# High-Level ab Initio Molecular Orbital Calculations of Imine Formation

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Ab initio molecular orbital calculations at the G2(MP2,SVP) level are reported for the reaction between methylamine and formaldehyde to form the Schiff-base, *N*-methylmethanimine, with loss of water. The gas-phase barrier to carbinolamine formation through intramolecular proton transfer is found to be dramatically reduced when explicit water molecules are employed to facilitate the proton transfer. The lowest barrier lies 14.7 kJ mol$^{-1}$ above the complex between methylamine, formaldehyde, and two water molecules and passes through a zwitterionic intermediate. The structural features of the transition state for this process closely resemble those predicted experimentally. Although intramolecular proton transfer through water molecules to form the imine from the carbinolamine requires significantly less energy than without the water, the barrier remains quite large. With two waters the barrier is calculated to be 111.9 kJ mol$^{-1}$. A considerably smaller barrier is predicted for the protonated carbinolamine, 67.9 kJ mol$^{-1}$, and while there is no experimental evidence for internal proton transfer, the calculated structure shows characteristics of the experimentally predicted transition state. Calculated aqueous-phase dissociation energies are too small in comparison with the experimentally observed equilibrium constants.

## Introduction

In solution, attack upon an aldehyde or ketone group by a primary amine leads to imine (Schiff base) formation via a carbinolamine intermediate.[1−3] The details of the mechanism for this reaction depend on the specific molecules which undergo reaction and the solution conditions. Imine formation from the neutral reactants will most often proceed through a three step process. Initially, a zwitterionic species ($T^{\pm}$) will form which subsequently undergoes an internal proton transfer from nitrogen to oxygen facilitated by two water molecules to give the neutral carbinolamine (T°).[4,5] Direct protonation of the carbinolamine hydroxyl group and loss of a water molecule or loss of a hydroxide ion results in formation of the iminium ion ($ImH^+$)[6] (Figure 1). In the reverse direction, imine hydrolysis by either hydroxide or water is found to only occur on this protonated iminium species.[7,8]

In low-pH conditions either the $O^-$ of the zwitterion or the nitrogen of the carbinolamine can become protonated to yield the positively charged carbinolamine ($T^+$). Intramolecular proton transfer from nitrogen to oxygen can then lead to iminium ion formation. Alternatively, formation of $T^+$ can occur without forming the zwitterion intermediate via direct protonation of the carbonyl oxygen. Protonation of the amine nitrogen precludes carbinolamine formation. In a basic environment one of the N-hydrogens of the amine or zwitterion can be abstracted, resulting in the negatively charged carbinolamine ($T^-$). The anionic carbinolamine must undergo reprotonation before the imine can be formed.

Computational studies investigating van der Waals complexes of ammonia and formaldehyde[9−11] and conformational energies of carbinolamines[12,13] have been reported previously. In addition, a detailed study of zwitterion formation between methylamine and formaldehyde has been reported recently.[14] We are unaware, however, of any theoretical studies of imine formation from a carbinolamine.

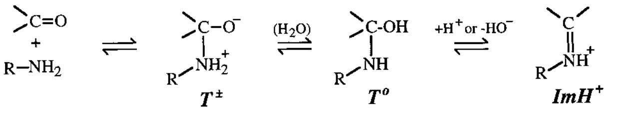

**Figure 1.** Likely pathways to iminium ion formation from neutral reactants.

A strained, high-energy, four-membered ring transition state (TS) linking the ammonia−formaldehyde complex and a carbinolamine has been calculated at various levels of theory.[15−17] This TS has the C−N bond almost fully formed and a proton transferring directly from the nitrogen of the ammonia to the oxygen of the formaldehyde. The effects of different substituents on the nitrogen and carbon atoms on the barrier and geometry of this transition state were found to be minor with the exception of a difluorinated amine, which has a much longer C−N distance in the transition state at the HF/3-21G level.[18] Williams[19] has reported the catalytic effects of water molecules on carbinolamine formation. The water molecules are involved directly, facilitating the proton-transfer process through six- and eight-membered ring transition states with one and two waters, respectively. Similarly, water molecules have been shown to dramatically reduce the barriers in the ketonization of vinyl alcohol[20,21] and several other 1,3-hydrogen rearrangement reactions.[22,23]

Abdulner[24] has investigated, using HF/STO-3G calculations, the proton transfer from a hydronium ion to formaldehyde in complex with ammonia, leading to protonated carbinolamine formation. Although geometries for these calculations were not optimized, the modeled protonation process was shown to be plausible.

In the study presented here, the mechanism of imine formation between methylamine and formaldehyde is investigated. Cal-

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culations of carbinolamine formation from a complex between these two species have been performed both with and without water molecules to facilitate the proton transfer from nitrogen to oxygen. A subsequent proton transfer from N to O results in the elimination of a water molecule and imine formation. The proton transfer from the nitrogen of N-protonated carbinolamine to the oxygen, forming an iminium ion (N-protonated imine), is also considered. The effect of solvent on the imine and iminium ion forming reactions is investigated through the inclusion of specific water molecules to facilitate proton transfer. The effect of the bulk solvent on these reactions is studied through calculation of the solvation free energies for all of the species involved.

## Methods and Results

Standard ab initio molecular orbital calculations[25] are performed at the G2(MP2,SVP) level of theory[26] using the Gaussian94[27] and GAMESS[28] packages. G2(MP2,SVP) is a modification of the hugely successful Gaussian-2 (G2)[29] theory and corresponds effectively to QCISD(T)/6-311+G(3df,2p) calculations performed upon geometries optimized at the MP2/6-31G(d) level. The G2(MP2,SVP) level of theory has been chosen for this study as a computationally accessible method that performs almost equally as well as G2 theory,[30] capable of producing energies within chemical accuracy.[31]

The G2 energy is obtained through additivity approximations that are based upon MP4/6-311G(d,p) energies augmented by corrections from higher level calculations. The additivity scheme of G2(MP2,SVP) theory, however, is based on QCISD(T)/6-31G(d) energies with a single basis set extension (ΔBSE) given by the difference in energy between MP2 calculations using the 6-311+G(3df,2p) and 6-31G(d) basis sets. A zero point vibrational energy correction (ZPVE) is calculated from scaled (0.8929) HF/6-31G(d) frequencies. In addition, a higher-level correction (HLC) is applied to account for remaining basis set deficiencies. This is $\mathrm{HLC} = -An_\beta - Bn_\alpha$, where $A = 5.13$ mhartrees and $B = 0.19$ mhartree and $n_\alpha$ and $n_\beta$ are the number of α and β valence electrons, respectively. Thus, the G2(MP2,SVP) energy is given by

$$E_0 = E[\mathrm{QCISD(T)/6\text{-}31G(d)}] + \Delta\mathrm{BSE} + \mathrm{ZPVE} + \mathrm{HLC} \tag{1}$$

To enable the calculation of enthalpies ($H_{298}$) and aqueous free energies ($G_{298}$(aq)), temperature corrections ($\Delta H_{298-0}$), entropies ($S$), and solvation free energies ($\Delta G_{\mathrm{solv}}$) have been determined. Standard thermodynamic methods using scaled (0.8929) HF/6-31G(d) frequencies (unless otherwise noted) are used for calculation of the enthalpy corrections and entropy contributions to yield the free energies. The total solvation free energy is given by the sum of electrostatic ($\Delta G_{\mathrm{e}}$) and nonelectrostatic ($\Delta G_{\mathrm{ne}}$) energies,

$$\Delta G_{\mathrm{solv}} = \Delta G_{\mathrm{e}} + \Delta G_{\mathrm{ne}} \tag{2}$$

The electrostatic contribution was calculated from the finite difference Poisson−Boltzmann (FDPB) method using the program DelPhi.[32] CHELPG charges[33] calculated at the HF/6-31+G(d) level (on the MP2/6-31G(d) optimized geometries) were used to obtain radii from the solvent interaction potential (SIP)[34] and in the FDPB calculations. This method has the advantage that the electrostatic component of the solvation energy is continuous and size-consistent. The nonelectrostatic component of the solvation free energy is assumed to be proportional to the solvent accessible surface area ($A_{\mathrm{SIP}}$),

$$\Delta G_{\mathrm{ne}} = \gamma A_{\mathrm{SIP}} + b \tag{3}$$

where $\gamma$ and $b$ have been taken to be 20.0 J mol$^{-1}$ Å$^{-2}$ and 3.5 kJ mol$^{-1}$, respectively,[35] and the accessible surface is defined by the SIP. The total aqueous free energies are calculated at the G2(MP2,SVP) level using eq 4.

$$G_{298}(\mathrm{aq}) = E_0 + \Delta H_{298-0} - ST + \Delta G_{\mathrm{solv}} \tag{4}$$

For the systems containing two additional water molecules, the vibrational frequencies used in the thermodynamic corrections have been calculated at the MP2/6-31G(d) level, scaled by a factor of 0.9646.[36] These MP2 frequencies are chosen in preference to HF frequencies as the HF surfaces did not (necessarily) coincide with the MP2 surface used to calculate the G2(MP2,SVP) energies. (The G2(MP2,SVP) method assumes that the geometry upon which the frequencies are calculated corresponds with the geometry in which the single-point energy calculations are performed.) Calculated energies are presented as Supporting Information. Unless otherwise noted, energies in the text refer to gas-phase enthalpies, $\Delta H_{298}$. Results reported here refer to geometries with an eclipsed conformation around the C−N bond such that the dihedral angle between the methyl and oxygen groups is approximately 60°. In addition, orientations of water molecules and the −OH group (of the carbinolamines) are chosen to provide the lowest energy transition-state structures. Where reported, CHELPG charges are those calculated at the HF/6-31+G(d) level.

## Neutral Species

The process of carbinolamine formation from a complex between methylamine and formaldehyde is found to proceed through a concerted proton-transfer reaction from the nitrogen of the methylamine to the oxygen of the formaldehyde via a four-membered ring transition state. Inclusion of one and two water molecules to facilitate this proton transfer allows geometrical relaxation of the strained transition state, resulting in six- and eight-membered rings, respectively. Subsequent transfer of a proton from nitrogen to oxygen of the carbinolamine results in imine formation. This transfer may also be facilitated in a concerted manner by one or two water molecules.

Structures of the stationary points, minima, and transition states, along these reaction paths, with and without water molecules are shown in Figures 2 and 3 with selected bond angles and distances included.

## Carbinolamine Formation

The complex formed between methylamine and formaldehyde (**1**) has a C−N distance of 2.727 Å. The transition state (**2**) leading to the formation of the carbinolamine (**3**) lies 112.3 kJ mol$^{-1}$ above the complex, while the carbinolamine (**3**) lies 46.0 kJ mol$^{-1}$ below the complex. The C−N bond (1.563 Å) is well-formed in the transition state which has H−N and H−O distances of 1.196 and 1.442 Å, respectively. CHELPG charges show a highly polarized charge distribution in this strained four-membered ring transition state. The charge on the oxygen atom of complex **1**, −0.53, increases by −0.33 to −0.86 in TS **2** and decreases to −0.72 in carbinolamine **3**.

Incorporation of a single water molecule to the complex (**4**) leads to a shorter C−N separation of 2.557 Å (cf. 2.727 for structure **1**). The water forms hydrogen bonds to the oxygen of the formaldehyde and one of the N-hydrogens of the methylamine to give a six-membered ring. With the single water molecule, the transition state (**5**) for formation of

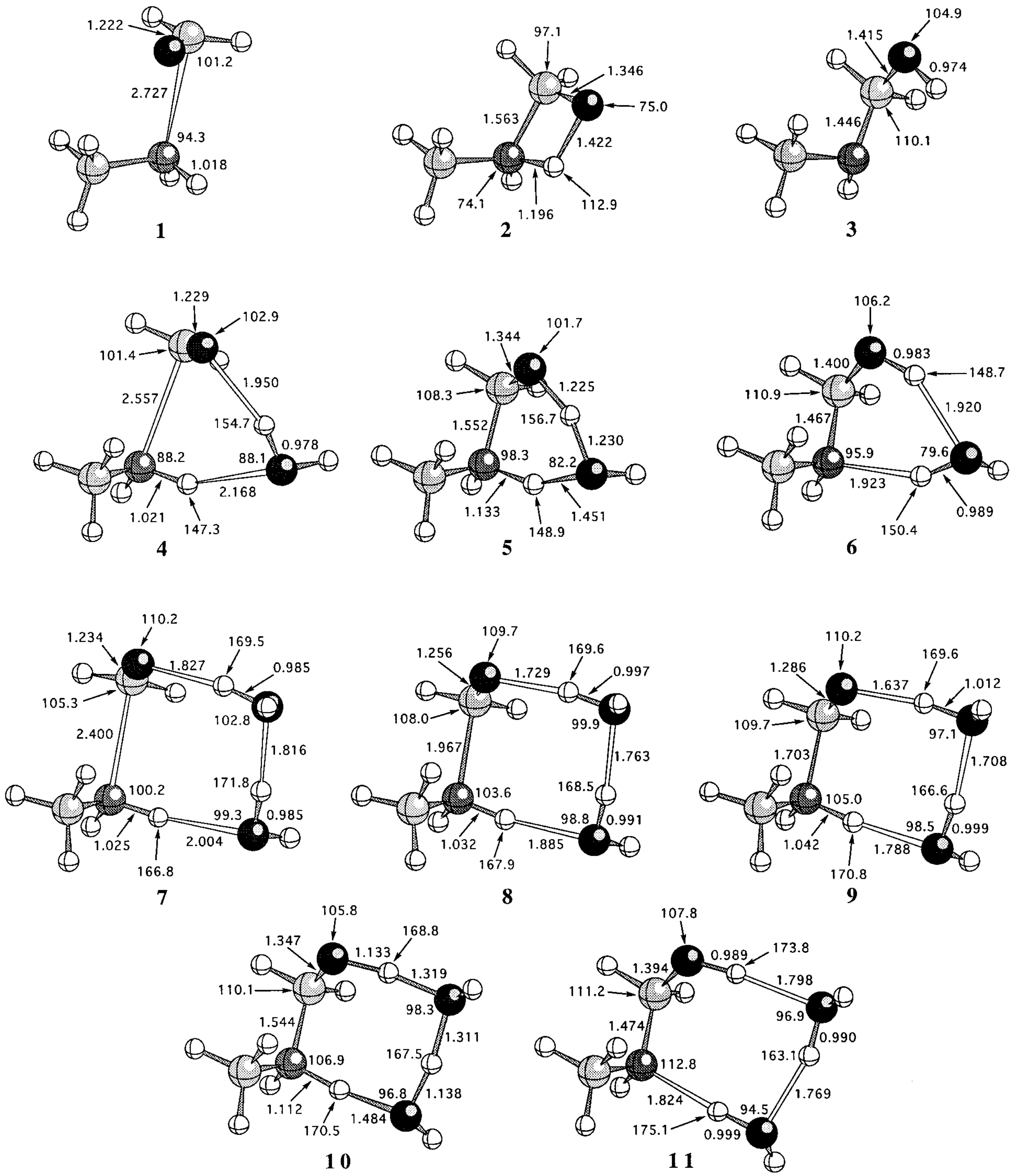


**Figure 2.** Selected bond lengths (angstroms) and angles (degrees) for stationary points along the path of carbinolamine formation from the van der Waals complex between methylamine and formaldehyde involving zero, one, and two water molecules.

carbinolamine **6** has a less strained six-membered ring with an internal CNH angle of 98.3° (cf. 74.1° in TS **2**). Transfer of the N-hydrogen onto the water−oxygen is less advanced than transfer of the hydrogen from this water to the oxygen of the formaldehyde. The C−N separation in TS **5** (1.552 Å) is similar to that found in TS **2** (1.563 Å). The barrier to formation of carbinolamine **6** from complex **4** via TS **5** is 37.6 kJ mol$^{-1}$, 84.7 kJ mol$^{-1}$ less than the barrier through TS **2**. The carbinolamine product (**6**) lies 50.9 kJ mol$^{-1}$ below **4**.

Incorporation of two water molecules in the process of carbinolamine formation is complicated by the presence of a zwitterionic minima **9**. The complex **7**, with a C−N distance of 2.400 Å, readily forms a zwitterion (**9**) which has a long C−N bond of 1.703 Å, and lies just 5.5 kJ mol$^{-1}$ above **7**. The transition state (**8**) connecting **7** and **9** lies 10.9 kJ mol$^{-1}$ above **7** with a C−N distance of 1.967 Å. The zwitterionic nature of structure **9** can best be illustrated through inspection of the CHELPG charges on the oxygen. The oxygen of the formaldehyde in **7** has a charge of −0.63. In the transition state this charge increases to −0.77 and increases further to −0.88 in the zwitterion (**9**). In addition, the length of the hydrogen bond between the formaldehyde oxygen and water proton is seen to decrease with increasing zwitterionic character of the system. The O−H distance, initially 1.827 Å in complex **7**, shortens to 1.729 Å in TS **8** and is further reduced to 1.637 Å in the zwitterion (**9**).

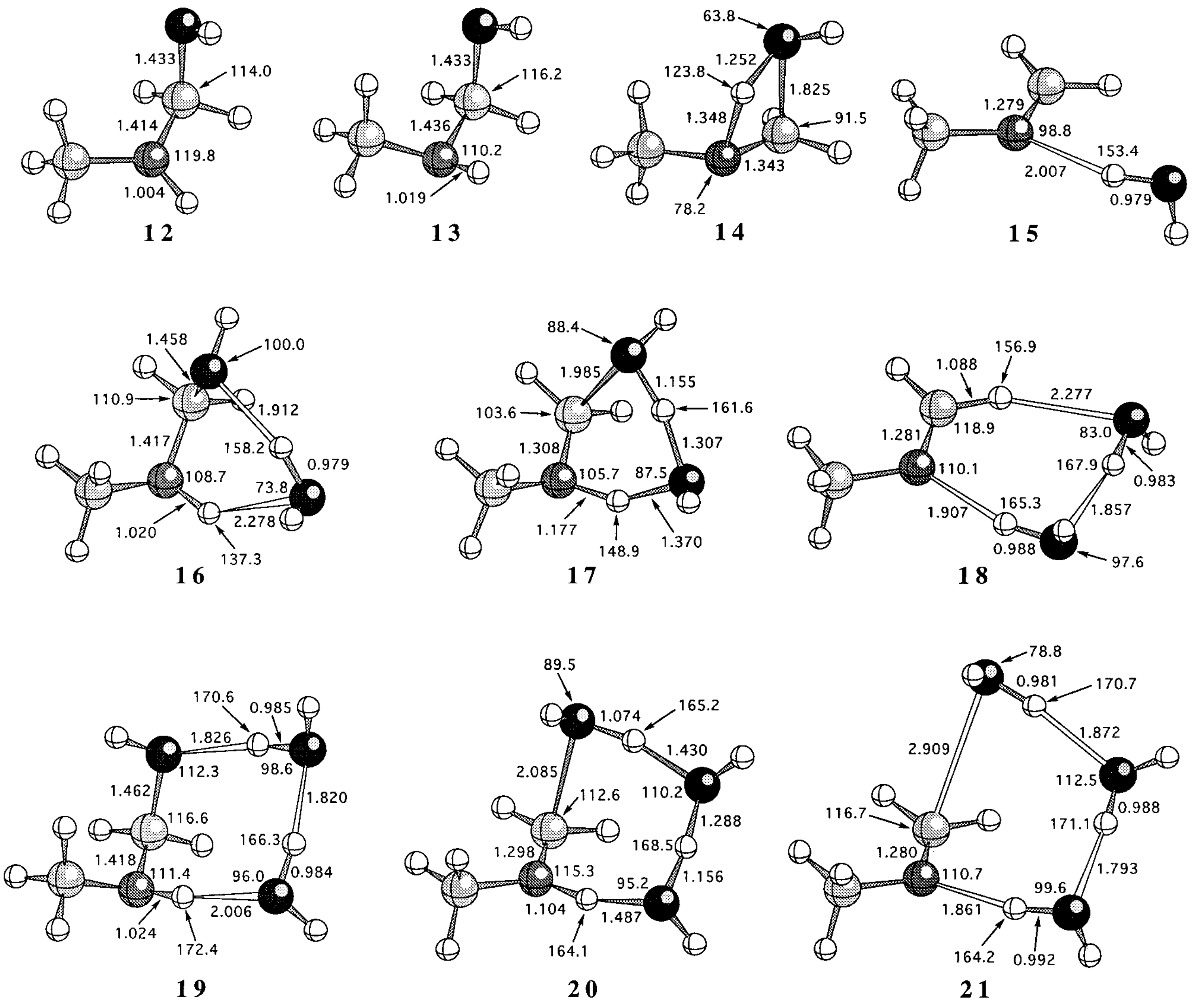


**Figure 3.** Selected bond lengths (angstroms) and angles (degrees) for stationary points along the path of imine formation from the carbinolamine involving zero, one, and two water molecules.

Carbinolamine formation (**11**) proceeds via TS **10** from the zwitterionic species **9**, with a barrier of 9.2 kJ mol$^{-1}$ (14.7 kJ mol$^{-1}$ above complex **7**). With two water molecules, carbinolamine **11** lies 57.6 kJ mol$^{-1}$ below complex **7**. TS **10** involves the concurrent transfer of three protons within the eight-membered ring, with transfer of the amine hydrogen less advanced than the transfer of a hydrogen onto the carbonyl oxygen. Despite the two transition states, **10** and **5**, connecting a zwitterionic species and complex respectively with a carbinolamine, the geometries of these transition states differ by less than 0.01 Å in terms of C−N and C−O distances. The similarity of these transition states, deriving from very different minima, indicates that the existence of the zwitterionic minima on the potential energy surface does not significantly alter the nature of the surrounding surface. A schematic energy profile for formation of carbinolamine from the formaldehyde-methylamine complex involving zero, one, and two water molecules is presented in Figure 4a.

## Imine Formation

Imine formation can proceed in the absence of water molecules via a four-membered ring transition state (**14**) in which the N-hydrogen of the carbinolamine (**13**) is transferred to the oxygen, resulting in the elimination of a single water molecule. The nitrogen of carbinolamine **3** must first undergo inversion through transition state **12** so as to present the N-hydrogen and the hydroxyl on to the same side of the molecule. The calculated barrier to nitrogen inversion is 9.5 kJ mol$^{-1}$. Alternatively, rotation around the C−N bond achieves the appropriate carbinolamine geometry, although this is likely to be a higher energy pathway. The strained four-membered ring TS **14**, lying 231.1 kJ mol$^{-1}$ above **13**, has internal bond angles of 78.2 and 63.8° for CNH and HOC, respectively. The water molecule eliminated by imine formation forms a hydrogen bond to the nitrogen atom of the imine (**15**).

Incorporation of a single water molecule produces a less-strained six-membered transition state (**17**) lying 139.0 kJ mol$^{-1}$ above the carbinolamine (**16**). This amounts to a 92.1 kJ mol$^{-1}$ reduction in the barrier by inclusion of a single water molecule (cf. TS **14** with no additional water molecules). The C−O bond in TS **17** is very long (1.985 Å), although the N−H bond remains short (1.177 Å). The resulting imine (**18**) has an eight-membered hydrogen-bonded ring structure which is almost planar, with most ring dihedral angles smaller than 5° and none larger than 14°.

The imine forming transition state (**20**) involving two water molecules to facilitate proton transfer lies 111.9 kJ mol$^{-1}$ above carbinolamine **19**, 27.1 kJ mol$^{-1}$ lower than the barrier with a

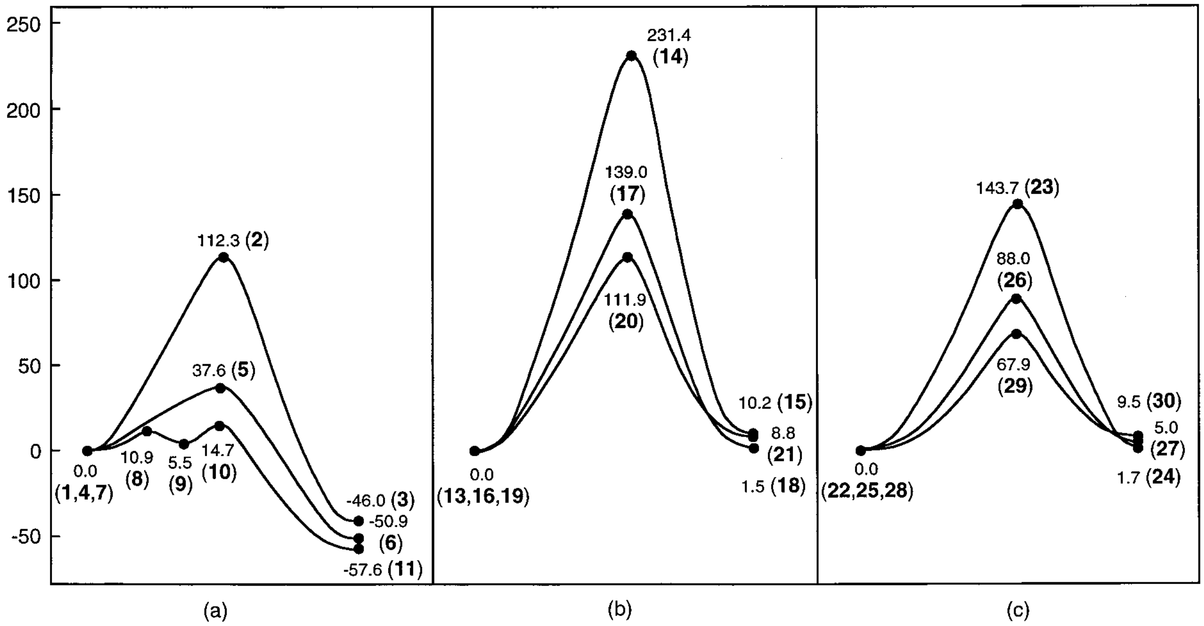


**Figure 4.** Schematic energy profile ($\Delta H_{298}$) of (a) carbinolamine formation, (b) imine formation, and (c) iminium ion formation, with zero, one, and two water molecules in the gas phase. Energies are in kilojoules per mole.

single water molecule (**17**). Water elimination is well-advanced in TS **20**, with a C−O distance of 2.085 Å, although the N−H distance is just 0.080 Å larger than in the carbinolamine (**19**). The resulting imine (**21**) has a nonplanar hydrogen bonding network where the eliminated water molecule is distantly removed from the methylene of the imine. Presented in Figure 4b is a schematic energy profile for imine formation from the carbinolamine for the systems with zero, one, and two water molecules.

## Iminium Ion Formation

In a concerted proton-transfer process similar to that of neutral imine formation, iminium ions (N-protonated imines) can form from N-protonated carbinolamines. Figure 5 contains structures with selected geometrical parameters of the stationary points along the path to iminium ion formation with and without the inclusion of water molecules. In the absence of any water molecules to facilitate transfer of a proton, a strained four-membered ring TS (**23**) links carbinolamine **22** with iminium **24**. This TS lies 143.7 kJ mol$^{-1}$ above the carbinolamine, while the iminium product lies 1.7 kJ mol$^{-1}$ above carbinolamine **22**. This barrier is 87.4 kJ mol$^{-1}$ smaller than for the corresponding neutral species which proceeds via transition state **14**. Structurally, the protonated carbinolamine (**22**) has a considerably longer C−N bond (1.528 Å) than the neutral carbinolamine **13** (1.436 Å). Similarly, the C−N length in the protonated TS **23** (1.452 Å) is longer than the corresponding neutral TS **14** (1.343 Å). Proton transfer from nitrogen to oxygen is more advanced (N−H = 1.466 Å and H−O = 1.171 Å) than for TS **14** (1.348 and 1.252 Å, respectively), although C−O bond cleavage is less advanced for the protonated system (**23**, 1.505 Å; **14**, 1.825 Å). The C−N distances in the protonated (**24**) and neutral (**15**) imines are almost identical (1.282 and 1.279 Å, respectively), although the water molecule liberated in the reactions interact at different sites.

Proton transfer through a single water molecule reduces the barrier to iminium ion formation from an N-protonated carbinolamine by 55.7 kJ mol$^{-1}$; the transition state (**26**) linking carbinolamine **25** with iminium **27** lies 88.0 kJ mol$^{-1}$ above **25**. The N-hydrogen in TS **26** is almost fully transferred onto the water, with an N−H distance of 2.155 Å and H−O length of 0.989 Å. Proton transfer onto the carbinolamine hydroxyl group is well-advanced with an H−O separation of only 1.174 Å. The resulting iminium (**27**) has the two water molecules interacting separately, one with the N-hydrogen and the other with the $CH_2$ group.

The barrier to iminium formation is further reduced to 67.9 kJ mol$^{-1}$ when proton transfer proceeds through two water molecules. In the TS (**29**), transfer of the N-proton of carbinolamine **28** onto the first water molecule is essentially complete. The TS also has a proton from this water molecule transferred onto the second water molecule. The iminium product (**30**) lies 9.5 kJ mol$^{-1}$ above **28** and forms an eight-membered hydrogen-bonded ring structure with the three water molecules. A schematic energy profile for iminium ion formation is presented in Figure 4c.

The structures of the neutral and protonated transition states involving two water molecules which lead to imine and iminium formation are very different (TS **20** and TS **29**, respectively). The protonated transition state has iminium formation more advanced at the nitrogen than at the hydroxyl, whereas the converse is true for the neutral transition state. The C−O distance remains short (1.495 Å) in TS **29**, whereas C−O cleavage is almost complete in **20** (the C−O distance is 2.085 Å). The N−C distance in **29** (1.411 Å) is much longer than in **20** (1.298 Å) and resembles more a single bond of a neutral carbinolamine (cf. **19**, 1.418 Å). Transfer of the N-hydrogen onto the water molecule is complete in **29** with a H−O distance of 0.973 Å, while in TS **20** the H−O distance is 1.487 Å and the N−H distance is 1.104 Å.

## Aqueous Free Energies

The barrier to carbinolamine formation via TS **2** in the gas phase is greatly reduced by incorporation of the solvation energy terms. The calculated solvation free energy for TS **2** is 49.6 kJ mol$^{-1}$ greater than for complex **1**. This is due to the highly polarized nature of the TS, with a large negative charge (−0.86) associated with the oxygen atom, compared to −0.53 in the van der Waals complex (**1**). The solvation energy contributions for the other neutral structures (containing no additional water

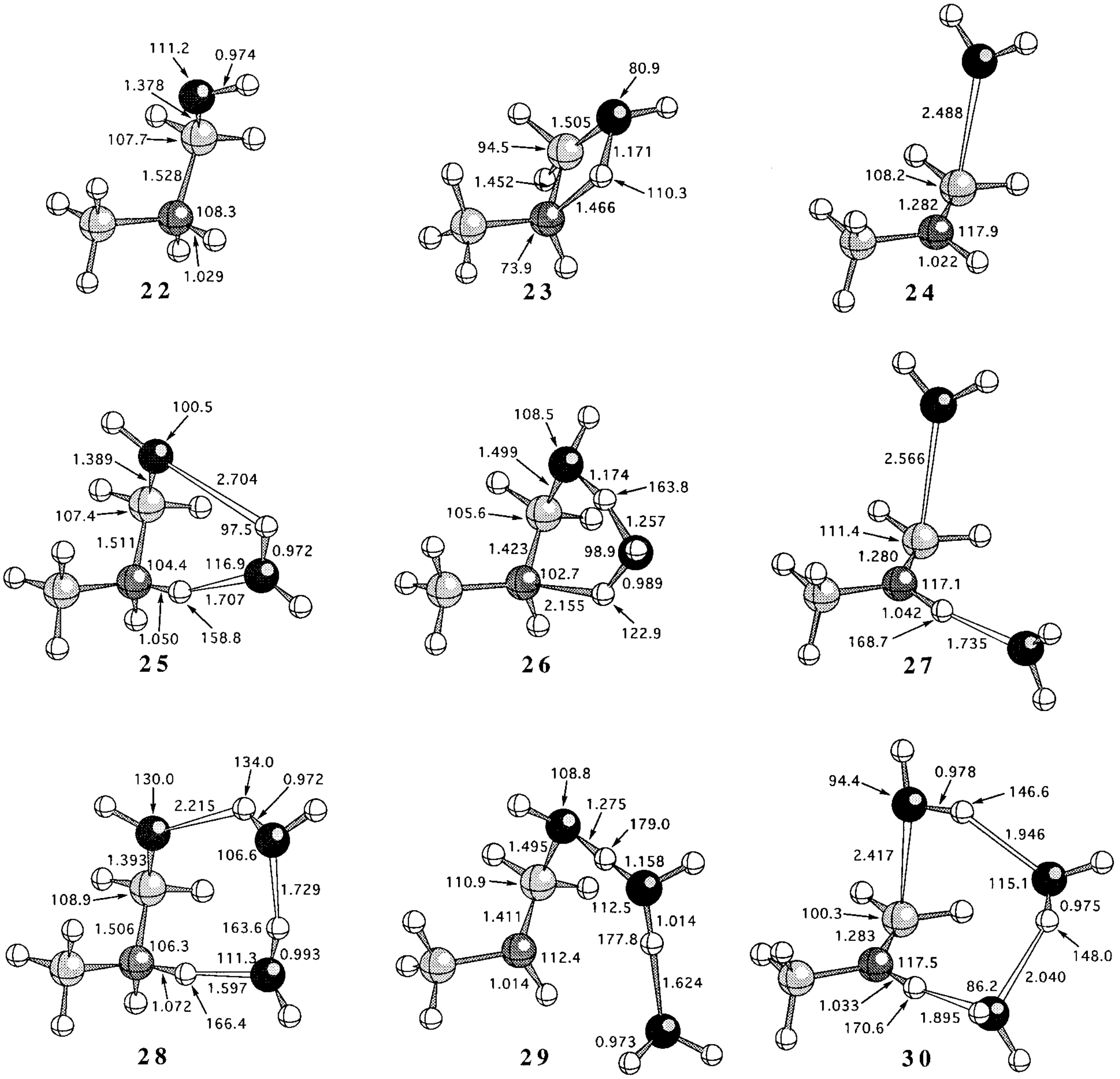


**Figure 5.** Selected bond lengths (angstroms) and angles (degrees) for stationary points along the path of iminium ion formation from the protonated carbinolamine involving zero, one, and two water molecules.

molecules), **1**, **3**, and **12**−**15**, differ by no more than 15 kJ mol$^{-1}$. Entropic contributions for the complexes **1** and **15** are larger than for the transition state and carbinolamine species. The complex **1** and structure **15** incorporate weak bonding interactions, whereas the other structures are all covalently bound. The corresponding difference in entropy between complex **1** and TS **2** is 20.8 kJ mol$^{-1}$. The calculated aqueous free energy required to proceed from the complex to carbinolamine **3** is 83.6 kJ mol$^{-1}$, while imine formation from carbinolamine **13** proceeds through a barrier of 227.8 kJ mol$^{-1}$. The calculated[37] association energy between methylamine and formaldehyde is 8.4 kJ mol$^{-1}$, which would appear to be too small in comparison with the experimental equilibrium constant[38] for the addition reaction of $3.4 \times 10^6$ M$^{-1}$.

Proton transfer facilitated by a single water molecule reveals a small barrier (TS **5**) of 25.5 kJ mol$^{-1}$ to carbinolamine formation (**6**). A much larger barrier is encountered to imine formation with TS **17** lying 118.2 kJ mol$^{-1}$ above **16**. Similar to TS **2**, the solvation term for TS **5** is larger than for complex **4** (a difference of 42.9 kJ mol$^{-1}$). The solvation energy contribution for TS **17** which leads to imine formation is also larger than the reactant carbinolamine **16** (a difference of 28.9 kJ mol$^{-1}$). This is in contrast to carbinolamine **13** and TS **14** with no waters, which have almost identical solvation energies. The larger solvation energy of TS **17** can be attributed to an increase in charge polarization; for example, on the oxygen of the water molecule the charge increases from −0.89 to −1.09. Again, entropic terms for complex **4** and imine **18** are larger than for the carbinolamine and transition-state structures **5**, **6**, **16**, and **17**.

With the inclusion of two explicit water molecules, carbinolamine formation can proceed via a shallow zwitterionic minima (**9**) which lies 15.0 kJ mol$^{-1}$ below **7** and is reached via a barrier (TS **8**) of 14.5 kJ mol$^{-1}$. A second small barrier (**10**) lying 19.1 kJ mol$^{-1}$ above **9** is encountered along the path to formation of carbinolamine **11**. Imine formation via TS **20** from **19** (following inversion at nitrogen) requires 97.4 kJ mol$^{-1}$.

A zwitterionic minimum is not predicted on the gas-phase energy surface when less than two water molecules are incorporated. A zwitterionic minimum can, however, be located at short C−N distances when the solvation free energy term is added to the electronic energies.[14] Accurate barriers to zwit-

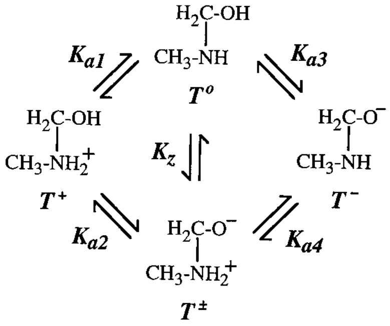


**Figure 6.** Carbinolamine acid−base equilibria scheme, relating different protonation states of the carbinolamine.

terion formation cannot be calculated for these systems with less than two water molecules as thermal corrections cannot be determined. It is clear, however, that the barrier to zwitterion formation is small.

The free energy barrier to imine formation in solution from a protonated carbinolamine via TS **23** without the inclusion of any explicit water molecules is 166.4 kJ $mol^{-1}$. This barrier is reduced to 100.6 kJ $mol^{-1}$ via TS **26** with the inclusion of one water molecule. With two waters, the barrier to iminium ion formation via TS **29** is reduced further to 64.1 kJ $mol^{-1}$. Solvation energies of the iminium complexes are all smaller than for the N-protonated carbinolamines, while the entropy terms are larger due to the elimination of a water molecule. The barriers to iminium ion formation for these protonated systems are all smaller than for neutral imine formation with the equivalent number of water molecules incorporated to facilitate the proton transfer. Thus, for example, with two waters the barrier is 64.1 kJ $mol^{-1}$ for the protonated species compared to 97.4 kJ $mol^{-1}$ from the neutral carbinolamine.

Iminium ion formation may also proceed from a neutral carbinolamine with the abstraction of hydroxide. This reaction, although having a very large dissociation energy in the gas phase (765 kJ $mol^{-1}$),[39] has been observed to proceed in solution.[5] The dissociation energy is calculated here[40] to be 6.8 kJ $mol^{-1}$, which would again appear to be too small in light of the experimental dissociation constant for $i$-PrCH═NH−$Me^+$ at 35 °C of $3.2 \times 10^5$ $M^{-1}$.[41]

## Acid−Base Equilibria of Carbinolamines

The acid−base equilibrium constants (p$K_a$) of the neutral (T°), N-protonated ($T^+$), anionic ($T^-$), and zwitterionic ($T^\pm$) carbinolamines have been calculated from the aqueous free energies of these species.[42] The relationship between these four carbinolamine species and the corresponding equilibrium constants, $K_a$, are shown in Figure 6.

Aqueous free energies of structures **13** and **22** are used for T° and $T^+$, respectively. For the zwitterion, the aqueous free energy is obtained by adding to the energy of **13** the difference in energy between **9** and **11**. The energy of the solvated proton, −0.423 52 hartree, is given by the sum of the experimental solvation energy (−413.54 mhartrees),[43] thermal correction (2.36 mhartrees), and entropic contribution at 298 K (12.34 mhartrees).

Calculated p$K_a$ values of these carbinolamines are presented in Table 1. The value calculated for p$K_{a1}$ is similar to the experimental p$K_a$ values of methylamine and dimethylamine (10.62 and 10.77, respectively).[44] The calculated p$K_{a3}$ value is somewhat larger than the experimental value of methanol (p$K_a$ = 15.5).[44] The slightly smaller value of p$K_{a2}$ is consistent with an increased acidity of the hydroxyl proton when the neighboring nitrogen is positively charged ($T^+$). The conversion of T° to $T^\pm$ may be estimated from the difference $pK_z = pK_{a1} - pK_{a2} = -5.1$.

**TABLE 1: Calculated p$K_a$ Values of Carbinolamine Acid−Base Equilibria**

| | | | |
|---|---|---|---|
| p$K_{a1}$ | 11.7 | p$K_{a3}$ | 18.7 |
| p$K_{a2}$ | 16.8 | p$K_{a4}$ | 13.6 |

[a] The G2(MP2,SVP) method assumes that the geometry upon which the frequencies are calculated corresponds with the geometry in which the single-point energy calculations are performed.

An estimated value of p$K_{a2}$ for $CH_3NH_2CH_2OH^+$ is 9.98, based on a measured p$K_a$ of 9.33 for $(Me)_3NCH_2OH^+$.[41,45] The value determine here for p$K_{a2}$, 16.8, differs by almost 7 p$K_a$ from the experimental value. The p$K_a$ of methanol is calculated to be 18.6 using G2(MP2,SVP) energies and SIP parameters for determining the FDPB solvation energy, in error by 3.1 units.[46] The calculated p$K_a$ of methylamine is 12.7,[46] 2.1 p$K_a$ units larger than the experimental value. It must be noted, however, that methylamine, methylammonium, methanol, and methoxide all form part of the parametrization set for the SIP method, and therefore errors in solvation energy calculations may be greater for the carbinolamine species.

Rosenberg et al.[4] have estimated the p$K_a$'s of $O$-methyloximes as p$K_{a1}$ = 2.0, p$K_{a2}$ = 8.5, p$K_{a3}$ = 13.8, and p$K_{a4}$ = 7.3. These values differ from the values determined for the simple carbinolamine studied here by 5−10 units, although the trend $pK_{a1} < pK_{a4} < pK_{a2} < pK_{a3}$ is in agreement with these results. The value of p$K_z$ = −6.5, however, is in close agreement with the one determined here.

Parameters, used in the determination of solvation energies obtained using the SIP method have been shown to reproduce experimental solvation energies of a parametrization set to within an accuracy of 10 kJ $mol^{-1}$, and as such, the uncertainty in any calculated p$K_a$ due to the solvation energy alone is of the order of 3.5 p$K_a$ units. An additional uncertainty of 3.5 p$K_a$ units may be associated with the G2(MP2,SVP) calculated energies. Thus, uncertainties in the calculated p$K_a$'s should be expected to be as large as 7.

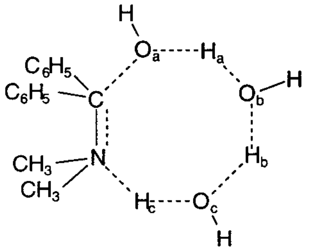
## Discussion

The exact nature of the carbinolamine forming transition state involving proton transfer that proceeds through two water molecules (cf. transition-state structure **10**) has been the subject of several previous studies. When such a transition state was first proposed,[4,47] the nature of its structure was predicted on the basis of secondary deuterium isotope effects and trends in rate constant with variation of electron withdrawing groups. Proton donation to oxygen was predicted to be further advanced than proton abstraction from nitrogen, with the carbinolamine possessing a partial positive charge.

A low-level (HF/3-21G) optimized structure for this TS was first calculated by Williams[19] between ammonia and formaldehyde. The geometry was in accordance with the experimental prediction of Rosenberg,[4] with two water molecules involved directly in proton transfer. The geometries and energies presented here, calculated at significantly higher level with methylamine in place of ammonia, confirm the results of the study by Williams.[19] Geometries of complexes (**1**, **4**, and **7**), transition states (**2**, **5**, and **10**), and carbinolamines (**3**, **6**, and **11**) differ only minimally from those calculated by Williams, with the exception of the hydrogen bond lengths, which are in general shorter at the HF/3-21G level. The G2(MP2,SVP) calculations of this study also confirm the barrier to carbinolamine formation is smallest when two water molecules facilitate the proton transfer (19.0 kJ $mol^{-1}$ from the zwitterion (**9**) or 4.0 kJ $mol^{-1}$ above the van der Waals complex (**7**)).

The change in partial positive charge in the transition state from carbinolamine to imine can be determined by summing the atomic charges on the carbinolamine moiety at each of the stationary points. Charges on the hydrogen atom that transfers from the nitrogen and the hydrogen atom that transfers onto the carbinolamine−oxygen have been constrained to zero in the TS and both minima,[48] thus avoiding any questions of charge assignment for these protons. Summing atomic charges, the total charge on the carbinolamine moiety in TS **10** is +0.44. This value is significantly larger than the charge on the zwitterion in **9** (+0.22) and the carbinolamine in **11** (+0.18) and is in agreement with the observation by Rosenberg of partial positive charge on the carbinolamine moiety in the two water carbinolamine forming transition state.

Currently, there is no experimental evidence to support the proposal of an internal proton transfer from N to O of either a neutral or N-protonated carbinolamine to yield the neutral or protonated imine. A transition state of this nature was proposed for the hydrolysis of the dimethylimine ion of benzophenone (**I**), although it was considered most unlikely.[49]



**I**

Solvent deuterium isotope effects indicate significant C−$O_a$ bond formation in the transition for the attack of water on the iminium ion. It is also likely that the $H_c$ proton is transferred onto solvent rather than onto the nitrogen as shown in structure I.[49]

The calculated transition state (TS **29**, equivalent to **I**) for the attack of water on the N-protonated iminium ion (**30**) has a C−O distance of 1.495 Å, only 0.102 Å longer than in carbinolamine **29**. The $H_a$−$O_b$ distance is 1.158 Å, 0.117 Å shorter than the $H_a$−$O_a$ distance. The oxygen, $O_b$, has three short bonds to hydrogens and resembles a hydronium ion. The distance between $H_c$ and N, however, is very large, 3.450 Å. In solution, it is possible that this proton ($H_c$) is able to transfer to other solvent molecules rather than the nitrogen without the requirement of major structural rearrangement. TS **29** therefore fulfils the requirements of the transition-state structure which is thought most likely for imine hydrolysis, where the C−O bond has formed and the $H_a$ proton is transferred to a water molecule to form a hydronium ion ($O_b$).[49] In addition, the calculated barrier in solution for carbinolamine formation through TS **29** from the imine (**30**) is only 28.5 kJ $mol^{-1}$, sufficiently small to suggest it as a probable route to hydrolysis in solution.

The transition state for neutral imine hydrolysis involving two water molecules (**20**) is very different from the transition state for iminium ion hydrolysis (TS **29**). Rather than having a short C−O bond in the transition state (**20**), the C and O atoms are separated by 2.085 Å. Transfer of the $H_c$ proton to the N is well-advanced (1.104 Å) such that the transition state resembles an iminium ion. This indicates that this reaction is driven by proton abstraction by the nitrogen rather than attack of water on the carbon. The calculated barrier to hydrolysis, 96.8 kJ $mol^{-1}$, is sufficiently large to preclude this process from proceeding readily in solution at room temperature. This is confirmed by experimental results showing no evidence of nucleophilic attack of water on the neutral imine species.[8]

## Conclusions

Structures and energies have been calculated for stationary points leading to imine formation from methylamine and formaldehyde. Two water molecules were found to reduce the reaction barriers of two successive concerted proton-transfer steps. With two water molecules, carbinolamine formation can proceed via a zwitterionic intermediate through a barrier in solution of 14.7 kJ $mol^{-1}$. Subsequent proton transfer through two waters via a low-energy transition state which lies 18.1 kJ $mol^{-1}$ above the zwitterion yields the carbinolamine. The calculated transition-state geometry of this proton transfer strongly resembles the experimentally predicted structure. Higher energy reaction barriers of 97.0 and 61.1 kJ $mol^{-1}$ to imine formation from a carbinolamine are predicted for both neutral and positively charged systems, respectively. These higher barriers may explain why reactions of this kind are not observed in solution. The calculated transition-state structure for attack of water on iminium ion, however, supports the structure proposed from experiment. Energies have been calculated for the addition reaction between methylamine and formaldehyde, and the hydroxide dissociation from the carbinolamine. These appear too small in comparison with the available experimental equilibrium constants. The calculated proton dissociation constant from the oxygen of $CH_3NH_2CH_2OH^+$ disagrees with experimental estimates by almost 7 $pK_a$ units, while the $pK_a$ value calculated for proton dissociation from nitrogen lies in the range expected for amines.

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**Supporting Information Available:** Tables listing calculated energies of minima and transition states (2 pages). Ordering and access information is given on any current masthead page.

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