heteroatoms. This and the presence of alkali metal counterions in most biological systems make the role of metal ions in reactions of oxygen radicals in biological systems a fascinating new area for further work.

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Supplementary Material Available: Gaussian 88 archive entries for the MP4 single points on the reactants, transition states, and products of the uncatalyzed reactions and those with Li^+, Na^+, K^+, Rb^+, and Cs^+ (10 pages). Ordering information is given on any current masthead page.

Aqueous Solvation of *N*-Methylacetamide Conformers: Comparison of Simulations and Integral Equation Theories

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Abstract: The aqueous solvation thermodynamics of *cis*- and *trans*-*N*-methylacetamide is studied by integral equation theories and molecular dynamics simulations and compared with Monte Carlo results (Jorgensen, W. L.; Gao, J. *J. Am. Chem. Soc.* **1988**, *110*, 4212). Although the hypernetted chain (HNC) approximation is generally recommended for polar systems, the solvation free energy derived from the Gaussian fluctuation (GF) approximation gives much better absolute solvation thermodynamics. With the same atomic charges for the two conformers, the difference in solvation free energy between the cis and trans conformers equals 1-2 kcal/mol from the HNC and GF approximations, in approximate agreement with the value of 2.2 kcal/mol from a Monte Carlo simulation with very similar parameters. The simpler superposition approximation introduced by Pettitt and Karplus (*Chem. Phys. Lett.* **1985**, *121*, 194) gives results for the relative solvation thermodynamics (cis versus trans conformers) that compare well with the more exact integral equation theories.

1. Introduction

Biological macromolecules are polymers composed of simple organic monomers;[1] e.g., proteins are composed of 20 different types of amino acids and nucleic acids of 4 different nucleotides. The covalent bonding in the biopolymers is such that the main chain structure is chemically homogeneous. In proteins, the main chain consists of $-(NHC^{\alpha}CO)_n-$, where n is the number of amino acids in the sequence; in nucleic acids, the main chain is $-(\text{phosphate-ribose})_n-$, where the ribose is oxy in RNA and deoxy in DNA. The heterogeneity of the polymers results from different amino acid side chains attached to the C^{α} atoms in proteins and the different purine/pyrimidine bases attached to the ribose in nucleic acids. From X-ray and NMR structural studies, it is known that the backbone is flexible due to the presence of soft (ϕ, ψ in proteins; α, β, γ, δ, ϵ in nucleic acids) and hard (ω in proteins) dihedral angle degrees of freedom and can assume a wide range of conformations. The relative stability of these conformations is determined by the intrinsic properties of the backbone, the nature of the monomers, and the solvent environment. For proteins in their native state, the prediction of the ϕ, ψ values expected for a given sequence corresponds to the solution of the *folding* problem, the object of much of the theoretical and computational analyses of these systems. For peptides and denatured proteins, both the main chain and side chain tend to have a high solvent exposure. An analysis of the structural properties of these systems requires a detailed understanding of the effect of solvent on the stability of different conformations.

Recent computational and theoretical developments have made it feasible to focus on the effects of solvent on the structural, dynamical, and thermodynamic properties of biological macromolecules.[2,3] For example, the stochastic boundary simulation method[4] was introduced to study the active site dynamics of proteins in the presence of solvent.[5,6] Such simulation methods,[7,8] although very useful, require extensive computational resources with the explicit inclusion of solvent being the most time-consuming element. An alternative is to use integral equation theories to describe the effect of solvation.[9,10] Although approximate, the results have been shown to be meaningful for pure liquids and solutions.[9-20] To apply integral equation theory in a simple form that is consistent with standard molecular mechanics/dynamics potentials,[2] a superposition approximation has been developed to decompose the solvation corrections into pairwise additive contributions.[21,22] It has been employed to study the effect of solvation

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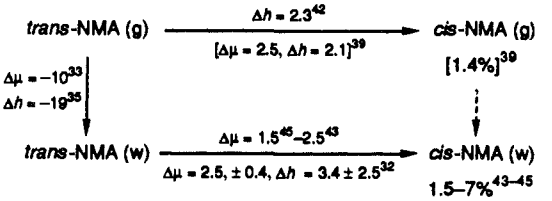
on the soft dihedral angle potential of the alanine[22] and glycine[23] dipeptides and a number of tripeptides.[24] Comparisons with a simulation study of the solvent correction for a number of conformers of the alanine dipeptide[25] and of the ϕ, ψ map in aqueous solution (a *solvated* Ramachandran plot)[26] suggest that the method gives a qualitatively correct estimate of relative solvation.

Since the accuracy of integral equation calculations has been found to depend on the strength of the interactions,[16,17,19,20] more studies and comparisons with simulations for complex systems are desirable. Also, it is important to compare the superposition approximation with the more rigorous full integral equation theory. This paper applies integral equation theory[9,10,21,27,28] to the aqueous solvation of the peptide group in *N*-methylacetamide (NMA), $CH_3CONHCH_3$.[29] An analysis is made of the variation of the solvation as a function of the stiff dihedral angle ω. Peptide group geometrics corresponding to both the trans ($\omega = 180°$) and cis ($\omega = 0°$) isomers of NMA are found in peptides and proteins,[30] and considerable experimental[31-35] and theoretical effort[36-41] has been expended to determine the solvation thermodynamics of the two isomers and the internal rotational barrier around the C–N bond. An infrared spectroscopic study of NMA in a nitrogen matrix at different temperatures has given an estimate of the relative "*gas-phase*" enthalpy of −2.3 kcal/mol in favor of *trans*-NMA.[42] The solvation free energy of NMA at 25 °C in water is approximately −10 kcal/mol with an estimated difference between cis and trans isomers of less than 0.1 kcal/mol.[33,34,43] The enthalpy of solvation estimated by Spencer et al. is −19 kcal/mol.[35] The equilibrium concentration of *cis*-NMA in water ranges from 1.5% to 7%.[34,44,45] This corresponds to a combined gas-phase and solvation free energy difference in the range −2.5 to −1.5 kcal/mol in favor of *trans*-NMA. Radzicka and Wolfenden[34] found that the distribution is relatively insensitive to solvent polarity; i.e., they found populations of *cis*-NMA equal to 1.5% in water, 3% in chloroform, and less than 2% in cyclohexane at 20 °C.[34] The barrier to internal rotation around the C–N bond in water at 60 °C measured by NMR spectroscopy corresponds to a free energy of 18.8 ± 0.3 kcal/mol from *cis*-NMA to *trans*-NMA and 21.3 ± 0.3 kcal/mol from *trans*-NMA to *cis*-NMA; this yields a relative stability of −2.5 ± 0.4 kcal/mol in favor of *trans*-NMA.[32] The corresponding data for the enthalpy barrier are 19.8 ± 1.8 kcal/mol from cis to trans and 23.2 ± 1.8 kcal/mol in the reverse direction; this corresponds to a relative value of −3.4 ± 2.5 kcal/mol in favor of *trans*-NMA.[32] However, since the 20 mol % concentration of NMA used in the study was high enough to form dimers or polymers, the rotational barrier for dilute NMA in water may be somewhat different.[32,46]

Theoretical studies on NMA have focused on the relative thermodynamics of the cis and trans isomers in the gas phase,[39-41,43] in the neat liquid,[37] and in water.[36,38,39] From an ab initio energy calculation at the MP2/6-31G(d)//6-31G(d) level and a vibrational analysis at the level of 3-21G//3-21G, *trans*-NMA in the gas phase at 25 °C is favored by −2.5 kcal/mol in free energy;[39] the enthalpic contribution of −2.1 kcal/mol is in agreement with the experimental estimate of −2.3 kcal/mol at 27 °C.[42] The calculated gas-phase *cis*-NMA population of 1.4% is similar to that observed in water.[33] Theoretical studies of the NMA in water show a significant dependence on the choice of model potentials.[39] The optimized potential for liquid simulations (OPLS)[38,39] used in a Monte Carlo (MC) simulation with TIP4P[47] water indicated that solvation favors *trans*-NMA by −2.2 kcal/mol in free energy. Combined with the gas-phase result, the *trans*-NMA in water would be favored by a total of −4.7 kcal/mol in free energy; this corresponds to 99.97% *trans*- and only 0.03% *cis*-NMA, in disagreement with experiment.[43,45] The favorable solvation of *trans*-NMA was attributed to the larger dipole moment (4.23 D relative to 3.86 D for *cis*-NMA) in the OPLS model.[39] This ordering of the dipole moment is opposite to the calculated ab initio values of 3.85 and 4.03 D for *trans*- and *cis*-NMA, respectively. With different partial charges on the *trans*- and *cis*-NMA interaction sites chosen so that the dipole moments agree with the ab initio result, the MC simulation in water yielded a negligible effect of solvation on the trans ⇌ cis equilibrium (−0.13 ± 0.30 kcal/mol in favor of *trans*-NMA).[39]

Some of the data quoted above are summarized in the diagram (all data are in kilocalories per mole for the temperature range 20 to 60 °C; see above; theoretical results are in parentheses).



The symbol g denotes the gas phase and w the water phase; $\Delta\mu$ and Δh are the relative free energy and enthalpy, respectively. Although there are considerable uncertainties in the experimental and theoretical results quoted here, they do provide data for comparison with the integral equation theory. Moreover, it is also possible to perform self-consistency tests, independent of the experimental data, by comparing simulation and integral equation results.

In this paper, integral equation calculations of the NMA trans ⇌ cis equilibrium in water are compared with available experimental data[33,35,45] and with the published MC simulations.[8,36] In addition, a molecular dynamics simulation for the solvation of

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NMA in TIP3P water[48] is performed. This set of results serves to assess the validity of the full integral equation theory. Both the hypernetted chain (HNC) closure[10] and the Gaussian fluctuation approximation[49] are compared within the extended *r*eference *i*nteraction *s*ite *m*odel (XRISM or HNC-RISM) formulation.[9,50] The Gaussian fluctuation approximation has been found to be better than the HNC approximation for the aqueous solvation of nonpolar solutes such as methane, ethane, and propane,[13] while the HNC approximation appears to be better for polar and ionic systems.[10] It is therefore of interest to compare the two approximations for a system with both nonpolar and strong polar interactions. In addition, the superposition approximation[21,22] is compared with the full integral equation theory. The aqueous solvation and trans ⇌ cis equilibrium of more complex peptides including the proline residue will be described separately.[51]

In section 2, we briefly outline the integral equation theory employed in this study and describe the model solutes and solvent. The results and discussion are presented in section 3. Conclusions drawn from the study are given in section 4.

2. Methods

2.1. Theory. Two complementary theoretical methods, integral equation theory[9,10,21,22] and molecular dynamics simulation,[52] are employed. We first describe the integral equation methods including the XRISM theory,[9,10,53] the Gaussian fluctuation approximation,[49,53] and the superposition approximation to these methods.[21,22] We then outline the methodology of the molecular dynamics simulation and present the parameters used to describe NMA and the aqueous solvent.

2.1.1. XRISM Integral Equations. The RISM integral equation theory of Chandler and Andersen[9] consists of two equations with two unknown functions, the total correlation functions, $\mathbf{h}(r)$, and the direct correlation functions, $\mathbf{c}(r)$, where r is the distance variable. The first equation in Fourier space, denoted by the caret, is (a more complete description is given in the cited references[9,10,27,28])

$$\hat{\mathbf{h}} = \hat{\mathbf{w}}\hat{\mathbf{c}}\hat{\mathbf{w}} + \hat{\mathbf{w}}\hat{\mathbf{c}}\rho\hat{\mathbf{h}} \tag{2.1}$$

where the intramolecular correlation function matrix $\hat{\mathbf{w}}$ has elements $\hat{w}_{\alpha\gamma}(k) = (\sin kL_{\alpha\gamma}/kL_{\alpha\gamma})$ with $L_{\alpha\gamma}$ the distance between sites α and γ; the symbol ρ is the number density matrix. The second equation in the XRISM theory is the site–site HNC closure introduced by Rossky and co-workers.[10,50,54] In this study, we used a slightly modified closure[28,55]

$$[\mathbf{h}]_{\alpha\gamma} = h_{\alpha\gamma}(r) = e^{-\beta U^{\mathrm{eff}}_{\alpha\gamma}(r)+h_{\alpha\gamma}(r)-c_{\alpha\gamma}(r)} - 1 \tag{2.2}$$

where α and γ are site labels; the symbol β is the inverse of the Boltzmann constant times the absolute temperature T. For the solvent sites v, an effective potential U^{eff}_{vv} is introduced; the form $U^{\mathrm{eff}}_{vv} = U^{*}_{vv} - A\phi_{vv}/\beta$ ensures that the calculated total solvent correlation functions are consistent with the macroscopic dielectric constant ϵ_0 of the solvent.[14,28,55-57] The quantity U^{*} is a short-range core potential for which the Lennard-Jones 6–12 interaction is used in the present case. The function $\phi_{\alpha\gamma}(r)$ is $-\beta z_\alpha z_\gamma/r$ with z_α being the charge on site α. The numerical factor A is given by[14,28,55-57]

$$A = \frac{1 + \epsilon_0(3y - 1)}{3y(\epsilon_0 - 1)}$$

with

$$y = \frac{4\pi\beta\rho_v\langle d_v^2\rangle}{9} \tag{2.3}$$

where $\langle d_v^2\rangle$ is the average squared dipole moment of the solvent molecule; for the rigid water model used here, $\langle d_v^2\rangle = d_v^2$. In eq 2.2, $A = 1$ if either α or γ is the solute (u) site. Equations 2.1 and 2.2 are solved by an iterative scheme.[10,54,58] Given their solutions, the solvation free energy, $\Delta\mu$, of introducing a solute from the gas phase into the solvent is[19,53]

$$\Delta\mu^{\mathrm{HNC}} = \frac{\rho_v}{\beta}\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int d\vec{r}[\tfrac{1}{2}h_{\alpha\gamma}^2(r) - c_{\alpha\gamma}(r) - \tfrac{1}{2}h_{\alpha\gamma}(r)c_{\alpha\gamma}(r)] \tag{2.4}$$

The corresponding equation for atomic systems (atomic solute and solvent) was given by Morita.[59,60] The superscript HNC emphasizes that the thermodynamics are calculated from the HNC closure without further approximation.

The enthalpic (energetic) and entropic contributions to the solvation free energy can be obtained from the derivatives of $\mathbf{h}$ and $\mathbf{c}$ with respect to temperature and density.[27,28] The method has been applied previously to the solvation thermodynamics of simple atomic solutes[27,28] and a chemical reaction in water.[20] The enthalpic component of the solvation free energy, Δh, is[19,28]

$$\Delta h^{\mathrm{HNC}} = \Delta\epsilon^{\mathrm{HNC}} + T\alpha_{v,P}\left[\Delta\mu^{\mathrm{HNC}} + \frac{\rho_v^2}{2\beta}\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int d\vec{r}[h_{\alpha\gamma}(r)\delta_{\rho_v}c_{\alpha\gamma}(r) - c_{\alpha\gamma}(r)\delta_{\rho_v}h_{\alpha\gamma}(r)]\right] \tag{2.5}$$

where $\alpha_{v,P}$ is the isobaric thermal expansion coefficient of the pure solvent. The symbol δ_{ρ_v} denotes the isobaric derivative with respect to the solvent density. The solvation energy, $\Delta\epsilon$, is calculated via the isochoric temperature derivative (δ_T) of the solvation free energy[19,28]

$$\Delta\epsilon^{\mathrm{HNC}} = \rho_v\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int d\vec{r}U_{\alpha\gamma}(r)[1 + h_{\alpha\gamma}(r)] + \frac{T\rho_v}{2\beta}\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int d\vec{r}[c_{\alpha\gamma}\delta_T h_{\alpha\gamma}(r) - h_{\alpha\gamma}\delta_T c_{\alpha\gamma}(r)] \tag{2.6}$$

The first term in eq 2.6 is the average solute–solvent interaction energy $\langle U_{uv}\rangle$, and the second term gives the solute-induced solvent reorganization energy. The solvation entropy is obtained from the thermodynamic relationship $\Delta s = (\Delta h - \Delta\mu)/T$. To simplify notations, we dropped the superscript (o) used to denote the limit of infinite dilution in earlier work;[27,28] the infinite dilution limit is assumed here.

2.1.2. Gaussian Fluctuation (GF) Approximation. Chandler, Singh, and Richardson[49] proposed an alternative solvation free energy functional

$$\Delta\mu^{\mathrm{GF}} = -\frac{\rho_v}{\beta}\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int d\vec{r}[c_{\alpha\gamma}(r) + \tfrac{1}{2}h_{\alpha\gamma}(r)c_{\alpha\gamma}(r)] \tag{2.7}$$

that differs from eq 2.4 by not having the positive semidefinite $^1/_2h_{\alpha\gamma}^2(r)$ term. Its derivation assumes that the solvent bath fluctuation obeys Gaussian statistics and that the solute couples linearly to the bath density with a strength determined by the direct correlation functions.[49] The same expression can be obtained if the free energy functional is truncated at the second order in the solute–solvent interaction.[49] For the aqueous solvation of nonpolar solutes, eq 2.7 appears to give better results than eq 2.4 when compared to experiments[13] and simulations.[61] It is thus of interest to compare the solvation thermodynamics obtained from the two methods in the case where both nonpolar and polar interactions are present. In using eq 2.7 in this study, all the correlation functions were calculated from the XRISM theory. We note that one can arrive at eq 2.7 by replacing the potential function with the direct correlation function in the coupling parameter integration formula;[62] i.e.

$$\Delta\mu = \rho_v\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int_0^1 d\lambda\int d\vec{r}\frac{\partial U_{\alpha\gamma}(r;\lambda)}{\partial\lambda}g_{\alpha\gamma}(r;\lambda) \tag{2.8}$$

is replaced by

$$\Delta\mu^{\mathrm{GF}} = \frac{-\rho_v}{\beta}\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int_0^1 d\lambda\int d\vec{r}\frac{\partial c_{\alpha\gamma}(r;\lambda)}{\partial\lambda}g_{\alpha\gamma}(r;\lambda) \tag{2.9}$$

where λ is the coupling parameter that switches the solute–solvent interaction from noninteracting ($\lambda = 0$) to fully interacting ($\lambda = 1$). Thus, the GF approximation has a feature of the mean-spherical approximation in that $c \sim -\beta U$.[63] Since there is no a priori reason for the validity of

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one over the other, the choice of HNC or GF free energy functionals must be judged by comparisons with simulations or experiments.[13]

Given the GF free energy expression, the decomposition into solvation enthalpy and entropy follows from earlier work;[19,27,28] that is

$$\Delta h^{GF} = \Delta\epsilon^{GF} + T\alpha_{v,P}\left[\Delta\mu^{GF} - \frac{\rho_v^2}{2\beta}\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int d\vec{r}[2\delta_{\rho_v}c_{\alpha\gamma}(r) + h_{\alpha\gamma}(r)\delta_{\rho_v}c_{\alpha\gamma}(r) + c_{\alpha\gamma}(r)\delta_{\rho_v}h_{\alpha\gamma}(r)]\right] \quad (2.10)$$

and

$$\Delta\epsilon^{GF} = \frac{T\rho_v}{2\beta}\sum_{\alpha=1}^{n_u}\sum_{\gamma=1}^{n_v}\int d\vec{r}[c_{\alpha\gamma}(r)\delta_T h_{\alpha\gamma}(r) + h_{\alpha\gamma}(r)\delta_T c_{\alpha\gamma}(r) - 2\delta_T c_{\alpha\gamma}(r)] \quad (2.11)$$

2.1.3. Superposition Approximation (SA). To develop an efficient simulation method for flexible polyatomic molecules in aqueous solution, a Kirkwood-like superposition approximation[62] has been used in conjunction with the XRISM integral equation[21-24] to calculate a solvent-modified intramolecular potential of mean force (PMF) for polyatomic solutes. The justification for introducing the approximation is based on the observation that two monatomic solutes in solution have a solvent-modified PMF that is qualitatively similar to that for two nonoverlapping solvent-exposed atoms in a polyatomic solute.[21,22,64] Atoms separated by three or more bonds (1,4 and higher nonbonded pairs) are usually far enough apart to be nonoverlapping. Since the bond 1,2 and bond angle 1,3 interactions in typical polyatomic molecules are sufficiently stiff that they are negligibly modified by the solvent, the SA can be and has been applied to study the effect of solvent on conformations by including only 1,4 and higher nonbonded pairs in solvent-exposed polyatomic solutes such as small peptides.[21-24]

Given the intramolecular conformation R_u of the polyatomic solute, the introduction of the pairwise additivity assumption in the SA reduces the calculation of the *solvent contribution* to the solute intramolecular PMF, $\Delta W\{R_u\}$, to one of calculating ΔW for pairs of atoms free in the solvent;[21,22] i.e.

$$\Delta W^{SA}\{R_u\} = \sum_{(\alpha,\gamma)\geq(1,4)}^{R_u}\Delta W\{L_{\alpha\gamma}\} = \sum_{(\alpha,\gamma)\geq(1,4)}^{R_u}\frac{1}{\beta}[c_{\alpha\gamma}(L_{\alpha\gamma}) - h_{\alpha\gamma}(L_{\alpha\gamma})] \quad (2.12)$$

where the HNC closure has been used to obtain the second equality.[14,28] In the full integral equation theory without the superposition approximation, $\Delta W\{R_u\}$ is given by

$$\Delta W\{R_u\} = \Delta\mu\{R_u\} - \sum_{\alpha}^{R_u}\Delta\mu\{\alpha\} \quad (2.13)$$

where $\Delta\mu\{\alpha\}$ is the excess solvation free energy of a solute interaction site α free in the solvent. In accord with the definition of the potential of mean force, $\Delta W\{R_u\}$ vanishes when all sites in the molecule are infinitely separated.

From comparison of eqs 2.12 and 2.13, it is clear that $\Delta W^{SA}\{R_u\}$ is not an approximation to the absolute value of $\Delta W\{R_u\}$ since, in addition to introducing the pairwise additivity assumption, the former neglects all 1,2 and 1,3 solute pairs. However, when the differences (instead of absolute values) in solvent-mediated PMF among a set of solvent-exposed solute conformations are of interest,[21,22] one may expect

$$\Delta\Delta\mu = \Delta\mu\{R_u\} - \Delta\mu\{R'_u\} \cong \Delta W^{SA}\{R_u\} + \sum_{\alpha}^{R_u}\Delta\mu\{\alpha\} - \Delta W^{SA}\{R'_u\} - \sum_{\alpha}^{R'_u}\Delta\mu\{\alpha\} \quad (2.14)$$

since the relative rigidity of 1,2 and 1,3 pairs results in the cancellation of their contribution when the difference is taken. When the potential parameters on the free sites are independent of conformations R_u or R'_u, we have

$$\sum_{\alpha}^{R_u}\Delta\mu\{\alpha\} = \sum_{\alpha}^{R'_u}\Delta\mu\{\alpha\}$$

and eq 2.14 simplies to

$$\Delta\Delta\mu \cong \Delta W^{SA}\{R_u\} - \Delta W^{SA}\{R'_u\} \quad (2.15)$$

(63) Hansen, J. P.; McDonald, I. R. *Theory of Simple Liquids*, 2nd ed.; Academic Press: New York, 1988.
(64) Pratt, L. R.; Chandler, D. *J. Chem. Phys.* **1980**, *73*, 3430–3433.

Table I. Model Potential Parameters for *N*-Methylacetamide and Water[a]

	σ, Å	ϵ, kcal/mol	q, e
H_w	0.40	0.046	0.417
O_w	3.15	0.152	−0.834
$CH_{3,C}$	3.91	0.16	0.0
C	3.75	0.105	0.5
C'_{cis}	3.75	0.105	0.53
C'_{trans}	3.75	0.105	0.58
O	2.96	0.21	−0.5
O′	2.96	0.21	−0.53
N	3.25	0.17	−0.57
N′	3.25	0.17	−0.55
H	0.4[b]	0.046[b]	0.37
H'_{cis}	0.4[b]	0.046[b]	0.35
H'_{trans}	0.4[b]	0.046[b]	0.30
$CH_{3,N}$	3.8	0.17	0.2

[a] OPLS parameters are used except for hydrogen site Lennard-Jones parameters. The superscript ′ denotes sites with modified charges. $CH_{3,C}$ is the methyl group bonded to the carbonyl carbon and $CH_{3,N}$ is the methyl group bonded to the nitrogen. [b] Modified to avoid a Coulombic singularity.[15,20]

The contribution from $\Delta\Delta h$ and $T\Delta\Delta s$ can be calculated by taking appropriate derivatives of the last expression in eq 2.14;[19,27,28] in an earlier study, numerical derivatives were employed.[65]

2.1.4. Molecular Dynamics (MD) Simulation. To complement the integral equation calculations, microcanonical molecular dynamics simulations, using the molecular mechanics/dynamics program CHARMM,[52] with periodic boundary conditions were used to study the aqueous solvation of *trans*- and *cis*-NMA. NMA was solvated by 304 water molecules in a cubic box of length 21 Å to give a bulk water density of 0.995 g/cm^3. The equations of motion were integrated with a time step of 1 fs with the nonbond list updated every 20 fs. A fourth-order switching function smoothly truncates the nonbond interaction from 7.5 to 8.5 Å based on groups.[52] The SHAKE[66] algorithm was used to remove all intramolecular degrees of freedom in the NMA, as well as the aqueous solvent, to permit direct comparison with the integral equation results. A method used earlier to circumvent numerical problems in applying SHAKE constraints to planar molecules of more than three atoms was adopted;[20] it is different from the method of quarternions in which generalized coordinates are introduced to solve explicitly for the rigid body motion.[67] Two dummy (i.e., *noninteracting*) atoms were introduced and all dummy atoms NMA distances were kept fixed. The dummy atoms were positioned at 0.5 Å from the nitrogen and the carbonyl carbon. Both were placed perpendicular to, but on opposite sides of, the planar NMA. The dummy atoms were assigned the mass of hydrogen, which increases the total mass of NMA by 1%. In principle, this does not alter the relative sampling of configurational space that determines equilibrium properties; in practice, small differences in the convergence of finite simulations may arise. The solvated NMA systems were equilibrated for 15 ps and trajectories were run for 33 ps with the coordinates saved every 5 fs for analysis. The statistical uncertainties for simulation data are calculated by subdividing the trajectory into blocks of 0.5 ps and treating the coarse-grained data as independent samples to calculate the root-mean-square fluctuations.

2.2. Models. Since one purpose of the present study was to compare the various results with the MC simulation study of Jorgensen and Gao,[39] we used a very similar model of NMA. The geometry for NMA was taken from Benedetti et al.[68] with the Lennard-Jones parameters and partial charges taken from Jorgensen et al.[37,39] In Table I two sets of partial charges (unprimed and primed) for NMA are listed. The unprimed set,[37] used unless specified otherwise, is independent of NMA conformation and is that employed to model protein peptide groups with the OPLS.[69] The two aliphatic carbons were represented as extended atoms without hydrogens.[39]

The solvent water was a three-site model similar to TIP3P water with a rigid molecular geometry given by R_{OH} = 0.9572 Å and $\angle_{HOH}$ =

(65) Pettitt, B. M.; Karplus, M. *J. Phys. Chem.* **1988**, *92*, 3994–3997.
(66) Ryckaert, J. P.; Ciccotti, G.; Berendsen, H. J. C. *J. Comput. Phys.* **1977**, *23*, 327–341.
(67) Allen, M. P.; Tildesley, D. J. *Computer Simulation of Liquids*; Oxford University Press: London, 1987.
(68) Benedetti, E. In *Proceedings of the Fifth American Peptide Symposium*; Goodman, M., Meienhofer, J., Eds.; Wiley: New York, 1977; pp 257–273.
(69) Jorgensen, W. L.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1988**, *110*, 1657–1666.

Table II. Average Solute–Solvent Interaction Energies (kcal/mol) for *trans*- and *cis*-NMA[a]

	$\langle U_{uv}\rangle^{trans}$		$\langle U_{uv}\rangle^{cis}$		$\langle U_{uv}\rangle^{cis} - \langle U_{uv}\rangle^{trans}$	
	HNC/GF	MD	HNC/GF	MD	HNC/GF	MD
$CH_{3,C}$	−1.2	−4.26 ± 0.04	−1.8	−4.17 ± 0.04	−0.6	0.09 ± 0.06
C=O	−20.3	−17.6 ± 0.2	−17.4	−16.4 ± 0.2	2.9	1.2 ± 0.3
C	10.3	1.0 ± 0.3	10.0	1.5 ± 0.3	−0.3	0.5 ± 0.4
O	−30.6	−18.5 ± 0.4	−27.4	−17.9 ± 0.4	3.2	0.6 ± 0.6
N–H	−13.3	−9.2 ± 0.2	−9.4	−6.3 ± 0.1	3.9	2.9 ± 0.2
N	−5.7	1.3 ± 0.4	−5.9	0.2 ± 0.4	−0.2	−1.1 ± 0.6
H	−7.6	−10.5 ± 0.3	−3.5	−6.4 ± 0.4	4.1	4.1 ± 0.5
$CH_{3,N}$	0.4	−3.3 ± 0.1	−1.6	−5.1 ± 0.1	−2.0	−1.8 ± 0.1
total	−34.4	−34.4 ± 0.4	−30.2	−32.0 ± 0.2	4.2	2.4 ± 0.4

[a] The root-mean-squared fluctuations of the simulation results are reported as the measure of uncertainties in the data (see text).

104.52°.[48] The interaction potential between solutes and water was modified slightly from the model developed by Jorgensen.[37,39] The short-range core interactions were given by the Lennard-Jones 6–12 potential; the long-range interaction was Coulombic. Parameters were combined by using the geometric mean, i.e., $\epsilon_{\alpha\gamma} = (\epsilon_\alpha\epsilon_\gamma)^{1/2}$ and $\sigma_{\alpha\gamma} = (\sigma_\alpha\sigma_\gamma)^{1/2}$, with the exception of the interaction involving hydrogens. For them, the arithmetic mean $\sigma_{H\gamma} = (\sigma_H + \sigma_\gamma)/2$ was used. The use of the geometric mean is in accord with the Jorgensen and Gao model, which differs from that used generally in molecular mechanics.[52] However, for NMA as for proteins, the difference is small. A somewhat larger effect arises in the water–NMR dimer interaction energies from the use of TIP3P rather than TIP4P water, the maximum difference occurs when the amide hydrogen in *trans*-NMA is solvated (c.f., Table III, configuration III of Jorgensen and Gao[39]); TIP3P water gives −7.3 kcal/mol whereas the TIP4P value equals −6.6 kcal/mol.

The thermodynamic conditions for all integral equation calculations were at a temperature of 25 °C and $\rho_{H_2O} = 0.997$ g/cm³ at 1 atm. In the MD simulation, the average temperature is 25 ± 8 °C for the *cis*-NMA and 23 ± 8 °C for the *trans*-NMA with $\rho_{H_2O} = 0.995$ g/cm³.

3. Results and Discussion

In section 3.1, the integral equation calculations using the HNC and GF approximations are compared to MC or MD simulations and experiments. The SA is compared with the HNC and GF approximations in section 3.2. The solvent reorganization induced by NMA is discussed in section 3.3. In section 3.4, the solvation thermodynamics of conformational dependent potential models of NMA is given; it demonstrates that caution is needed in using the SA in the cases where contributions from 1,2 and 1,3 pairs do not cancel.

3.1. HNC and GF Approximations Compared with Simulations and Experiments. 3.1.1. Average Interaction Energy (HNC/GF and MD). Since the average solute–solvent interaction energies $\langle U_{uv}\rangle$ are an essential part of the solvation thermodynamics (see eqs 2.6 and 2.11), we compare the results for NMA in water from XRISM theory and the MD simulation in Table II; the same value is obtained from the HNC and GF approximations. The total $\langle U_{uv}\rangle$ from the XRISM treatment of the *trans*- and *cis*-NMA are −34.4 and −30.2 kcal/mol, which are in very good agreement with the MD results of −34.4 ± 0.4 and −32.0 ± 0.2 kcal/mol, respectively. MC simulations for NMA in TIP4P[47] water gave less negative values of −26.3 ± 1.6 (−27.7 ± 0.4[38]) kcal/mol for *trans*-NMA and −24.7 ± 0.8 kcal/mol for *cis*-NMA.[36] Although the absolute values depend on the water model, the differences between *cis*- and *trans*-NMA are within the statistical errors of each other; i.e., the value of 2.4 ± 0.4 kcal/mol obtained with TIP3P and 1.6 ± 1.8 kcal/mol with TIP4P.[36] Both the integral equation theory and the simulations favor the average *trans*-NMA–water interaction energy. As suggested previously,[38] this is likely to result from the larger dipole moment of the *trans*-NMA model.

The contribution from individual solute sites to the average interaction energy show larger differences than the total. For the carbonyl oxygen site the XRISM gives −30.6 kcal/mol in *trans*-NMA and −27.4 kcal/mol in *cis*-NMA. These are much larger than the MD simulation values of −18.5 ± 0.4 and −17.9 ± 0.4 kcal/mol, respectively. However, it should be noted that the nonbonded interactions were truncated between 7.5 and 8.5 Å in the simulation while the XRISM values are calculated without a cutoff. The discrepancy between XRISM and simulation for the solute–solvent interaction energy of charged sites may result in part from the truncation in the simulation;[70,71] for the entire NMA molecule and the nonpolar $CH_{3,C}$ site, both of which are neutral, the discrepancies introduced by truncation are expected to be smaller. Much better agreement (within 3 kcal/mol) was found for the difference between *cis*- and *trans*-NMA when the component atoms are grouped chemically into $CH_{3,C}$ (the methyl on the carbonyl carbon), $CH_{3,N}$ (the methyl on the nitrogen), C=O, and N—H (see Table II). This type of cancellation of errors seems to be a rather general feature of the thermodynamics computed from simulations or integral equations. Earlier studies showed the XRISM calculations are most useful when differences, rather than absolute values, of the solvation thermodynamics are of interest.[19,20] The favorable comparison with MD simulation on the overall and group interaction energy is encouraging.

Table III. Aqueous Solvation Thermodynamics (kcal/mol) for *trans*- and *cis*-NMA

		trans		cis	
	expt[a]	HNC	GF	HNC	GF
		NMA			
$\Delta\mu$	−10	7.0	−9.8	8.3	−7.8
Δh	−19	−12.2	−17.1	−10.4	−15.0
$T\Delta s$	−9	−19.2	−7.3	−18.7	−7.2
		NMA'[b]			
$\Delta\mu$	−10	8.7	−8.1	7.6	−8.5
Δh	−19	−10.1	−15.0	−11.2	−15.9
$T\Delta s$	−9	−18.9	−6.9	−18.8	−7.4

[a] Experimental data are from Wolfenden[33] and Spencer et al.[35] The distribution is 98.5% *trans*- and 1.5% *cis*-NMA.[33] [b] The modified charges for NMA are used (see Table I, primed).

3.1.2. Absolute Solvation Thermodynamics. In Table III, the calculated solvation thermodynamics are compared with experiment. The absolute solvation thermodynamics calculated from the HNC (eqs 2.4–2.6) and the GF (eqs 2.7–2.11) approximations are significantly different. This is not surprising since the $^1/_2h^2_{\alpha\gamma}(r)$ terms can be important for polar solutes. The HNC results predict a *positive* solvation free energy of 7–8 kcal/mol whereas the GF value of −9.8 kcal/mol for *trans*-NMA agrees well with the experimental data of −10 kcal/mol.[33] The solvation enthalpy from the GF of −17.1 kcal/mol for *trans*-NMA is also closer to the experimental estimate of −19 kcal/mol[35] than the HNC value of −12.2 kcal/mol. For the strong polar interaction in this system, as well as for alkanes in water,[13] the absolute values from the GF approximation are better than the HNC approximation. For monovalent ions, the GF approximation predicts more favorable solvation free energy of −4.5 kcal/mol for Na^+ and −6 kcal/mol for K^+, Cl^-, and Br^- than those of the HNC approximation; the GF leads to better agreement with experiments than HNC for cations but it is worse for anions.[28,72] When compared to experiments,[33,35] the HNC underestimates the enthalpy of solvation

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Table IV. Group Decomposition of the Solvation Thermodynamics (kcal/mol) of *trans*- and *cis*-NMA

	$\Delta\mu$, ΔH, or $T\Delta s$				$\Delta\Delta\mu$, $\Delta\Delta h$, or $T\Delta\Delta s$		
	trans-NMA		*cis*-NMA		*trans*-NMA → *cis*-NMA		
group	HNC	GF	HNC	GF	HNC	GF	SA
			$\Delta\mu$			$\Delta\Delta\mu$ (2.2 ± 0.3)[a]	
$CH_{3,C}$	9.7	6.5	7.8	4.8	−1.9	−1.7	−1.5
C=O	−7.6	−13.2	−5.1	−10.7	2.5	2.5	2.5
N—H	−3.6	−8.2	−1.0	−5.1	2.6	3.1	2.4
$CH_{3,N}$	8.5	5.1	6.6	3.2	−1.9	−1.9	−1.4
total	7.0	−9.8	8.3	−7.8	1.3	2.0	2.0
		Δh				$\Delta\Delta h$	
$CH_{3,C}$	4.2	3.3	2.9	2.2	−1.3	−1.1	−1.1
C=O	−13.2	−15.0	−11.0	−13.0	2.2	2.0	2.3
N—H	−6.2	−7.3	−3.7	−4.7	2.5	2.6	2.4
$CH_{3,N}$	3.0	1.9	1.4	0.5	−1.6	−1.4	−1.3
total	−12.2	−17.1	−10.4	−15.0	1.8	2.1	2.3
		$T\Delta s$				$T\Delta\Delta s$	
$CH_{3,C}$	−5.5	−3.2	−4.9	−2.6	0.6	0.6	0.4
C=O	−5.6	−1.8	−5.9	−2.3	−0.3	−0.5	−0.2
N—H	−2.6	0.9	−2.7	0.4	−0.1	−0.5	0.0
$CH_{3,N}$	−5.5	−3.2	−5.2	−2.7	0.3	0.5	0.1
total	−19.2	−7.3	−18.7	−7.2	0.5	0.1	0.3

[a] From MC simulation in TIP4P water.[39]

for NMA by 40% and overestimates the entropy by 100%. Since the average interaction energies from the HNC (same as the GF) approximations are close to values from the MD simulation, the error in the HNC enthalpy comes from an overestimate of the solvent reorganization energy (by ~5 kcal/mol; see Table VI).

The contribution from individual groups in NMA to the solvation thermodynamics is given in Table IV. The values of HNC and GF approximations are different, but both indicate that it is unfavorable to solvate nonpolar hydrophobic groups ($CH_{3,C}$ and $CH_{3,N}$) and favorable to solvate polar hydrophilic groups (C=O and N—H) in water. This is consistent with the accepted concepts of solution chemistry. For polar groups, the solvation is dominated by enthalpy; for nonpolar groups, the entropic contribution is either comparable to or more important than the enthalpy. In the *relative* solvation thermodynamics, the enthalpy dominates for both hydrophilic and hydrophobic groups. The enthalpy of solvation for C=O is about twice as favorable than for N—H. This result is consistent with the ability of C=O to form two hydrogen bonds in water compared with only one for N—H.

3.1.3. Relative Solvation Thermodynamics. The *solvent contribution* to the relative solvation thermodynamics is plotted in Figure 1. The top panel shows the difference in solvation free energy between the two isomers, $\Delta\Delta\mu = \Delta\mu^{cis} - \Delta\mu^{trans}$. Both the HNC and GF approximations give results that are qualitatively similar to the MC simulation.[39] The MC results have a small peak near 90°, which may be an artifact. Water disfavors *cis*-NMA by 1.3 and 2.0 kcal/mol from HNC and GF, respectively (see Table IV). The MC simulation predicts a free energy difference of 2.2 ± 0.3 kcal/mol;[39] this is comparable to the difference in the average interaction energy of 1.6 ± 1.8 kcal/mol in TIP4P water.[36] The calculated 2.5 ± 0.4 kcal/mol average interaction energy difference between *cis*- and *trans*-NMA in TIP3P water from the MD simulation suggests a MD free energy difference in TIP3P water of 1–2 kcal/mol, similar to results of the integral equation theory. The favorable solvation of *trans*-NMA is dominated by enthalpy ($\Delta\Delta h$), as shown in the second panel of Figure 1; it results from the larger dipole moment of *trans*-NMA. *cis*- and *trans*-NMA differ only slightly in solvation entropy (see Figure 1, $T\Delta\Delta s$).

The contribution from individual groups in NMA to the relative solvation thermodynamics is given in Table IV. In the HNC approximation, the solvation free energy favors *cis*-NMA by −1.9 kcal/mol each from $CH_{3,C}$ and $CH_{3,N}$; it is 2.5 and 2.6 kcal/mol less favorable from the C=O and N—H groups, respectively. The enthalpy dominates the solvation and is similar to the average interaction energy (see Table II) in that it also favors $CH_{3,C}$, $CH_{3,N}$ and disfavors C=O, N—H in *cis*-NMA. The results of the GF approximation are similar to the HNC approximation.

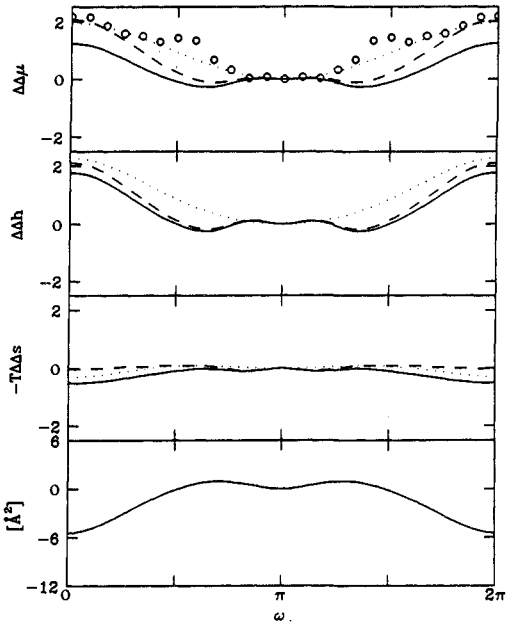

Figure 1. Solvent contribution to the relative solvation thermodynamics of the *cis*-NMA ($\omega = 0$) and *trans*-NMA ($\omega = \pi$). (—) HNC; (– –) GF; (···) SA; (○) MC simulation.[39] Top, $\Delta\Delta\mu$; second, $\Delta\Delta h$; third, $-T\Delta\Delta s$; bottom, the relative solvent-accessible surface area (Å²) based on a spherical probe of 1.4 Å.[73]

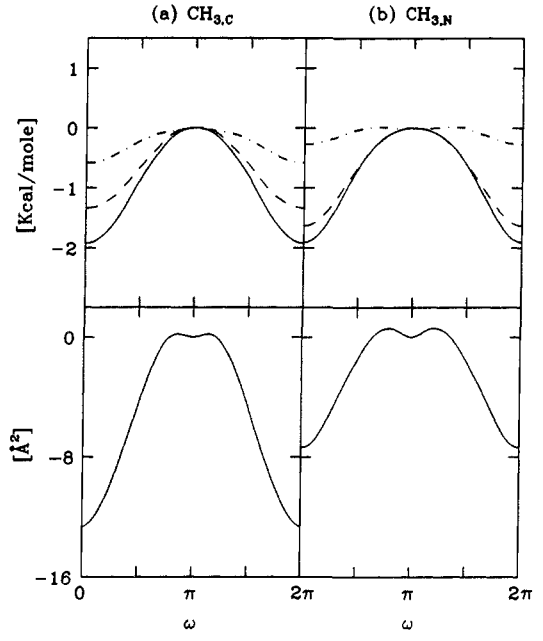

Figure 2. Relative solvation thermodynamics of the *cis*-NMA ($\omega = 0$) and *trans*-NMA ($\omega = \pi$) from the methyl carbons. Upper: (—) $\Delta\Delta\mu$; (– –) $\Delta\Delta h$; (–·–) $-T\Delta\Delta s$. Lower: the relative solvent accessible surface area. (a) $CH_{3,C}$. (b) $CH_{3,N}$.

In Figures 2 and 3, the relative solvation thermodynamics from the HNC approximation and the solvent-accessible surface area are plotted as a function of the peptide dihedral angle ω for $CH_{3,C}$, $CH_{3,N}$, C=O, and N–H. The solvent-accessible surface area is calculated by rolling a spherical probe of radius 1.4 Å (the size of water) over defined boundaries of the solute atoms.[73,74] Both interatomic distances where the short-range Lennard-Jones core potential is zero (the parameter σ) and where the potential is a minimum (the parameter r_{min}; $r_{min} = 2^{1/6}\sigma$) have been used to define the solute boundaries.[73-75] In Table V, the solvent-accessible

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Table V. Solvent-Accessible Surface Area (Å²) for *trans*- and *cis*-NMA[a]

	trans-NMA			*cis*-NMA			*trans*-NMA → *cis*-NMA		
	OPLS[b]		Ooi,[c]	OPLS[b]		Ooi,[c]	OPLS[b]		Ooi,[c]
group	σ	r_{min}	σ	σ	r_{min}	σ	σ	r_{min}	σ
$CH_{3,C}$	84	96	93	71	81	77	−13	−15	−16
C	12	13	2	15	17	3	3	4	1
O	35	37	33	42	45	43	7	8	10
N—H	16	15	11	20	21	19	4	6	8
$CH_{3,N}$	82	93	94	75	84	84	−7	−9	−10
total	229	254	234	223	248	226	−6	−6	−8

[a] The surface algorithm of Lee and Richards[73] implemented in the program CHARMM[52] is used. [b] The Lennard-Jones σ and r_{min}'s used are based on Table I. [c] The Lennard-Jones σ's used are 4.0 Å for $CH_{3,N}$ and $CH_{3,C}$, 3.1 Å for N and C, and 2.8 Å for O.[75]

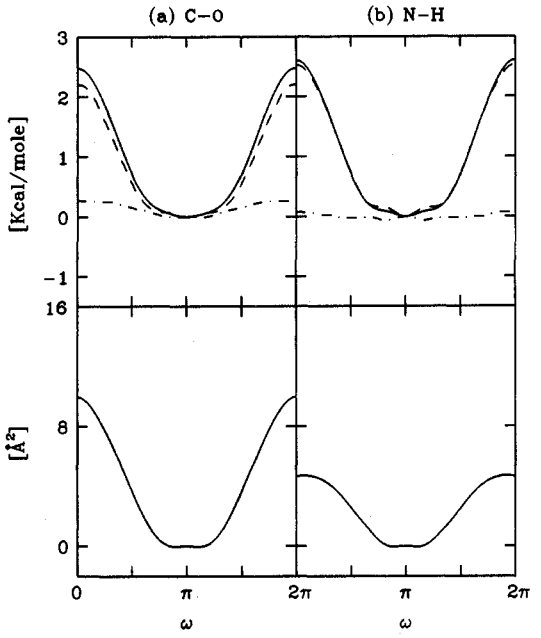

Figure 3. Relative solvation thermodynamics of the *cis*-NMA ($\omega = 0$) and *trans*-NMA ($\omega = \pi$) from the carbonyl and amide groups. Upper: (—) $\Delta\Delta\mu$; (--) $\Delta\Delta h$; (-·-) $-T\Delta\Delta s$. Lower: the relative solvent-accessible surface area. (a) Carbonyl group. (b) Amide group.

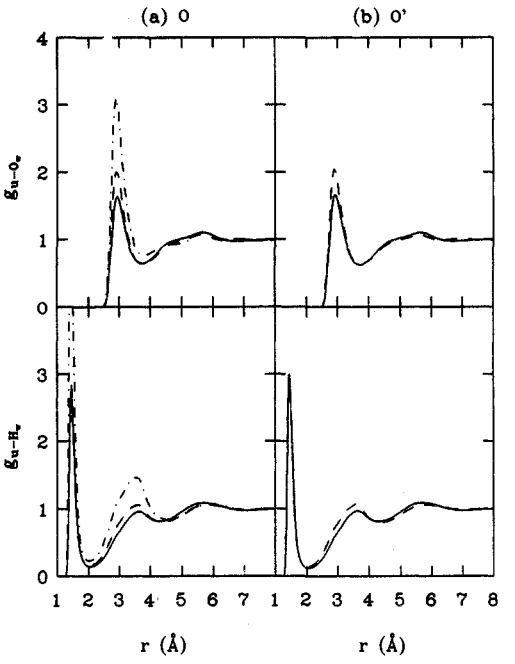

Figure 4. XRISM radial distribution functions for the carbonyl oxygen, (—) *trans*-NMA, (--) *cis*-NMA, and (-·-) free site in water. (a) Carbonyl oxygen. Upper, O–O_w; lower, O–H_w. (b) Carbonyl oxygen with modified charge. Upper, O′–O_w; lower, O′–H_w.

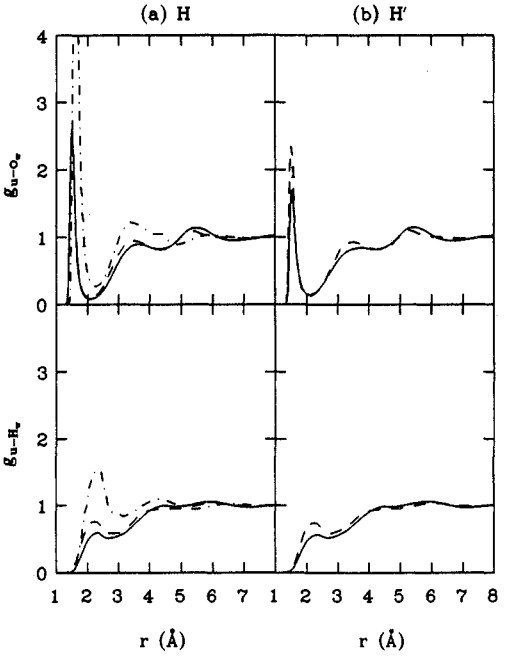

Figure 5. XRISM radial distribution functions for the amide hydrogen, (—) *trans*-NMA, (--) *cis*-NMA, and (-·-) free site in water. (a) Amide hydrogen. Upper, H–O_w; lower, H–H_w. (b) Amide hydrogen with modified charge. Upper, H′–O_w; lower, H′–H_w.

surface areas for NMA calculated with σ or r_{min} from Table I are listed. Differences up to 10% arise for the absolute solvent-accessible surface area between using σ or r_{min} to define the solute boundary. However, the difference in accessible surface area between NMA isomers is not sensitive to the choice of σ or r_{min}. In accord with Ooi et al.,[75] we use σ in the present analysis.

Parts a and b of Figure 2 show a definite correlation between the solvent-accessible surface area of the methyl groups and the solvation thermodynamics. A favorable relative solvation free energy of −1.9 kcal/mol each is accompanied by a reduction in the solvent-accessible surface area of −13 Å² in $CH_{3,C}$ and −7 Å² in $CH_{3,N}$. Such an observation supports the hypothesis that it is favorable to bury hydrophobic surface in aqueous solvent.[76] Of the −1.9 kcal/mol free energy, the entropy contributes 30% in the case of $CH_{3,C}$ ($q = 0.0$); this is larger than the 14% in the less hydrophobic $CH_{3,N}$ ($q = 0.2$).

For the hydrophilic groups C=O and N—H, Figure 3 also shows correlation between the solvation thermodynamics and the solvent-accessible surface area. Intuitively, one expects that a larger accessible hydrophilic surface will lead to more favorable solvation. However, the contrary is observed for both C=O and N—H. The more accessible C=O of 10 Å² in *cis*-NMA leads to an unfavorable relative solvation free energy of 2.5 kcal/mol. For N—H, the penalty in free energy is 2.6 kcal/mol for 5 Å² increased solvent accessibility. The unfavorable relative free

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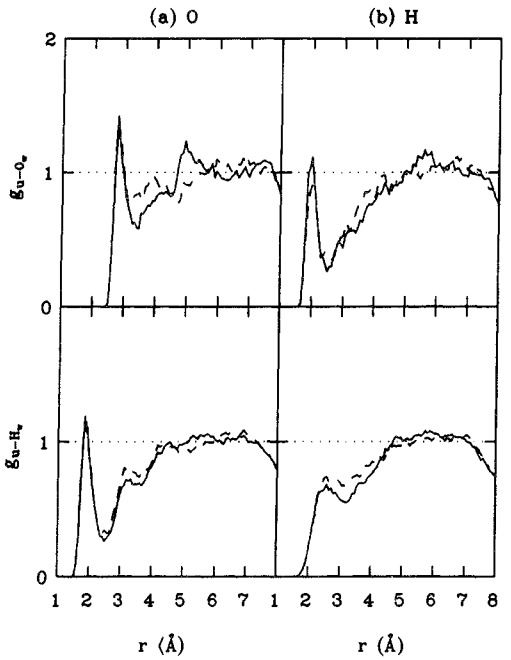

Figure 6. MD radial distribution functions for the carbonyl oxygen and amide hydrogen, (—) *trans*-NMA, and (--) *cis*-NMA. (a) Carbonyl oxygen. Upper, O–O_w; lower, O–H_w. (b) Amide hydrogen. Upper, H–O_w; lower, H–H_w.

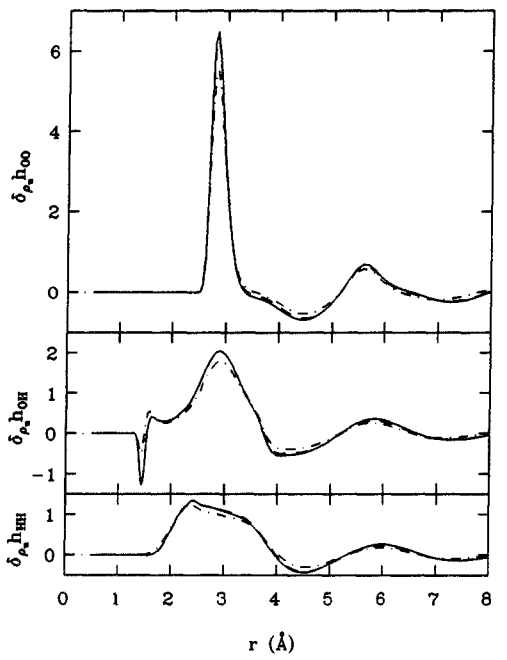

Figure 7. Solute-induced modification in the solvent radial distribution functions, (—) *trans*-NMA, (--) *cis*-NMA, and (-·-) Lennard-Jones sphere (see text). Top, $\delta_{\rho_u} h_{OO}$; middle, $\delta_{\rho_u} h_{OH}$, bottom, $\delta_{\rho_u} h_{HH}$. All data have been scaled by $\rho_{H_2O}/2$.

energies of the hydrophilic groups are enthalpy dominated (≥90%) to an extent greater than the hydrophobic $CH_{3,C}$ (70%) but only slightly more so than $CH_{3,N}$ (86%).

The counterintuitive results of the hydrophilic groups can be understood by examining their radial distribution functions (rdf). The solute–water rdf from the XRISM theory for the carbonyl oxygen and the amide hydrogen in *trans*-NMA and *cis*-NMA are given in Figures 4a and 5a. The higher first peak of g_{O-O_w} (upper panel of Figure 4a) for *cis*-NMA reflects the greater solvent accessibility of the carbonyl oxygen. In spite of this, the hydrogen-bonding peak in *cis*-NMA is slightly weaker than in *trans*-NMA (see Figure 4a lower panel); i.e., the *cis*-NMA carbonyl oxygen does not make more or stronger hydrogen bonds with the greater number of available water molecules. This is likely to result from stronger interference from nearby amide hydrogen (q = 0.37) in *cis*-NMA than the $CH_{3,N}$ (q = 0.2) in *trans*-NMA. The repulsive electrostatic interaction between sites $CH_{3,N}$ and H in *cis*-NMA and water hydrogens positioned 1.5 Å away from the carbonyl oxygen is 5–10% greater than in *trans*-NMA. That the amide H interferes with the solvation of the carbonyl O (or vice versa) is supported experimentally by the observation that the acetamide solvation free energy of −9.7 kcal/mol[75] is slightly less favorable than the value of −10 kcal/mol for NMA. For the solvation of the amide hydrogen, the same argument is applicable (see Figure 5a).

Thus, the solvation thermodynamic contribution of a given group is found to depend not only on its own chemical properties (charge and van der Waals radius) and the excluded volume effects due to its neighbors but also on the charge of its neighbors. For instance, a positively charged site with a given solvent exposure contributes differently to solvation depending on whether its neighbors carry positive, negative, or no charge since the solvating water behaves differently. This suggests that the attempts to apply atomic solvation parameters, based on charge and solvent accessibility alone,[75,77] may not be adequate since they do not take such correlations into account.[78] Because of the importance of this result, it is necessary to confirm that it is not an artifact of the XRISM integral equation theory. In Figure 6, the solute–solvent rdf for the carbonyl oxygen and the amide hydrogen from the MD simulation are given. They are qualitatively similar to the XRISM rdf (see Figures 4 and 5). In particular, they show the same lack of correspondence between exposure and solvation behavior.

3.2. SA vs HNC and GF Approximations. Since the potential parameters used for NMA are independent of its conformations, eq 2.15 is used for the calculation of the superposition approximation to the more complete HNC and GF integral equation theories. The *solvent contribution* to the relative solvation thermodynamics calculated from the SA approximation is given in Figure 1. The results are in rather good agreement with the HNC and GF approximations, as well as the MC simulation[39] for the free energy; in fact the SA agrees better with the MC results than either HNC or GF values, though this is likely to be accidental. Table IV shows that water disfavors *cis*-NMA by 2.0 kcal/mol from SA compared with 1.3 and 2.0 kcal/mol from HNC and GF, respectively. The 2.3 kcal/mol enthalpy of solvation from SA is also similar to that of 1.8 and 2.1 kcal/mol predicted by HNC and GF approximations, respectively.

For the group decomposition in SA, where pairwise interactions are obtained as a result of assumption, we assign equal weighting to the two atoms in the pairwise $\Delta W\{L_{\alpha\gamma}\}$ of eq 2.12. In principle, other weighting schemes based on atomic Lennard-Jones parameters and partial charges can be used. Table IV suggests that the simple equal weighting is appropriate since it leads to results from the SA that are similar to the HNC and GF approximations. The similarity indicates that the computationally much less demanding superposition approximation[21,22] provides useful information of comparable quality to the more rigorous theory in this case where contributions from 1,2 and 1,3 pairs cancel exactly. However, the SA as described in section 2.1.3, is not applicable when the contributions from 1,2 and 1,3 pairs do not cancel. This is shown in section 3.4, where conformational dependent potential parameters were used for NMA.

In the SA, the solute sites are treated as free sites in water. In Figures 4a and 5a, the dot–dash lines give the rdf for water and free monatomic carbonyl oxygen and amide hydrogen sites, respectively. The lack of excluded volume effect from neighboring groups results in a much greater magnitude near contact for the free sites.

3.3. NMA-Induced Solvent Reorganization. The solvent reorganization induced by the NMA solute can be determined from the calculated changes in the water site–site radial distribution

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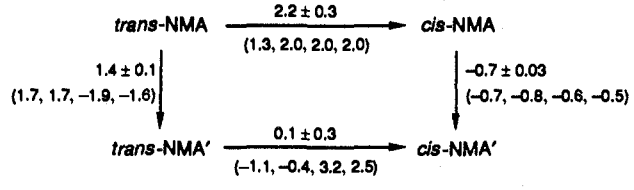
Table VI. Solvent Reorganization Energy (kcal/mol) of *trans*- and *cis*-NMA

	trans-NMA		*cis*-NMA		*trans*-NMA → *cis*-NMA	
group	HNC	GF	HNC	GF	HNC	GF
$CH_{3,C}$	3.2	2.3	2.7	2.0	−0.5	−0.3
C=O	6.4	4.5	5.5	3.5	−0.9	−1.0
N-H	6.7	5.6	5.2	4.2	−1.5	−1.4
$CH_{3,N}$	0.8	−0.4	1.3	0.4	0.5	0.8
total	17.0	12.0	14.7	10.1	−2.3	−1.9

functions $\delta_{p_u}h$'s (see eq 2.5).[27] As has been pointed out in earlier work,[27,28] even at the infinite dilution limit the solvent reorganization contributes to the solvation enthalpy and entropy. The results for *cis*-NMA and *trans*-NMA are shown in Figure 7. The changes induced by a Lennard-Jones solute of σ = 5.15 Å, chosen to have excluded volume comparable to the NMA molecule, and an ϵ of 0.16 kcal/mol equal that of the site $CH_{3,C}$, are included to provide a reference for comparison. Physically, a larger solute-excluded volume leads to a greater increase in the effective solvent density, which in turn induces larger oscillations of $\delta_{p_u}h$'s.[27,79] A polar solute competes with bulk water for hydrogen bonding and tends to produce greater reorganization of the solvent than a nonpolar solute of comparable size.[27] Figure 7 shows that the two NMA isomers have generally similar effects. Both induce somewhat larger changes than the Lennard-Jones solute due to their being polar molecule conformers. The first peak in the $\delta_{p_u}h_{OO}$ for *trans*-NMA is slightly higher than that for *cis*-NMA as a result of *trans*-NMA being slightly more polar and larger in volume (by 2%). In $\delta_{p_u}h_{OH}$, the first negative dip near r_{OH} = 1.5 Å reflects the NMA–water hydrogen bonding (e.g., that of the carbonyl oxygen site, Figure 4a) that replaces some water hydrogens in the first solvation shell of bulk water molecules.[27] Despite the fact that five out of the six sites in NMA are charged, the overall features resemble a simple nonpolar solute more than one with a net charge (cf. Figure 7 in ref 27). Thus for neutral NMA, no one single site dominates the solvent reorganization. This contrasts with the neutral water molecule in which the negatively charged oxygen site dominates.[27]

The solvent reorganization energy induced by NMA is given in Table VI. The more compact *cis*-NMA, with its smaller dipole moment in the model, results in a smaller energy of water reorganization of 15 (10) kcal/mol compared with the value of 17 (12) kcal/mol for *trans*-NMA from the HNC (GF) approximation. They are much larger than the HNC and GF values of 3.5 and 2 kcal/mol, respectively, for the reference nonpolar Lennard-Jones solute. The relative value is −2 kcal/mol in favor of *cis*-NMA from either HNC or GF approximations. Earlier study by Zichi and Rossky[19] found a water reorganization energy of −1.0 kcal/mol in favor of *cis*-*n*-butane relative to *trans*-*n*-butane and 1.3 kcal/mol that disfavors *cis*-1,2-dichloroethane relative to *trans*-1,2-dichloroethane, which has zero dipole moment. These observations reflect the fact that the water reorganization energy is smaller for more compact and for less polar solutes. In the case of NMA, both effects combine to favor the *cis*-NMA; in 1,2-dichloroethane the effect of polarity dominates that of the excluded volume. The decomposition into groups shows that the polar C=O and N—H groups dominate the less polar $CH_{3,N}$ and the nonpolar $CH_{3,C}$ in the energetics of water reorganization.

3.4. Conformational Dependent Potential Models of NMA. Since the standard OPLS parameters, which are the same for *cis*- and *trans*-NMA, did not give the correct solvation free energy difference, Jorgensen and Gao[39] introduced a special model in which the parameters are different for the two isomers (see Table I). The exact procedure for obtaining the modified charges was not described, but with the modified charges, the dipole moment of *cis*-NMA′ is 5% larger than that of *trans*-NMA′, in agreement with ab initio results but contrary to the result from the OPLS charges.[39] The comparison of the relative solvation free energy between the OPLS (NMA) and the charge-modified (NMA′) models is summarized in the diagram (all values are in kilocalories per mole).



The MC simulation data of Jorgensen and Gao[39] and their uncertainties are given without parentheses. The results in parentheses are those from HNC, GF, and SA approximations arranged in the order (HNC, GF, SA^{HNC}, SA^{GF}). SA^{HNC} and SA^{GF} denote the results of using HNC and GF free energy functionals in eq 2.14 for the $\Delta\mu$ of free sites, respectively. The two NMA′ parameter sets are very similar to the OPLS set so that the effect on the absolute thermodynamics is small (see Table III). However, there are significant difference in the relative solvation thermodynamics. Although all values for the OPLS set are similar, only the GF result is close to the MC simulation value of 0.1 ± 0.3 kcal/mol for the primed set.[39] Combined with the ab initio gas-phase relative free energy of −2.5 kcal/mol in favor of *trans*-NMA′,[39] the GF approximation predicts a *total* relative free energy of −2.1 kcal/mol in favor of *trans*-NMA′. This is in excellent agreement with −2.1 kcal/mol at 35 °C[44] to −2.5 ± 0.4 kcal/mol at 60 °C[32] measured by NMR studies and the value of −2.4 ± 0.3 kcal/mol from the fitted MC simulation.[39] The *total* relative enthalpy of −1.2 kcal/mol in favor of *trans*-NMA′ predicted by the GF approximation is within the experimental uncertainty of −3.4 ± 2.5 kcal/mol.[32] Thus, for the modified model of NMA′, the calculated thermodynamics from the GF approximation are again better than that of the HNC approximation although the latter gives the same qualitative prediction that solvation favors *cis*-NMA′.

By contrast, the superposition approximation to the HNC and GF gave an unfavorable solvation free energy of 3.2 (in contrast to the HNC value of −1.1) and 2.5 (in contrast to the GF value of −0.4) kcal/mol, respectively, for *cis*-NMA′ relative to *trans*-NMA′ (see Table III). The failure of the SA to approximate HNC or GF in this case results from the assumption made in its formulation. A large part of the discrepancy comes from the contribution of 1,2 and 1,3 pairs that do not cancel each other when the conformational change is accompanied by a change in potential parameters; the 1,4 pairs of *trans*-NMA′ have a total charge of −0.03e that differs from the value of 0.02e for *cis*-NMA′. The inclusion of 1,2 and 1,3 pairs in eqs 2.12 and 2.14 leads to significantly better values of 0.8 and 0.1 kcal/mol as approximations to HNC and GF, respectively. Both are improved, but the quality of the SA approximation to HNC is not as good as when the contributions from 1,2 and 1,3 pairs cancel exactly, as in the case of NMA. The SA approximation result of 0.1 kcal/mol with the GF model is in good agreement with the more complete GF value of −0.4 kcal/mol and the value of 0.1 ± 0.3 kcal/mol from the MC simulation.

As already stated, the original formulation of the SA approximation[21,22] was not designed to include changes in 1,2 and 1,3 solvation. Such changes may be the result of the softening of some 1,2 and 1,3 degrees of freedom due to the solvation. In the special case where the change is due to the use of conformational dependent potential parameters, the method may still be useful when contributions from 1,2 and 1,3 pairs are properly accounted for.

In Figures 4b and 5b, the XRISM solute–solvent rdf for the carbonyl oxygen and the amide hydrogen of NMA′ are given. The larger dipole of *cis*-NMA′ leads to a higher hydrogen-bonding peak at the amide hydrogen than *trans*-NMA′ (see Figure 5b, upper panel). This is consistent with the more favorable solvation free energy and enthalpy for *cis*-NMA′ than *trans*-NMA′ (see Table III).

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4. Conclusions

An analysis has been made of the utility of integral equation theory for the study of the solvation thermodynamics of *N*-methylacetamide, a model of the peptide group in proteins. Conclusions are drawn from comparisons of two forms of the complete integral equation theory (HNC and GF) and a superposition approximation with experimental, molecular dynamics, and Monte Carlo simulation data.

The agreement in average solute–solvent (overall and group) interaction energy between the HNC/GF approximations and a molecular dynamics simulation of the same model is encouraging and provides a self-consistency test. The HNC approximation was found to be poor for the *absolute* solvation thermodynamic calculations of NMA when compared with experimental data; the values from the GF approximation were in good agreement with experiment. In light of the earlier success of the GF approximation for the aqueous solvation of nonpolar solutes, this suggests that the GF approximation is more promising overall for absolute solvation thermodynamics. The calculated relative solvation thermodynamics (cis vs trans conformers) were much less sensitive to the choice of HNC or GF free energy functionals. By analysis of the contributions to the relative solvation thermodynamics from various functional groups in NMA, it was found that correlations among groups (in particular, polar groups) can interfere with the solvation requirements of one another. As a result, the more exposed C=O and N—H in *cis*-NMA were found to have an unfavorable solvation free energy relative to that of *trans*-NMA. Such correlated interference can have important effects on protein solvation and stability. For the main chain and polar side chains, even if the solvent-accessible surface areas of the donor and acceptor groups increase or remain the same, intramolecular hydrogen-bonded conformation can be expected to be disfavored by correlation effects in aqueous solvation. The relation of these results to atomic solvation parameters[75,77] will be considered separately.[78]

The superposition approximation gives relative solvation results that are similar to the more rigorous HNC or GF approximations. Thus, the superposition approximation is likely to be useful due to its significant computational advantage over the HNC and GF integral equation theories. When the potential parameters depend on the cis and trans conformations, the cancellation of 1,2 and 1,3 contributions assumed in the superposition approximation does not occur. As expected, it fails to approximate the more rigorous integral equation theory for this case. Inclusion of the contributions from the 1,2 and 1,3 pairs in the superposition approximation improves the results. For many problems in biopolymer thermodynamics such cancellation is implicit in the choice of potential functions so that neglect of these contributions is expected to be unimportant.

The computational simplicity and the capacity of the superposition approximation to take account of pairwise correlations, and the capacity of the accessible surface area models to partly remedy the pairwise additivity assumption in the superposition approximation, make it of interest to develop a scheme that combines the two. A possible route is to scale the superposition approximation pairwise free energy by the calculated solvent-accessible surface area of the pair. This would remove the contributions of interior atoms to which the superposition approximation does not apply. It should also improve on the scheme of assigning the free energy of solvation on the basis of uncorrelated solvent-accessible surface area alone. Of particular interest may be its application to computing the entropy and other properties of peptides and denatured proteins, which cannot be studied in detail by full simulation methods at the present time. The solvent-modified potential of mean force so derived can also be combined with the empirical potential energy functions used in molecular mechanics programs to simulate complex biological macromolecules in water without the explicit presence of water molecules. Since the potential of mean force from the integral equation calculation includes only the static effect of the solvent, the dynamical solvent effects have to be included by introducing models of stochastic and dissipative forces. Such a simplified simulation approach is being compared to detailed simulations with explicit water molecules to assess its usefulness.[80]

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Intrinsic Barriers of Some Model S_N2 Reactions: Second-Order Møller–Plesset Perturbation Calculations

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Abstract: Ab initio calculations including electron correlation are used to determine the factors which govern the height of the intrinsic barriers of S_N2 reactions. It is shown that the reactions can be classified according to the hybridization of the leaving group and the electronic structure of the transition state. A sp-hybridized atom leads to a high intrinsic barrier. A large contribution of the $N:^- R^+ :X^-$ configuration to the transition state (in addition to its contribution to the reactant and product) lowers the intrinsic barrier. Within each group, the intrinsic barrier is related to the electronegativity of the leaving group. As the electronegativity of the leaving group increases, the intrinsic barrier decreases. Within each group there is a linear relationship between $\Delta E^{\ddagger}$ and ΔE°_c. Results are presented for $N^- + CH_3X \rightarrow CH_3N + X^-$, where X = H, CCH, *C*N, *N*C, PH_2, SH, Cl, NH_2, OH, OOH, and F for N = H; X = H, CCH, *C*N, *N*C, PH_2, SH, Cl, NH_2, OH, and F for N = F; and X = N = CCH, *C*N, *N*C, PH_2, SH, Cl, NH_2, OH, and OOH.

Introduction

The concept of an intrinsic barrier was introduced by Marcus[1] within the framework of a theory for electron-transfer reactions. He proposed an equation in which the free energy of activation ($\Delta G^{\ddagger}$) is related (eq 1) not only to the free energy of a reaction

$$\Delta G^{\ddagger} = \Delta G^{\ddagger}_0 + 0.5\Delta G^{\circ} + [(\Delta G^{\circ})^2/16\Delta G^{\ddagger}_0] \quad (1)$$

(ΔG°) but also to the intrinsic barrier ($\Delta G^{\ddagger}_0$). Marcus interpreted $\Delta G^{\ddagger}_0$ as the reorganization energy, i.e., the energy changes nec-

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