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Solvation Effects on Zwitterion Formation

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Several methods for determining solvation free energies are compared for the formation of a zwitterionic intermediate between methylamine and formaldehyde. While in the gas phase no minimum exists for C−N separations less than that found in the van der Waals complex, all methods examined here for determining the solvation free energy predict a stable zwitterionic minimum. The most stable minimum exists using the polarized continuum model (PCM). The finite difference Poisson−Boltzmann method yields comparable results when parameters from a solvent interaction potential are used. A stable zwitterion was also found when two explicit molecules of water were included.

Introduction

Zwitterions differ from ordinary amphoteric substances in that at neutral pH values both acidic and basic groups are ionized. These molecules therefore behave more like ions than their total charge would convey, and their stability depends very strongly on the solvent in which they are found. The role of solvation in zwitterions has been the subject of much attention.[2]

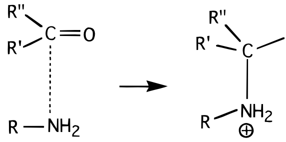
The interaction of an amine with a carbonyl group of an aldehyde or ketone leads to, in many cases, the formation of a zwitterion, **II** (Scheme 1), where the nitrogen has a formal positive charge and oxygen a formal negative charge. This zwitterion formation can proceed with primary,[3] secondary,[4] or tertiary[5] amines and is found to be more favorable with increased basicity of the amine.

Experimental studies investigating zwitterion formation have all been performed in aqueous solutions, and the effect of other solvents on the formation and stability of this zwitterion is unknown. The zwitterion, irrespective of the substituents on the amine or carbonyl, is found to be an unstable intermediate and has never been isolated.

The existence of a gas-phase zwitterionic minimum between ammonia and formaldehyde has been investigated using small[6,7] and large[8] basis set Hartree−Fock calculations, with no zwitterionic minima being located. Semiempirical studies[7,9] have varied in their prediction of such zwitterionic minima, although inclusion of water molecules to form a supermolecular system has a stabilizing effect on the system at zwitterionic distances.[7]

This system provides an interesting test for the calculation of solvation effects as they are clearly important for the stabilization of a zwitterion. The work here involves the study of zwitterion formation between methylamine and formaldehyde. Gas-phase calculations are performed over a range of C−N distances and a solvation free energy term added to determine the profile of zwitterion formation in solution. A comparison of a variety of methods used for the calculation of solvation energies is performed. The effect of including one and two explicit water molecules on zwitterion formation is also investigated.

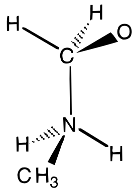
SCHEME 1: Zwitterion Formation between a Primary Amine and a Carbonyl Group of an Aldehyde or Ketone

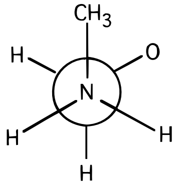


I **II**

Computational Methods

Standard ab initio molecular orbital calculations[10] are performed using the Gaussian94[11] and GAMESS[12] programs. Geometries at various fixed C−N separations of the methylamine−formaldehyde system have been optimized at the MP2/6-31G(d) level. The orientation of the formaldehyde oxygen about the methyl group of the methylamine is chosen to be gauche (approximately 60°).





Approximate gas-phase QCISD(T)/6-311+G(3df,2p) energies were obtained using the additivity scheme of the electronic component of G2(MP2,SVP) theory.[13−15] The QCISD(T) energy is calculated at the 6-31G(d) basis level, and a basis set extension energy (ΔBSE) is added. The basis set extension is given by the difference in MP2(fc) energies calculated using the 6-311+G(3df,2p) and 6-31G(d) basis sets. QCI energies in the text refer to these QCISD(T)/6-311+G(3df,2p) energies. Unless otherwise noted, no ZPVE or thermal corrections[16] are included, as vibrational analysis is possible only at stationary points.

The electrostatic component of the solvation free energies is calculated at each of the various fixed C−N distance geometries.

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These energies are evaluated using either the finite difference Poisson−Boltzmann (FDPB) method, the iterative Langevin dipole (ILD) method,[17,18] or quantum-mechanical self-consistent reaction field (SCRF) methods. In the FDPB approach, three alternative radii are used to define the solute cavity, from the solvent interaction potential[19] (r_{SIP}), fixed atom-specific radii (r_{A}), and radii from the electron isodensity surface (r_ρ).

r_{SIP} are obtained from the solvent accessible surface calculated from the interaction of a probe with the solute. The probe has the electrostatic properties of the solvent of interest (water), including dipole and quadrupole moments, and polarizability. A Lennard-Jones (LJ) potential provides the van der Waals interaction energy which includes both repulsive and attractive dispersion terms. The total interaction potential is given by the sum of the van der Waals, ion−dipole, ion−quadrupole, and ion−induced dipole energies.

CHELPG[20] charges on the solute atoms were evaluated at the HF/6-31+G(d) level. The van der Waals radii for each atom, as well as a parameter to account for the offset of the center of the probe and its center of mass, have been obtained by minimizing the calculated error in the solvation free energy of a collection of small molecules whose solvation free energy was well-known. This parametrization set included both neutral and charged species. The loci of minima in this potential define the solvent accessible surface. The r_{SIP} are the individual radii which best reproduce this surface.

Fixed atom-specific radii (r_{A}: H, 1.04; C, 1.69; N, 2.12; and O, 1.57 Å) were obtained by minimizing the error in the calculated solvation free energy of the SIP parametrization set.[19] The electron isodensity surface used to determine the r_ρ radii were evaluated at the HF/6-31+G(d) level. A cutoff value of 0.0017 e·bohr^{-1} was used. Again, this value was found to minimize the error in the calculated solvation free energy of the SIP parametrization set.[19]

Solvation free energies determined from FDPB calculations all incorporate a nonelectrostatic solvation energy term calculated from the solvent accessible surface area (A_{SIP}) defined by the SIP, using the expression

$$\Delta G_{\text{nonelec}} = \gamma A_{\text{SIP}} + b \tag{1}$$

where the parameters γ (20.0 J mol^{-1} Å^{-2}) and b (3.5 kJ mol^{-1}) are taken from Sitkoff et al.[21]

Solvation free energies using several SCRF methods are also calculated at each geometry. The SCRF calculations are performed at the HF/6-31+G(d) level of theory, the same basis set used to calculate the CHELPG charges employed in FDPB calculations. Solvation energies for these SCRF methods are obtained from the difference in the aqueous-phase SCRF energies and gas-phase HF energies. These solvation energies are purely electronic and do not include any explicit nonelectrostatic solvation energy terms.

PCM[22−24] calculations are performed using 300 points per sphere. Calculations using 600 points per sphere show little difference. The default, Merz−Kollman (Pauling),[25] radii were used to construct the solute boundary (1.2 Å for H, 1.4 Å for O, and 1.5 Å for C and N).

Electron density cutoffs of $\rho = 0.0004$ and $\rho = 0.001$ were used to determine the solute boundary for the IPCM[26] and SCI−PCM[27] calculations. The choice of cutoff is somewhat arbitrary; the values used here cover the ranges suggested by the authors of these methods.

The spherical solute cavity of the Onsager[28] (or dipole) SCRF method is defined by a single cavity radius of 3.60 Å for all geometries. This radius is obtained from a scaled molar volume, calculated using a electron density cutoff of 0.001 au. An additive factor of 0.5 Å is used to account for the nearest approach of solvent molecules.[29] A constant cavity radius was chosen since no reliable trend in radii was found over the C−N distance range. SCRF Onsager geometry optimizations do not permit the cavity size to vary, giving further reason to maintain a constant cavity radius.

TABLE 1: Calculated Gas-Phase Energies of the Methylamine−Formaldehyde Complex at Various C−N Distances

r(C−N) (Å)	MP2(fc)/ 6-31G(d)[a]	ΔQCI[b,c]	ΔBSE[b,d]	QCISD(T)/ 6-311+G(3df,2p)[a,e]
1.40	−209.632 49	−54.88	−293.70	−209.981 07
1.50	−209.646 52	−54.98	−291.40	−209.990 29
1.60	−209.653 99	−55.01	−289.38	−209.998 39
1.70	−209.658 93	−55.04	−287.60	−210.001 57
1.80	−209.663 05	−55.16	−286.13	−210.004 34
1.90	−209.666 89	−55.42	−284.98	−210.007 29
2.00	−209.670 48	−55.80	−284.15	−210.010 43
2.20	−209.676 54	−56.60	−283.27	−210.016 41
2.40	−209.680 41	−57.19	−283.08	−210.020 68
2.60	−209.682 11	−57.55	−283.17	−210.022 82
2.727[f]	−209.682 37	−57.69	−283.27	−210.023 33

[a] Energies in hartrees. [b] Energy corrections in millihartrees. [c] Δ*Q*CI = QCISD(T)/6-31G(d) − MP2/6-31G(d). [d] Δ*B*SE = MP2/6-31+G(3df,2p) − MP2/6-31G(d). [e] QCISD(T)/6-311+G(3df,2p) ≈ MP2/6-31G(d) + ΔQCI + Δ*B*SE. [f] Optimized gas-phase C−N distance at MP2/6-31G(d).

Geometry optimizations carried out using the Onsager method, at the HF/6-31+G(d) level, found no zwitterionic minimum on the potential energy surface. When optimizing geometries using SCI−PCM calculations, SCF convergence problems prohibited the location of any minima. Consequently, these methods were used only to determine solvation energies at the MP2/6-31G(d) optimized geometries.

Comparisons with the recently reparametrized ILD model have also been included.[17] With this method the van der Waals radii of the atoms are assigned according to their hybridization state and chemical environment; thus, for example, oxygen has a different radii depending on whether it is sp^3 or sp^2 hybidized or when it is not bonded to carbon. During the process of zwitterion formation between formaldehyde and methylamine, however, both the carbon and oxygen of the formaldehye change hybridization from sp^2 to sp^3, leaving an ambiguity as to which parameters should be used. The parameters for the sp^3 carbon have been applied in this work.

Results and Discussion

The gas-phase van der Waals complex formed between methylamine and formaldehyde is calculated to have a C−N separation of 2.727 Å at the MP2/6-31G(d) level. The electronic interaction at shorter C−N distances is repulsive. At a zwitterionic-type distance, 1.6 Å, the energy lies 65.6 kJ mol^{-1} above the complex. Total electronic energies of the complex covering the range of C−N distances from 1.4 to 2.727 Å are presented in Table 1. Table 2 contains solvation energies calculated using the various methods.

Energy profiles of zwitterion formation (Figure 1) are generated by adding the solvation energies, ΔG_{solv}, calculated using the FDPB, SCRF, and ILD solvation methods, to the QCI energies. Energies are presented relative to the van der Waals complex. A zwitterionic minimum is located with incorporation of all solvation methods, with the exception of the Onsager method. The interpolated energies (based on a fifth-order polynomial fit to the data) and C−N distances of the zwitterionic

TABLE 2: Calculated Solvation Energies (kJ mol^{-1}) of Methylamine−Formaldehyde Complexes from Various Methods

r(C−N) (Å)	FDPB r_{SIP}	FDPB r_A	FDPB r_ρ	PCM	IPCM $\rho = 0.001$	IPCM $\rho = 0.0004$	SCI-PCM $\rho = 0.0001$	SCI-PCM $\rho = 0.0004$	ILD	Onsager $r = 3.60$ Å
1.40	−128.1	−119.8	−103.8	−145.9	−111.5	−85.2	−119.9	−89.0	−111.7	−47.0
1.50	−117.1	−109.8	−95.4	−135.6	−104.0	−79.4	−111.9	−84.2	−103.3	−44.0
1.60	−102.4	−97.0	−84.2	−122.7	−94.5	−71.9	−100.9	−76.0	−95.0	−39.7
1.70	−86.6	−83.2	−72.1	−111.5	−83.5	−63.3	−88.5	−66.6	−83.7	−34.5
1.80	−71.0	−69.1	−60.3	−96.2	−72.4	−54.4	−76.2	−57.0	−73.2	−29.2
1.90	−57.9	−57.1	−48.9	−82.3	−62.2	−46.3	−62.8	−48.2	−63.6	−24.2
2.00	−47.7	−47.2	−40.0	−70.7	−53.7	−39.5	−54.8	−40.8	−54.8	−19.9
2.20	−34.5	−34.7	−28.6	−55.9	−42.1	−30.4	−42.2	−30.7	−42.7	−13.9
2.40	−28.2	−29.4	−23.9	−47.7	−37.0	−26.2	−36.5	−25.9	−35.6	−10.6
2.60	−25.6	−27.1	−22.0	NA[a]	−34.9	−23.3	−34.5	−23.8	−32.2	−9.0
2.727	−24.9	−26.6	−21.9	−45.9	−34.2	−23.8	−34.2	−23.2	−30.1	−8.2

[a] PCM calculation failed to converge.

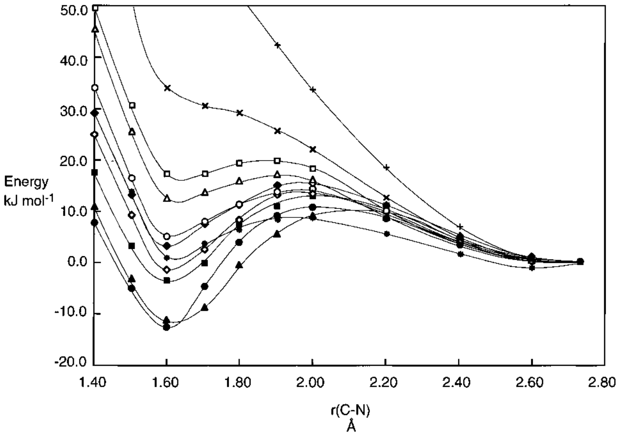


Figure 1. Profiles of QCI electronic energy (+) incorporating solvation free energies calculated from the FDPB method using r_{SIP} (●), r_A (■), and r_ρ (♦) radii, from the ILD method (*), and from the SCRF methods Osager (×), PCM (▲), IPCM with cutoffs of 0.001 (○) and 0.0004 (□), and SCI−PCM with cutoffs of 0.001 (◊) and 0.0004 (△).

TABLE 3: Interpolated Methylamine−Formaldehyde Minima and Transition State Distances and Energies for Zwitterion Formation

method	r_{zwit} (Å)	E_{zwit} (kJ mol^{-1})	r_{TS} (Å)	E_{TS} (kJ mol^{-1})
FDPB:				
r_{SIP}	1.56	−10.1	2.05	11.7
r_A	1.57	−5.4	2.02	14.1
r_ρ	1.59	2.9	1.99	16.5
ILD:	1.65	3.1	2.01	9.2
SCRF:				
PCM	1.58	−12.7	2.08	9.6
IPCM, $\rho = 0.001$	1.61	5.1	1.98	15.3
IPCM, $\rho = 0.0004$	1.65	16.5	1.90	19.9
SCI−PCM, $\rho = 0.001$	1.59	−1.5	2.01	14.4
SCI−PCM, $\rho = 0.0004$	1.64	11.9	1.94	17.6

minimum and transition state (connecting this minimum to the van der Waals complex) are presented in Table 3.

Using radii from the SIP, the FDPB solvation energies yield a zwitterionic minima with a C−N separation of 1.56 Å lying 10.1 kJ mol^{-1} below the van der Waals complex at 2.727 Å. The transition state connecting the zwitterion to the complex occurs at a C−N distance of 2.05 Å and lies 11.7 kJ mol^{-1} above the complex. All of the FDPB calculations produce similar C−N distances for the zwitterion and transition state. There is more variation in the relative energies of the zwitterionic minima than in the transition states, indicating larger differences between the methods at shorter C−N separations. Thus, while the energy of the zwitterion covers the range from −10.1 kJ mol^{-1} to +2.9 kJ mol^{-1}, the transition state barriers vary between +11.7 and +16.5 kJ mol^{-1}. The most stable zwitterion is predicted using the r_{SIP} radii, which also give the lowest barrier. These energies correspond to the shortest zwitterion C−N distance and longest C−N distance in the transition state. Conversely, r_ρ predicts the least stable zwitterion and highest barrier, with corresponding longest zwitterion C−N distance and shortest C−N distance in the transition state.

The PCM results compare favorably to the SIP results with relative energies and C−N distances of the zwitterionic minimum and transition state within 3 kJ mol^{-1} and 0.02 and 0.03 Å, respectively. Although the relative energies are similar, the difference in absolute solvation energies are on the order of 20 kJ mol^{-1}, the PCM method predicting the larger (more negative) energies. Half of the difference arises from the nonelectrostatic energy component which is incorporated into the SIP solvation energies but not the PCM energies. The $\Delta G_{nonelec}$ values from the r_{SIP} calculations range from 10.3 kJ mol^{-1} at a C−N distance of 2.727 Å to 9.7 kJ mol^{-1} at 1.60 Å.

The IPCM method, with electron isodensity cutoff values of $\rho = 0.001$ and $\rho = 0.0004$, predicts less stable zwitterions with larger C−N distances than those from the PCM method. The transition state barriers are larger and have shorter C−N distances. SCI−PCM results resemble IPCM results with the same cutoff, although slightly larger solvation energies are predicted at shorter C−N distances. The methods that define the solute boundary by the electron isodensity surface (IPCM, SCI−PCM, and r$_\rho$) all yield the least stable zwitterions. The diffuse electron distribution of the negatively charged oxygen leads to a larger surface about that atom. However, electrostatic interactions between the solute and solvent should reduce the cavity about negatively charged atoms.

The ILD method produces solvation energies that are very similar to those obtained from the IPCM method ($\rho = 0.001$) for all C−N separations but those near the complex. These differences may be related to the inappropriate use of sp^3 parameters for C and O for these geometries. As a result of this, the total energy (electronic + solvation) decreases when the C−N distance is shortened from 2.727 Å in the (gas-phase) complex to 2.6 Å, and the energies of the transition state and zwitterion are both smaller than that found for the IPCM method.

The Onsager method fails to predict a zwitterionic minimum when a constant radius of 3.6 Å is used. The nonphysical cavity shape and size, and the simple dipole representation, result in much smaller solvation energies at zwitterionic distances than those calculated with all of the other methods. The difference in solvation energies between structures with C−N distances of 2.727 and 1.6 Å is 31.5 kJ mol^{-1} with the Onsager method, while for the r$_{SIP}$ method this difference is 76.0 kJ mol^{-1}. Investigations using a smaller constant cavity radius of 3.0 Å

TABLE 4: Selected HF/6-31+G(d) CHELPG Charges (*Q*) and Atomic Radii Used in FDPB Calculations and Derived from SCRF Calculations for Complexes with C−N Distances of 2.727 and 1.60 Å[a]

	Q		r_{SIP}		r_ρ		IPCM[b]		SCI−PCM[b]	
	2.727	1.60	2.727	1.60	2.727	1.60	2.727	1.60	2.727	1.60
O	−0.53	−0.88	1.59	1.54	1.69	1.75	1.82	1.91	1.81	1.88
C	0.50	0.62	1.86	1.72	1.74	1.74	1.87	1.98	1.86	1.97
N	−0.88	−0.20	2.07	2.06	1.84	1.85	1.98	1.93	1.97	1.93
H	0.35	0.27	1.06	1.04	1.14	1.10	1.22	1.16	1.22	1.14
H′	0.31	0.21	1.10	1.07	1.15	1.11	1.22	1.19	1.22	1.15

[a] The carbon atom is of the formaldehyde moiety and hydrogens are those attached to the nitrogen. [b] Isodensity cutoff, 0.001 *e*.

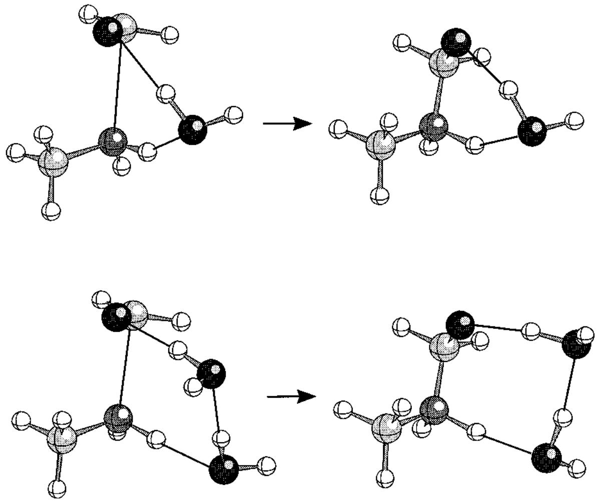
(i.e., 0.6 Å smaller than that calculated from the molar volume) predict a zwitterionic minima which lies 4.6 kJ mol^{-1} above the complex and has a C−N distance of 1.63 Å. The transition state has a (comparatively) short C−N distance of 1.95 Å and lies 11.7 kJ mol^{-1} above the complex. The difference in solvation energies between structures with C−N distances of 2.727 and 1.6 Å with a constant cavity radius of 3.0 Å is 60.5 kJ mol^{-1}, resembling more the r_{SIP} results. The selection of cavity radius for Onsager calculations is of critical importance, and currently, methods for determining the solute radius cannot be reliably applied for the calculation of solvation energies. Luzhkov and Warshel[30] have shown that the correct Onsager cavity is a strange function that would not usually be deduced from the size of the molecule.

The effect of the dipolar nature of the zwitterion on the SIP radii can best be seen through investigation of selected CHELPG atomic charges and atomic radii of the complex at C−N distances of 2.727 and 1.60 Å. These are presented in Table 4 along with the radii determined from several other methods. The negative charge on the oxygen atom increases by 0.35 *e* as the C−N distance is shortened from 2.727 to 1.60 Å. Associated with this increase in charge, the SIP radius for oxygen decreases by 0.05 Å. There is a much larger decrease in the radius on the formaldehyde carbon of 0.14 Å, while the partial atomic charge increases by just 0.12 *e*. The charges on the hydrogens decrease by roughly 0.10 *e*, while the negative charge on the nitrogen increases by 0.68 *e*. The radii of the nitrogen and N-hydrogens, however, decrease no more than 0.03 Å upon shortening the C−N distance. It is clearly evident that there is no direct relationship between partial atomic charges and atomic radii.

Radii can also be abstracted from the IPCM and SCI−PCM isodensity surfaces. Presented in Table 4 are the radii from the 0.001 *e* isodensity surfaces. The radii from both methods are quite similar at both C−N separations and are considerably larger than the r_{SIP} and r_ρ radii. For all methods based on an isodensity surface, including the r_ρ radii, the oxygen radius is larger at the shorter C−N separation.

The methylamine−formaldehyde zwitterion system has also been investigated in an aqueous environment using the AM1-SM2[31,32] and PM3-SM3[31,33] semiempirical methods. The AM1-SM2 method predicts a zwitterionic minimum, while PM3-SM3 fails to do so. The AM1-SM2 minimum is found at a C−N distance of 1.60 Å, similar to the FDPB distances. The transition state has a much shorter C−N distance, 1.84 Å, than calculated with the FDPB and SCRF methods, and the complex between the methylamine and formaldehyde species has a very large C−N separation of 3.35 Å. The transition state lies 9 kJ mol^{-1} above the zwitterion, which is similar to the FDPB and SCRF results.

SCHEME 2: One and Two Specific Water Molecules



Incorporation of Specific Water Molecules

Gas-phase calculations of zwitterion formation between methylamine and formaldehyde have been carried out with the inclusion of one and two water molecules. These waters bridge the N-bound hydrogen to the oxygen atom via six- and eight-membered hydrogen bonded ring complexes, respectively (Scheme 2). Fixed C−N distance geometry optimizations were carried out at the MP2(full)/6-31G(d) level and QCI energies obtained as before. Calculated electronic energies are presented in Table 5, and profiles obtained from these energies are presented in Figure 2 (with the energy of the complex used as the zero reference in each case).

With incorporation of a single water molecule, the electronic interaction between the methylamine and formaldehyde is repulsive at all C−N distances less than the van der Waals minimum at 2.557 Å. There is, however, a significant flattening of the electronic energy surface at shorter C−N distances in comparison to the system with no explicit waters. Inclusion of two water molecules reduces the C−N distance in the van der Waals minimum to 2.400 Å. A zwitterionic gas-phase minimum is located at a C−N distance of 1.703 Å. The transition state linking the zwitterion and the complex has a C−N separation of 1.967 Å.

Solvation free energies of the complexes with discrete waters have also been calculated using the solvent interaction potential method with atomic radii, r_{SIP}. These are also presented in Table 5. Figure 2 contains profiles which incorporate the continuum solvation energy contribution, in addition to (gas-phase) profiles of the electronic energy.

All three systems present a zwitterionic minimum. The C−N separation in the transition state increases as the number of water molecules increases, from 2.05 Å when no water molecules are included, to 2.15 and 2.21 Å with one and two water molecules. The energy of the transition state, relative to the complex, decreases as more water molecules are included (11.7, 4.0, and 0.3 kJ mol^{-1} with zero, one, and two water molecules, respectively). In contrast, the difference in energy between the complex and the zwitterionic minimum increases as more water molecules are included (−10.1, −30.9, and −39.9 kJ mol^{-1} with zero, one, and two water molecules, respectively). The C−N distance in the minimum is roughly the same in all three systems, 1.55−1.56 Å. The location of stationary points on such potentials should, however, be treated with caution since they do not reflect nonequilibrium solvation effects.[34]

TABLE 5: Calculated Electronic and Solvation Free Energies for Methylamine−Formaldehyde Complexes with One and Two Water Molecules

	one water					two waters				
r(C−N) (Å)	MP2(fc)/ 6-31G(d)[a]	ΔQCI[b,c]	ΔBSE[b,d]	QCISD(T)/ 6-311+G(3df,2p)[a,e]	ΔG_{solv}[f]	MP2(fc)/ 6-31G(d)[a]	ΔQCI[b,c]	ΔBSE[b,d]	QCISD(T)/ 6-311+G(3df,2p)[a,e]	ΔG_{solv}[f]
1.40	−285.871 52	−63.56	−406.57	−286.341 54	−108.6	−362.097 43	−73.10	−522.40	−362.692 93	−120.0
1.50	−285.883 42	−64.09	−404.85	−286.352 36	−100.7	−362.108 73	−73.65	−520.69	−362.703 07	−114.2
1.60	−285.888 03	−64.51	−403.49	−286.356 03	−92.5	−362.112 61	−74.12	−519.36	−362.706 09	−105.4
1.70	−285.889 67	−64.87	−402.39	−286.356 93	−82.3					
1.703[g]						−362.113 39	−74.56	−518.27	−362.706 22	−97.2
1.80	−285.890 47	−65.21	−401.51	−286.357 19	−71.3	−362.113 23	−74.98	−517.48	−362.705 69	−88.3
1.90	−285.891 23	−65.61	−400.93	−286.357 77	−62.3					
1.967[h]						−362.112 99	−75.81	−516.73	−362.705 53	−75.4
2.00	−285.892 17	−66.07	−400.51	−286.358 75	−53.7					
2.20	−285.894 34	−66.95	−400.25	−286.361 54	−44.0	−362.113 54	−77.00	−516.47	−362.707 01	−65.2
2.400[i]	−285.895 91	−67.58	−400.39	−286.363 88	−39.9	−362.113 96	−77.71	−516.76	−362.708 43	−61.6
2.557[j]	−285.896 30	−67.90	−400.54	−286.364 74	−39.6					

[a−e] See foornotes $a-e$ of Table 1. [f] Units are kilojoules per mol. [g] Optimized zwitterion distance with two water molecules. [h] Optimized transition state distance with two water molecules. [i] Optimized van der Waals distance with two water molecules. [j] Optimized van der Waals distance with one water molecule.

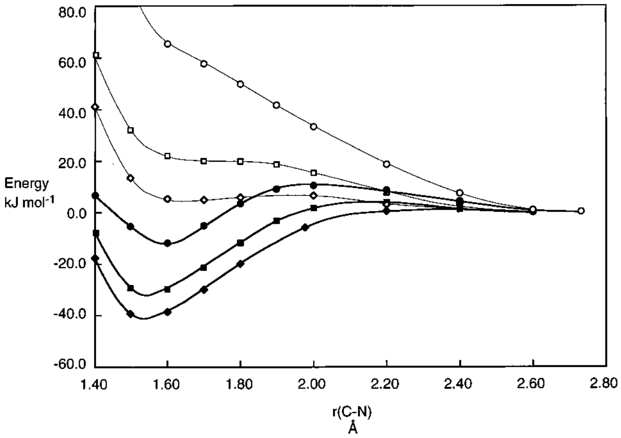


Figure 2. Profiles of QCI electronic energy with zero (○), one (□) and two (◇) water molecules, and including solvation energies with zero (●), one (■), and two (◆) water molecules.

Incorporation of temperature and entropic corrections[35] to the QCI electronic and FDPB solvation energies provide aqueous free energies, ΔG_{298}(aq), at the G2(MP2,SVP) level. These ΔG_{298}(aq) energies predict a larger barrier to zwitterion formation in solution of 6.0 kJ mol^{-1} (at the C−N separation of 1.967 Å). The zwitterion now lies 19.4 kJ mol^{-1} below the complex. The dominant factor in increasing the aqueous-phase barrier is the difference of 17.4 kJ mol^{-1} in the calculated entropy between the van der Waals complex and transition state (the thermal enthalpic correction of the transition state is 5.1 kJ mol^{-1} less than in the complex). The entropy of the transition state is much lower due to the fewer number of small vibrational frequencies, a consequence of the stronger C−N interaction and tighter hydrogen bonding interactions in the transition state between the water molecules and methylamine and formaldehyde moieties.

Concluding Remarks

The solvent is a critical factor in the formation and stability of a zwitterionic minima between methylamine and formaldehyde. No zwitterionic minimum is predicted on the gas-phase profile (without the addition of specific water molecules), although through the inclusion of a solvation free energy term a zwitterionic minimum is located. Similar results are found for the neutral and zwitterionic forms of glycine.[36,37] In the gas phase, only the neutral form of glycine is stable, although, upon addition of two or more waters[36] or continuum solvation energy contributions,[37] the zwitterionic form becomes a stable minima.

The solvent plays a critical role in the stability and geometry of the zwitterion. To accurately calculate these properties, a realistic solute cavity shape and size must be used to determine the solvation energy contribution. Methods based on isodensity surfaces, in particular, are unable to deal satisfactorily with the dipolar charge distribution of the zwitterion. Parametrized sets of atomic centered radii are more reliable than isodensity surfaces for cavity definition, with PCM producing similar results to those obtained through the SIP method. The absolute solvation energies of the PCM and SIP methods differ by 20 kJ mol^{-1}, of which 10 kJ mol^{-1} may be accounted for by inclusion of a nonelectrostatic term to the free energy of solvation. The ILD method provides solvation energies that are very similar to those obtained using the IPCM model.

Inclusion of specific water molecules provides sufficient stabilization for a zwitterionic minima in the gas phase. Addition of a continuum based solvation free energy term to the gas-phase profile with and without specific waters provides similar aqueous profiles. The stability of the zwitterion, however, is increased by inclusion of the specific waters and a continuum solvation energy.

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