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Potential of Mean Force for the Isomerization of DMF in Aqueous Solution: A Monte Carlo QM/MM Simulation Study

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Abstract: Potential of mean force for the isomerization of a tertiary peptide bond in *N*,*N*-dimethylformamide (DMF) is determined using a combined quantum mechanical and molecular mechanical (QM/MM) potential in Monte Carlo simulations. Both the anti and syn transformations were considered. The computed free energy of activation in the gas phase is 19.8 kcal/mol for the anti transition state and 20.2 kcal/mol for the syn form. This is in excellent agreement with the gas-phase NMR measurements (19.4 ± 0.1 kcal/mol). The solvent effects were found to nicely mirror the change of dipole moment for DMF in water, with predicted solvation destabilizations of the transition states by 2.7 ± 0.2 and 0.5 ± 0.1 kcal/mol for the anti and syn forms, respectively. The results are in accord with previous theoretical studies of *N*,*N*-dimethylacetamide (DMA) in water and CCl_4 by Duffy et al. The computed free energy of activation (20.8 kcal/mol) in water is consistent with experimental findings for DMF in pure liquid and other solvents. In addition, the finding that DMF was polarized more favorably in the ground states than the rotamers suggests that it is necessary to include explicit polarization terms in empirical potential functions for fluid simulations.

The cis/trans isomerization about peptide bonds, particularly those preceding proline residues, plays an important role in protein folding and substrate–enzyme binding.[1,2] The early pioneering work of Drakenberg et al. and subsequent gas-phase NMR studies demonstrated a significant solvent effect on the rate of amides isomerization.[3-5] Recently, a desolvation effect has been interpreted as to enhance the enzyme catalysis of peptide isomerization in complexes of the immunosuppressive agents FK506 and rapamycin with their immunophilin, FKBP-12.[6] On the theoretical side, the internal rotation about amide bonds has been extensively investigated through ab initio molecular orbital and empirical force field methods,[5,7,8] and has been extended to condensed-phase simulations.[9] Duffy et al. carried out ab initio and Monte Carlo calculations to characterize the solvent effects on the rotational barrier to isomerization of *N*,*N*-dimethylacetamide (DMA).[9] Although the computed free energies of activation for DMA in water and in CCl_4 were found in good agreement with experimental data, detailed free-energy profiles in solution are not available due to the lack of appropriate potential functions along the *entire* torsional angle. To provide a complete understanding and additional insight into the solvation effects on this important transformation, the potential of mean force (pmf) for the C–N rotation in *N*,*N*-dimethylformamide (DMF) is determined here by Monte Carlo calculations with a combined quantum mechanical and molecular mechanical (QM/MM) simulation approach.[10]

The use of the hybrid QM/MM simulation method is particularly advantageous in the present study because the often concerned bias of empirical potential functions in favor of any conformers in solution is eliminated.[9,11] This stems from the fact that the solute molecule is treated explicitly by quantum mechanical Hartree–Fock theory throughout the QM/MM simulations,[12] while there is no parameter adjustment necessary along the whole rotational coordinate. Furthermore, electronic polarization effects and changes in atomic charge and the dipole moment of DMF in water can be evaluated,[13] providing the opportunity for further analysis of the solute–solvent interactions that are not possible from investigations based on empirical potential functions. The Monte Carlo QM/MM simulation method has recently been used in the study of the torsional rotation in acetic acid and was found to yield excellent agreement with experimental and previous theoretical results.[14,15] The present investigation is an extension of our efforts in this area.

Determination of the Free-Energy Profile in the Gas Phase

The gas-phase geometries for the isomerization of DMF was determined by ab initio calculations with the 6-31G(d) basis set

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Table I. Experimental and Computed Structural Data for DMF[a]

	ground state			anti TS		syn TS	
	6-31G(d)	AM1	exp	6-31G(d)	AM1	6-31G(d)	AM1
C=O	1.197	1.242	1.20	1.184	1.233	1.180	1.229
C—H	1.091	1.115		1.089	1.114	1.098	1.120
C—N	1.349	1.380	1.340	1.424	1.440	1.419	1.440
N—C_{cis}	1.446	1.435	1.45	1.458	1.447	1.455	1.442
N—C_{trans}	1.443	1.433		1.458	1.447	1.455	1.442
∠N—C=O	125.9	122.9	129	124.9	125.1	124.4	121.8
∠C_{cis}—N—C	120.6	121.8	117.5	111.4	113.1	111.6	113.0
∠C_{trans}—N—C	122.0	121.3	117.5	111.4	113.1	111.6	113.0
θ(C_{trans}—N—C=O)	180.0	180.0	180.0	63.1	65.5	117.4	113.9

[a] Bond lengths, bond angles, and dihedral angles are given in angstroms and degrees.

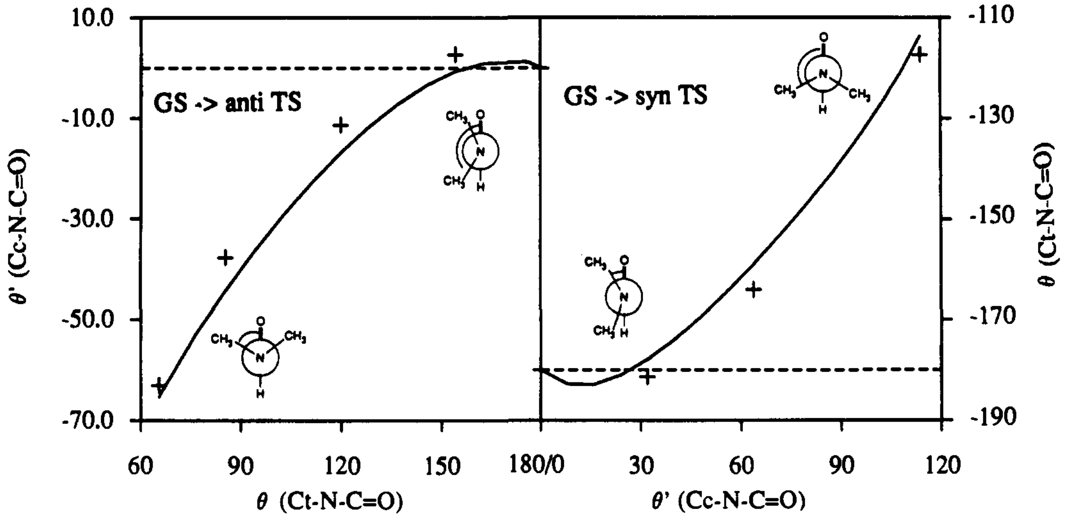
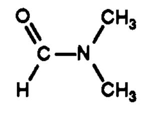
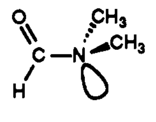


Figure 1. Dependence of the methyl group dihedral angles in DMF along the reaction coordinate for the anti and syn transition states computed with the AM1 method (curve) and the 6-31G(d) basis set (points).

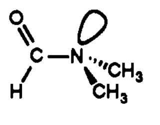
using Gaussian 90.[16] The 6-31G(d) basis set is a split valence type with d functions on nonhydrogen atoms, which has been shown to yield excellent results for the structure of simple organic compounds.[17] The computed structural parameters were found to be in good agreement with electron diffraction data for the ground-state (GS) structure (Table I).[8d,18] The fully optimized C_1 geometry (with an out-of-plan torsion of less than 0.1°) was found to be the global minimum, though constraint to a C_s conformation shows virtually no change in energy (<0.1 kcal/mol). Two transition-state structures were located for the cis/trans isomerization of DMF, both in C_s symmetry corresponding to the anti and syn relationships between the carbonyl oxygen and the amino lone pair.



DMF, GS



anti TS



syn TS

These structures along with the rotational profiles were also determined by the AM1 method,[19] which is used in the Monte Carlo QM/MM simulations (Figure 1). Calculations of the 6-31G(d) and AM1 vibrational frequencies, respectively, confirmed both the anti and syn forms as real transition states, and allowed evaluation of thermochemical properties. As found previously,[7-9] the most notable structural changes upon the C–N rotation to the transition states (TS) include pyramidalization at the nitrogen center and an elongation of the C–N bond distance from 1.35 to 1.42 Å. Importantly, structural parameters predicted by the AM1 theory are in good accord with the ab initio 6-31G(d) results (Table I, Figure 1), indicating that the AM1 geometry can be used in subsequent condensed-phase simulations.

Table II. Thermochemical Results for Isomerization of DMF in the Gas Phase[a]

ground state	→	anti TS	syn TS	exp[4]
ΔE_e^0		19.87	20.46	
ΔE_v^0		−0.43	−0.66	
$\Delta\Delta E_v^{298}$		0.01	0.03	
ΔH^{298}		19.45	19.83	19.7 ± 0.3
ΔS^{298}		−1.18	−1.37	1.0 ± 0.8
ΔG^{298}		19.80	20.24	19.4 ± 0.1

[a] Units are kcal/mol for energies and cal/mol·K for entropies. ΔG^{298} is computed at the MP4(SDTQ)/6-31G(d)//6-31G(d) level with 6-31G(d) vibrational frequencies.

Energetic results were computed with the inclusion of correlation energy from single point calculations at the MP4(SDTQ)/6-31G(d)//6-31G(d) level. Enthalpy and entropy were then determined using the standard method based on 6-31G(d) vibrational frequencies.[17] The results are summarized in Table II along with the experimental data. The correlation correction increases the barrier height by 1.1 and 0.7 kcal/mol for the anti and syn TS's. In computing the zero-point energies, all vibrational frequencies were scaled by a factor of 0.9,[17] whereas low-frequency vibrations (<500 cm^{-1}) were treated as rotations. The imaginary frequency in the transition state was ignored. Entropy was computed following the treatment detailed recently by Duffy et

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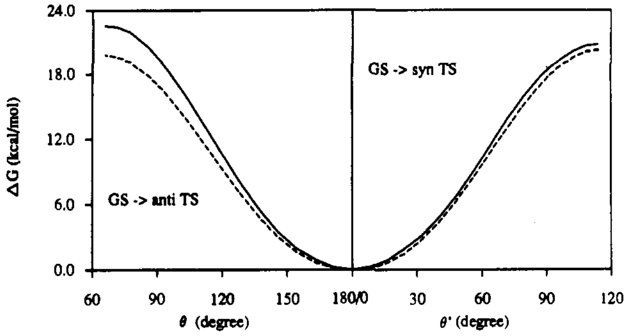

Figure 2. Computed potential of mean force for the isomerization of DMF in the gas phase (dashed curve) and aqueous solution (solid curve) at 25 °C.

al.[9] The computed free energy of activation ($\Delta G^{\ddagger}$) for the anti structure is 19.8 kcal/mol, in excellent accord with the gas-phase NMR measurements of 19.4 ± 0.1 kcal/mol,[4a] whereas $\Delta G^{\ddagger}$ for the syn TS is only 0.4 kcal/mol above the anti form, suggesting that the two isomerization channels are competitive in the gas phase. This result may be compared with a difference of 4.1 kcal/mol for the two transition states in *N*,*N*-dimethylacetamide (DMA) and a free energy of activation of 14.6 kcal/mol for the anti transition state in DMA.[9] It is well-known that α substitution in DMA has significant influence on the barrier height of isomerizations.[3,4] The present computation results show that the methyl group also contributes differently to the two transition states. The AM1 calculations yield barrier heights that are too low by 8–10 kcal/mol in comparison with the ab initio and experimental results. Typically, molecular mechanics type terms are needed to correct the torsional energy for amide isomerization in the AM1 treatment.[19] The dashed curves in Figure 2 give the scaled AM1 profiles such that the ab initio barrier heights ($\Delta G^{\ddagger}$) obtained at the MP4(SDTQ)/6-31G(d) level are reproduced (constant scaling factors of 2.05 and 1.57 are used for the anti and syn isomerization, respectively). This along with the contributions from solvation free energies discussed below forms the potential of mean force for DMF isomerization in water.

Monte Carlo QM/MM Simulations for the Solvation Effect

Intermolecular Potential Functions. In the combined QM/MM approach, the solute molecule is treated quantum mechanically with Hartree–Fock (HF) molecular orbital theory, whereas the solvent molecules are approximated by the empirical TIP3P model for water.[10,12] In order to be able to compute the QM energies throughout the fluid simulations, a computationally efficient method must be adopted. In the present case, the semiempirical Austin Model 1 (AM1) theory developed by Dewar and co-workers was used.[19] As mentioned above, since geometric predictions are in good accord with ab initio 6-31G(d) and available experimental results (Table I), it appears to be reasonable to use the AM1 geometry to evaluate solvation free energies in simulation calculations. The AM1/TIP3P method has been recently shown to be able to provide reliable estimate of solvation free energies for organic compounds in aqueous solution.[13-15]

In the present study, DMF is described by the valence electrons and nuclear cores with the restricted HF wave function, Φ, approximated by a single Slater determinant of all doubly occupied molecular orbitals.[10,12,19] The total potential energy of the system is given by the equation

$$E_{\mathrm{tot}}(\theta) = E_{\mathrm{mm}} + \Delta E_{\mathrm{qm}}(\theta) + E_{\mathrm{qm/mm}}(\theta) \qquad (1)$$

where θ is the reaction coordinate for the CH_3—N—C=O rotation, E_{mm} is the total MM pair interaction energy, $\Delta E_{\mathrm{qm}}(\theta)$ is the internal energy of the QM molecule DMF in water (see below), and $E_{\mathrm{qm/mm}}$ is the interaction energy between the solute and solvent molecules.[10] For the convenience of the present study, the reaction coordinates for the anti and syn transformations were defined, respectively, as θ for the anti form representing the CH_3^{trans}—N—C=O dihedral angle and θ' for the syn denoting the CH_3^{cis}—N—C=O dihedral angle (Figure 1). CH_3^{trans} and CH_3^{cis} are methyl groups trans and cis to the carbonyl oxygen that become equivalent in the transition states. Thus, θ varies from 180° (GS) to 65.5° (anti TS), and θ' varies from 0° (GS) to 113.9° (syn TS). All other geometric parameters are fully optimized with the AM1 Hamiltonian in the calculations (Figure 1).

It is convenient to discuss the gas-phase torsional energy and the solvent contributions separately. Consequently, ΔE_{qm} is further decomposed into an electronic distortion energy ΔE_{dist} and a gas-phase torsional energy $E_{\mathrm{tor}}(\theta)$ (eq 2).[15] This separation enables the use of high-level ab initio results to replace AM1 torsional energies.

$$\Delta E_{\mathrm{qm}} = \Delta E_{\mathrm{dist}} + E_{\mathrm{tor}}(\theta) = (\langle \Phi|\hat{H}_{\mathrm{qm}}(\theta)|\Phi\rangle - \langle \Phi^{\circ}|\hat{H}_{\mathrm{qm}}(\theta)|\Phi^{\circ}\rangle) + (\langle \Phi^{\circ}|\hat{H}_{\mathrm{qm}}(\theta)|\Phi^{\circ}\rangle - \langle \Phi^{\circ}|\hat{H}_{\mathrm{qm}}(\theta_{\mathrm{min}})|\Phi^{\circ}\rangle) \qquad (2)$$

Here, θ_{min} is the dihedral angle corresponding to the ground state of DMF ($\theta_{\mathrm{min}} = 180°$ for the anti and $\theta'_{\mathrm{min}} = 0°$ for the syn transition states). In eq 2, $\hat{H}_{\mathrm{qm}}(\theta)$ is the electronic Hamiltonian for DMF, and Φ° and Φ are, respectively, the wave functions of the QM molecule in the gas phase and water. Note that ΔE_{dist} is the result of an energy penalty due to the solvent effect, which is compensated by more favorable solute–solvent interactions, leading to the polarization energy. Reference 13 contains a detailed analysis. To obtain Φ for new configurations in the Metropolis Monte Carlo sampling, a full Hartree–Fock self-consistent-field calculation is iterated whenever there is a solute move, a solvent move that is within 5.5 Å of any solute atoms, and 20 successive distant solvent moves.[10] Finally, the solute–solvent interaction term is given as follows:

$$E_{\mathrm{qm/mm}}(\theta) = \langle \Phi|\hat{H}_{\mathrm{qm/mm}}(\theta)|\Phi\rangle + \sum_{i}^{\mathrm{solute}} \sum_{s}^{\mathrm{water}} 4\epsilon_{is}[(\sigma_{is}/R_{is})^{12} - (\sigma_{is}/R_{is})^{6}] \qquad (3)$$

where $\hat{H}_{\mathrm{qm/mm}}(\theta)$ is the QM/MM interaction Hamiltonian defined previously.[10,12] The Lennard-Jones term is required because of the hybrid nature in the QM/MM model, which accounts for dispersion interactions that are omitted by the off-diagonal elements in the total density matrix.[12] The values for σ and ϵ are the same as reported previously.[13,15]

As usual, the intermolecular energy for a TIP3P water dimer in the MM region is computed as the sum of Coulombic interactions between all atomic pairs and a single Lennard–Jones term between the two oxygen atoms (eq 4).[20]

$$\Delta E_{ab} = \sum_{i}^{\mathrm{on\ a}} \sum_{j}^{\mathrm{on\ b}} (q_i q_j / r_{ij}) + 4\epsilon_{\mathrm{OO}}[(\sigma_{\mathrm{OO}}/r_{\mathrm{OO}})^{12} - (\sigma_{\mathrm{OO}}/r_{\mathrm{OO}})^{6}] \qquad (4)$$

The TIP3P model has been shown to be appropriate for studying hydration properties of bioorganic molecules.[21]

Free-Energy Profile of Solvation. Statistical mechanical Monte Carlo simulations were carried out with the QM/MM-AM1/TIP3P potential function to calculate the free energy of solvation for systems of 1 DMF and 216 water molecules.[10] The pmf is determined via statistical perturbation theory (eq 5) by computing free energy changes along the reaction coordinates, θ and θ', in steps of about ±8° that transform the GS to the TS's;[22]

$$\Delta G(\theta_0 \rightarrow \theta_1) = -kT \ln \langle e^{-\Delta E(\theta_0 \rightarrow \theta_1)/kT} \rangle_0 \qquad (5)$$

where $\langle\ \rangle_0$ represents the ensemble average with the Hamiltonian

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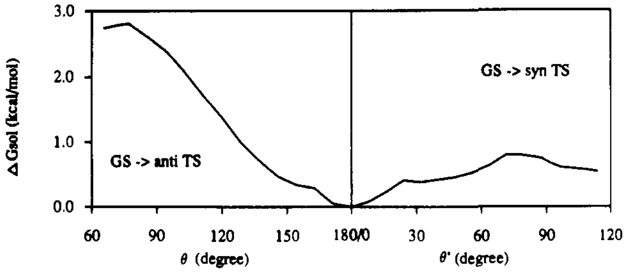

Figure 3. Computed changes in free energy of hydration for the C–N rotation in DMF from the ground state to transition states.

$\hat{H}(\theta_0)$ and $\Delta E(\theta_0 \rightarrow \theta_1)$ is the energy difference at the reference θ_0 and perturbed θ_1 values of the dihedral reaction coordinate θ. A cutoff distance of 9 Å was used to evaluate the interaction energies. The procedure is the same as in our previous study of the torsional profile for acetic acid in water.[14,23] In all calculations, at least 500K configurations were initiated in equilibrium followed by 1–1.5 M configurations for averaging at 25 °C and 1 atm with the NPT ensemble.[10,15] Error bars were estimated over averages of blocks of 100K configurations. The fluid simulations took about 8 months primarily with two SUN SLC computers in our laboratory, while the ab initio calculations were carried out on a Cray Y/MP computer at the Pittsburgh Supercomputing Center.

The key results are shown in Figures 2 and 3. Evidently, the aqueous solvation effect increases the activation free energy for the anti TS by 2.7 ± 0.2 kcal/mol, while the change for the syn TS is moderate, being destabilized by only 0.5 ± 0.1 kcal/mol relative to the ground state. In conjunction with the gas-phase ab initio MP4(SDTQ)/6-31G(d) results (Table II), our best estimate of the free energy of activation for DMF isomerization in water is 22.5 ± 0.2 kcal/mol for the anti form and 20.8 ± 0.1 kcal/mol for the syn form. Thus, the predicted increase in ΔG^{*} is about 1 kcal/mol (20.8–19.8) in aqueous solution over the gas-phase value. Experimental ΔG^{*} values do not appear to be available for DMF in water, though the computed solvent effect is consistent with findings for other solvents and with those of DMA in water.[3,4] The free energy of activation for DMF increases by ca. 1.5 kcal/mol upon transferring from the gas phase into pure liquid DMF and the solution of CCl_4; however, the latter has been complicated by amide associations. ΔG^{*} values for DMA are 15.3, 18.1, 17.3, and 19.3 kcal/mol for the gas-phase, neat DMA, and solutions in CCl_4 and water, respectively.[3,4] Duffy et al. predicted that the anti TS for DMA is destabilized by 2.1 ± 0.1 kcal/mol in water based on OPLS-type potential functions,[9] which is in good accord with our number for DMF (2.7). It should be mentioned that in that study the syn TS was found to be *stabilized* relative to the GS by 1.8 ± 0.1 kcal/mol in aqueous solution, placing the syn structure only 0.2 kcal/mol above the anti. Consequently, they suggested that the two transition states of DMA are energetically competitive in aqueous solution.[9] The present AM1/TIP3P result for DMF indicates that the solvent effect is still destabilizing for the syn form. However, a reversal of the barrier heights for the anti and syn transition states is observed because the small intrinsic energy difference (19.8 versus 20.2) between the two transition states is not enough to offset the much larger solvent destabilizing effects on the anti form (2.7 versus 0.5). So, the syn structure is predicted to be the favored transition state for the isomerization of DMF in water.

The nature of the solvent effects on the DMF isomerization in water can be rationalized by examining the computed dipole moments and atomic charges along the reaction coordinate. Figure 4 displays the computed dipole moments in the gas phase and water, whereas charge variations are given in Figure 5. For comparison, the 6-31G(d) calculations yield gas-phase dipole moments of 4.09, 2.02, and 3.67 D for the GS, anti, and syn structures, while the AM1 results are 3.55, 1.58, and 3.36, respectively. The two experimental values for DMF are 3.77 and 3.92 D.[24] Thus, both 6-31G(d) and AM1 predictions are reasonable, though the AM1 results appeared to be about 0.3–0.5 D smaller than the corresponding ab initio data. Most significant is the change of dipole moment in water as depicted by Figure 4 from the AM1/TIP3P simulations. The induced dipole moment for DMF in water is significant along the entire torsional transition, with the largest increase at the planar ground-state conformation leading to an average aqueous dipole moment of 5.08 ± 0.04 D. This gives an induced dipole moment of 1.53 D for the GS structure, which contrasts the induced values of 0.43 and 1.07 ± 0.05 D for the anti and syn TS's. Furthermore, the trends in solvation free energy mirror nicely the magnitude of the aqueous dipole moments (Figures 3 and 4), emphasizing the importance of detailed molecular polarization effects in these calculations. This is further supported by the computed polarization energies (E_{pol}) of −3.50, −0.86, and −1.91 ± 0.1 kcal/mol for the GS, anti, and syn structures.[13,15] Of course, details of hydrogen-bonding interactions are also critical in controlling the solvation free energy.[9] Quantitatively, the results demonstrate the utility of the combined QM/MM-AM1/TIP3P approach for study of conformational transformations in solution. The large unbalanced polarization effects for different conformers of the same molecule indicate that consideration of the trend of gas-phase electrostatic properties alone is perhaps insufficient to account for detailed condensed-phase phenomena. Consequently, it is of interest to investigate if polarizable intermolecular potential functions can reproduce these results.

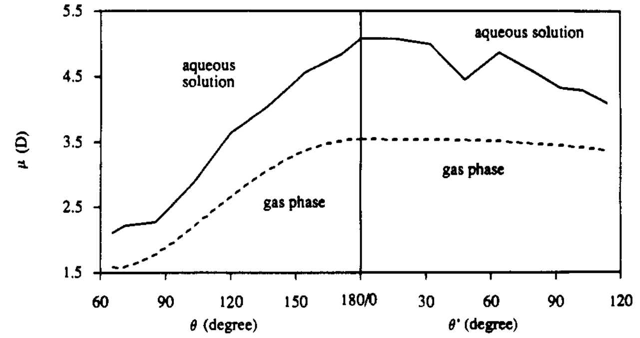

Figure 4. Computed dipole moments along the torsional reaction coordinates for the isomerization of DMF in the gas phase and aqueous solution.

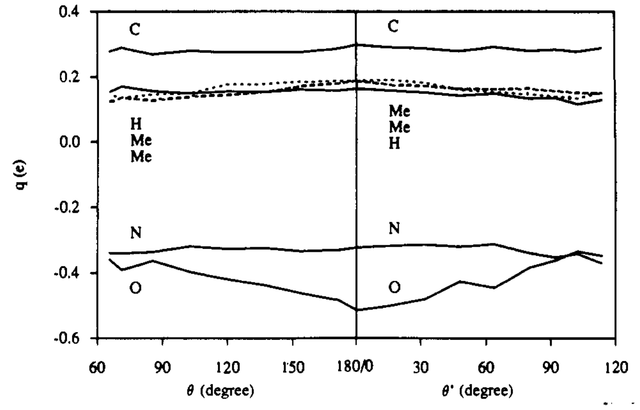

Figure 5. Changes in average atomic charges obtained from Mulliken population analysis for DMF in water for converting from the ground state to transition states in water.

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[23] All simulations were performed using the BOSS (Version 2.9; Jorgensen, W. L., Yale University, 1990) and MCQUB (Monte Carlo QM/MM at UB, Gao, J., SUNY at Buffalo, 1992) programs. The quantum mechanical energy was evaluated with MOPAC, ref 19b.

[24] (a) Meighan, R. M. *Diss. Abstr.* **1985**, *25*, 4427. (b) Lee, C. M.; Kumler, W. D. *J. Am. Chem. Soc.* **1962**, *84*, 571.

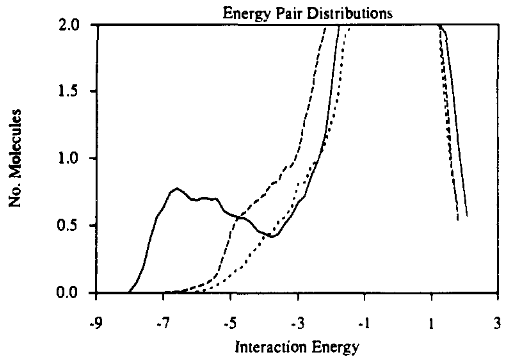

Figure 6. Computed distributions of DMF–water pair interaction energy for the ground state (solid curve) and the anti (dotted curve) and syn (dashed curve) transition states. Interaction energy is given in kcal/mol, while unit for the ordinate is number of solvent molecules per kcal/mol.

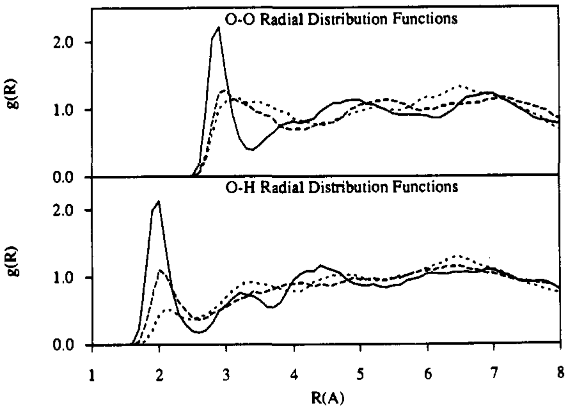

Figure 7. Carbonyl oxygen–water oxygen (top) and hydrogen (bottom) radial distribution functions obtained using the AM1/TIP3P model. Solid curves are for the ground state, dotted curves are for the anti transition state, and dashed curves are for the syn form. This convention is used throughout.

Atomic charges computed by Mulliken population analysis were also averaged in the QM/MM simulations (Figure 5).[25] However, they may only be considered as a qualitative, provocative indication of the charge separations since the Mulliken population analysis itself is open to criticism.[17] Nevertheless, it is instructive to see that large charge variations only occur on the carbonyl oxygen with a decrease of the partial charge from −0.515 ± 0.002 e in the ground state to −0.359 and −0.348 ± 0.007 e in the anti and syn transition states. These charges are primarily transferred to the methyl groups on nitrogen. Interestingly, the charge patterns are nearly identical for both the anti and syn transformations (Figure 5), supporting the use of a single charge distribution for both transition states.[9] The charge patterns are also reflected in the energy pair distribution functions (Figure 6), which provide details of solute–water interaction energies. The low-energy band for the GS in Figure 6 is due to hydrogen bonds to the carbonyl oxygen, which is replaced by broad, higher-energy "shoulders" for the transition states. The qualitative features of Figure 6 are in good accord with the results of Duffy et al., though the bands for the transition-state structures are more ordered in their study.[9] Another difference between the two studies is that the hydrogen-bonding interaction predicted by the AM1/TIP3P method is about 1 kcal/mol stronger for the ground state in the energy pair distributions.

Radial Distribution Functions. Specific hydrogen-bonding interactions are revealed in the radial distribution functions (rdf's) computed for the ground state and transition states (Figures 7–10). In these figures, the first atom for an xy distribution, $g_{xy}(r)$, refers to an atom of DMF, and the second atom is either the oxygen or the hydrogen of water. All rdf's have been normalized to the bulk density of solvent atoms. The error range in these plots is estimated to be one-half of the bin size (0.05 Å) used in data collection.

The OO and OH rdf's in Figure 7 have well-defined first peaks at 2.9 and 2.0 Å, though the minima in the OO rdf for the transition states are smeared out. The striking first peak representing hydrogen bonds between carbonyl oxygen and water hydrogen perhaps is an over-estimate in the present AM1/TIP3P model in comparison with previous studies with the OPLS function.[26]

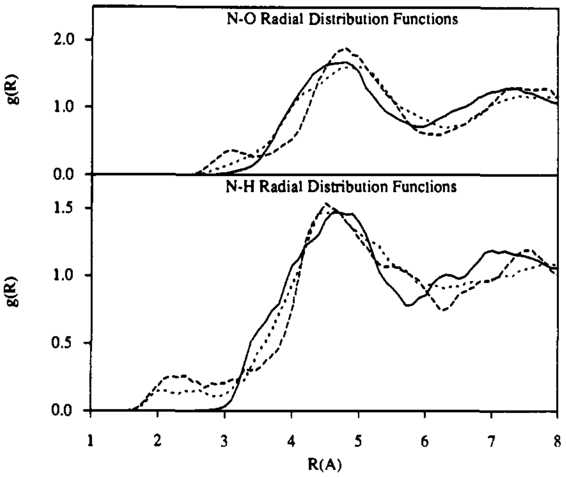

Figure 8. DMF nitrogen–water oxygen (top) and hydrogen (bottom) radial distribution functions.

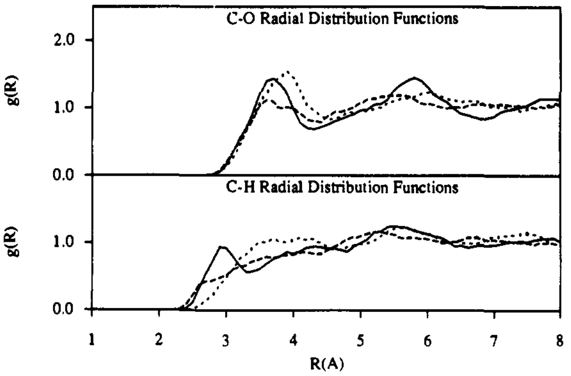

Figure 9. Carbonyl carbon–water oxygen (top) and hydrogen (bottom) radial distribution functions.

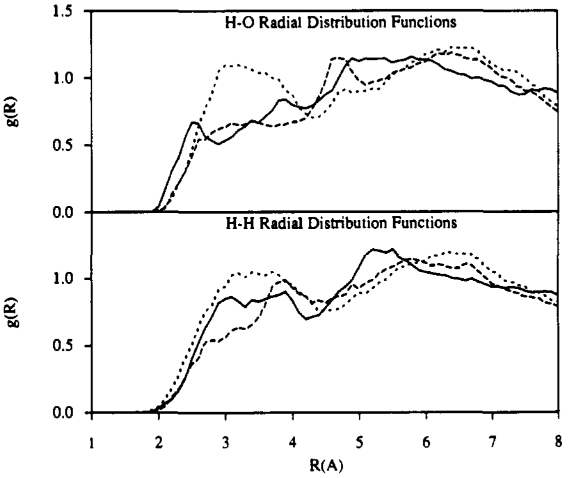

Figure 10. Carbonyl hydrogen–water oxygen (top) and hydrogen (bottom) radial distribution functions.

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(25) Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833.

(26) Jorgensen, W. L.; Swenson, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 569, 1489.

Integration to 2.5 Å of the OH rdf's gives nearest neighbors of 2.9, 1.1, and 2.1 waters for the GS, anti, and syn monomers, respectively. Jorgensen and Swenson predicted a coordination number of 2.0 for DMF with the OPLS function.[26] A more recent study yielded 1.7 neighbors with the modified parameters for ground-state DMA.[9] However, the trends of diminishing first peaks upon rotation to the transition states (1.1 and 1.9 neighbors for anti and syn)[9] are in good accord with the present results.

For the NH and NO rdf's (Figure 8), the AM1/TIP3P model predicts no hydrogen bonding for the ground state in accord with the OPLS function, while integration to 2.5 Å of the small hydrogen-bonding peaks for the anti and syn forms yields 0.4 and 0.7 hydrogen. This may be compared with the findings of 0.4 and 0.6 neighbor for DMA by Duffy et al.[9] Although the total number of hydrogen bonds for the syn form is complicated by the possibility of hydrogen bonding to both the carbonyl oxygen and amino nitrogen as pointed out by Duffy et al.,[9] further hydrogen-bond analysis was not performed here. The rdf's for the carbonyl C also show some structural features, which may be assigned to hydrogen-bonding waters to other sites (Figure 9). It is also interesting to notice that the HO rdf for the anti TS showed somewhat stronger first peaks (Figure 10). This is consistent with simultaneous hydrogen bonding of a water with nitrogen and the carbonyl hydrogen. The methyl–water radial distribution functions exhibited the usual broad features,[15] which are not shown here.

Conclusion

The present combined QM/MM AM1/TIP3P simulation study of the isomerization of *N,N*-dimethylformamide in water yielded new insight on the origin of the solvent effects. The computed free energy of activation (19.8 and 20.2 kcal/mol for anti and syn forms) at the MP4(SDTQ)/6-31G(d) level is in excellent agreement with gas-phase NMR measurements (19.4 kcal/mol), whereas the predicted ΔG^* for the isomerization of DMF in water is 20.8 kcal/mol. It was found that the trends in solvation free energy mirror nicely the change of dipole moments in water. The predicted solvent destabilization of transition states by 2.7 and 0.5 kcal/mol for the anti and syn forms relative to the ground state is consistent with experimental findings and in agreement with previous simulation studies.[3,4,9] While Duffy et al. found that the two transition states for *N,N*-dimethylacetamide were competitive in water,[9] the syn form is predicted here to be the preferred transition state for DMF in water. This stems from the fact that the small difference in gas-phase energy between the transition states is not enough to offset the much larger destabilizing solvation effects on the anti rotamer in water. In addition, the finding that DMF was polarized more favorably in the ground state than in the rotated conformers suggests that it is important to include explicit polarization effects into the empirical potential functions.[27] Further studies of the solvent effects and catalytic conditions on peptidyl prolyl systems in both water and nonaqueous solutions should be informative.[1,2,9,28]

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Supplementary Material Available: Details of the energetic, geometrical, and vibrational frequency results for the ground state, anti, and syn transition states computed at the MP4-(SDTQ)/6-31G(d) and 6-31G(d) levels, respectively (6 pages). Ordering information is given on any current masthead page.

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[27] Caldwell, J.; Dang, L. X.; Kollman, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 9144.

[28] Fischer, S. Ph.D. Thesis, Harvard University, 1992.