (298 K, 55.5 M) is given by⁹

$$S''_{\text{aq}} = 0.54S^\circ - 32.4 \text{ J K}^{-1} \text{ mol}^{-1}$$

As the data of Table VII show, the positive enthalpies of desolvation outweigh the negative intrinsic association enthalpies, and together with the entropic terms they give free energies of association of 14, 48, and 65 kJ mol⁻¹ respectively for R, RW, and R2W. Assuming again that the energetics of the activation process within the encounter complex are the same as in the gas phase (i.e., ignoring the dielectric effect of the aqueous medium), the overall free energies of activation ΔG^* may be obtained.

The catalytic effect of specific solvation by 1 or 2 water molecules is undoubtedly overestimated at the HF/3-21G level of calculation. The prime sources of error are the too-large potential-energy changes predicted for hydrogen-bonding interactions; the non-potential-energy changes $\Delta(H - E)$ and ΔS are likely to be estimated reasonably well in 3-21G. More realistic values of ΔE for hydrogen bonds are perhaps obtained by dividing the 3-21G energies by two: this (arbitrary) procedure may then somewhat underestimate the strengths of hydrogen bonds (cf. Table II). The "best" estimates for the overall Gibbs free energies of activation given in Table VIII, for the reactions in various media, are obtained as follows. The solute-reorganization contribution to ΔE^* (Table VI) is subtracted from the overall potential energy of activation ΔE^* , and then half the result is summed with

Table VIII. "Best" Estimates for Gibbs Free Energies of Activation (kJ mol⁻¹), Relative to Isolated Reagents, for Addition of Ammonia to Formaldehyde at 298 K Catalyzed by *n* Water Molecules

<i>n</i>	gaseous ^a	dioxan ^b	aqueous ^c
0	191	180	182
1	152	126	143
2	141	101	133

^aStandard state 1 atm. ^bStandard state 1 M. ^cStandard state 1 M for NH₃ and CH₂O and 55.5 M for H₂O.

the overall non-potential-energy term $\Delta(G - E)^*$ and the solute-reorganization energy ΔE^* (solute) is added back on:

$$\Delta G^*(\text{best}) = \frac{1}{2}[\Delta E^* - \Delta E^*(\text{solute})] + \Delta(G - E)^* + \Delta E^*(\text{solute})$$

The estimates for ΔG^* (best) in Table VIII show that the catalyzed reactions involve substantially lower barriers than the uncatalyzed reaction in all three media. More interestingly, these results suggest that the 2-water-catalyzed reaction is favored by about 10 kJ mol⁻¹ over the 1-water reaction in both the gaseous and aqueous phases and by about 25 kJ mol⁻¹ in a nonpolar aprotic solvent. The absolute values of these activation energies may alter with the use of a higher level of theory (e.g., geometry optimization with a correlated wave function using an extended basis), but the relative values, which are of more interest, are not expected to vary greatly. While the present theoretical results agree with the conclusions of recent experimental studies in non-hydroxylic solvents of low dielectric constant (e.g., cyclic, hydrogen-bonded activated complexes for addition of water or alcohols to ketenes in dioxan solution⁵²), the omission of dielectric effects must prejudice the predictions of the specific solvation model for aqueous media. In earlier work it was shown⁹ that just four specifically solvating water molecules were sufficient to stabilize the H₂O⁺-CH₂O⁻ zwitterion. Partially charge separated species, such as T, TW, and T2W, will doubtless be stabilized by dielectric effects; consequently the relative energetics of the various concerted and stepwise mechanisms will be altered. It would be of interest to employ the strategy advocated by Tapia,⁵³ whereby a Monte Carlo simulation of aqueous solvation would be performed, using a simple solute-solvent potential, to generate averaged solvent structures which would then be subjected to study the self-consistent reaction field method.⁵⁴

Conclusions

Calculations at the HF/3-21G level of theory predict that nucleophilic addition of ammonia to formaldehyde is catalyzed by 1 or 2 water molecules participating bifunctionally in cyclic activated complexes. The catalysis arises from the increased strength of hydrogen-bonding interactions between the water molecule(s) and the zwitterion-like ammonia-formaldehyde moiety in the activated complex. The 2-water-catalyzed process is preferred over the 1-water reaction in all media considered. Active catalysis by specifically solvating water molecules represents an efficient way to avoid the unfavorable charge separation accompanying the uncatalyzed reaction.

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Supplementary Material Available: Listing of full geometries for the structures shown in Figure 2, optimized in 3-21G and in AM1 (7 pages). Ordering information is given on any current masthead page.

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