A Quantum Mechanical Investigation of the Conformational Energetics of the Alanine and Glycine Dipeptides in the Gas Phase and in Aqueous Solution

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Abstract: The low-energy conformers of alanine and glycine dipeptide have been modeled in the gas phase and in aqueous solution using *ab initio* methods. In the gas phase, seven low-energy minima have been located for the alanine dipeptide (AD), compared to six for the analogue (ADA), without terminal methyl groups. For the glycine dipeptide (GD), four minima are found, compared to two for the corresponding analogue (GDA). The effect of solvent has been included using both the self-consistent reaction field (SCRF) and polarized continuum (PCM) methods. Calculations of the solvated dipeptide were performed using both the gas-phase and the SCRF-optimized structures. For alanine dipeptide, solvation calculations performed with the free molecule-optimized structures using the PCM predicts the C5 conformation to be the most stable, which is not in agreement with the limited experimental data or with molecular dynamics simulations. For the SCRF model, using free molecule-optimized structures, the β_2 conformation is predicted to be the most stable with the C5 the next most stable. Optimization of the alanine dipeptide conformations within the SCRF model still predicts the β_2 conformation to be the most stable. However, the β conformation is only slightly higher in energy, while the α_R conformation is not a stationary point. Application of the PCM method to the SCRF-optimized structures reverses the conformational preference of β_2 and β. For glycine dipeptide, using free molecule-optimized structures, the PCM method predicts C5 to be the most stable conformation, while for the SCRF method the C5 and β_2 conformations are predicted to be the most stable. Optimization of the glycine conformations with the SCRF method results in only two conformations, the modified left- and right-handed α conformations which are equivalent in energy. A comparison of these results with those from explicit inclusion of solvent molecules is made.

Introduction

The modeling of the structural, dynamical, and equilibrium thermodynamic properties of proteins and nucleic acids is currently underpinned by the application of empirical potential functions to represent the inter- and intramolecular forces.[1] The commonly available and used molecular modeling programs AMBER,[2] GROMOS,[3] DISCOVER,[4] CHARMM,[5] and ECEPP[6] are all based upon the application of suitably parameterized empirical force fields to determine the energetics and geometries of molecules of biological interest. It is naturally the quality of these force fields and their parameters which ultimately determine the degree of confidence which may be placed on such simulations.

One favored method for the critical evaluation of such force fields has been their ability to reproduce the structures and energetics of a small group of molecules that may be regarded as models for larger peptides, for which there are comparable experimental or theoretical data. The peptides 1-(acetylamino)-*N*-methylethanamide (GD) and 1-(acetylamino)-*N*-methylpropanamide (AD) have been widely studied by both force field methods[1-6] and *ab initio* quantum mechanical[7-14] calculations, since they show conformational variations which are similar to proteins and thus they may be viewed as model dipeptides. Recently, there have been several high-level *ab initio* studies of AD by Head-Gordon et al.,[12] Bohm and Brode,[13] and Gould and Kollman[14] which have used good quality basis sets and have included the effect of electron correlation at the MP2 level.

The various structures are characterized by the Ramachandran angles (Φ, Ψ)[15] (Figure 1). The general conclusions of the free molecule calculations on model alanine dipeptide systems is that the internally hydrogen bonded conformation, the cyclic $C7_{eq}$, and the extended C5 structures are of lowest energy, corresponding to angles of (-86°, 79°) and (-157°, 160°) respectively.[14] Those structures analogous to α helical conformations (α_R, α_L) and to the β conformation were predicted to be of significantly higher energy. (A simplified "derivation diagram"[16] for the Ramachandran plot is reproduced in Figure 2 to allow a more convenient discussion of the structures to be described.)

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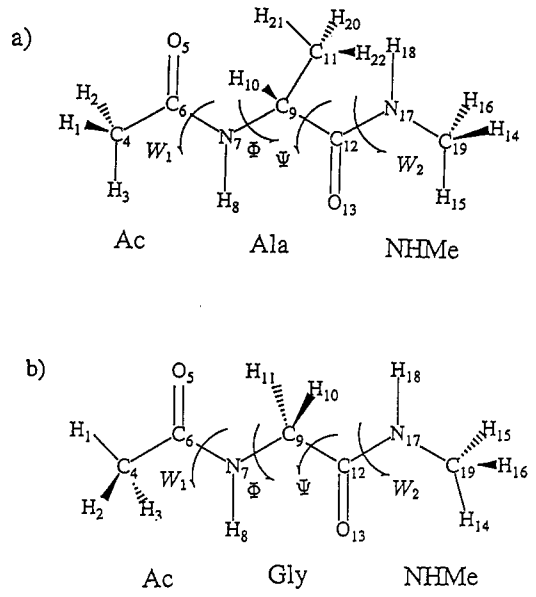

Figure 1. Structures of (a) alanine dipeptide and (b) glycine dipeptide with the angles Φ, Ψ, W_1, and W_2 indicated. The blocking group Ac, the alanine residue, Ala, and the C-terminal blocking group, NHMe, are indicated.

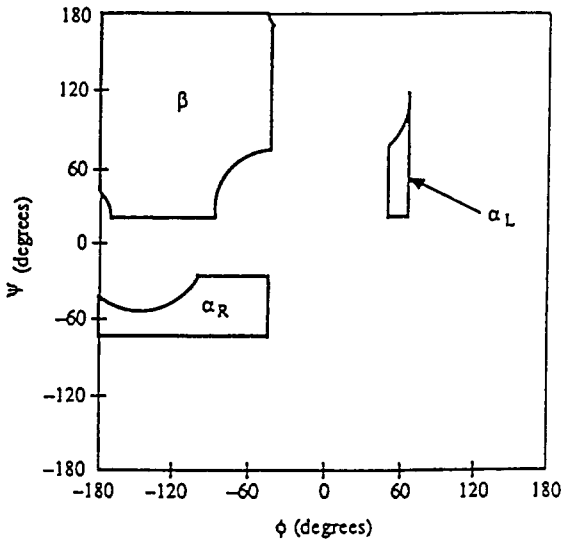

Figure 2. Simplified "derivation diagram" for the Ramachandran plot (after ref 16).

However, these high-level *ab initio* calculations are for the free molecule, while the experimental data which are available for AD is for the dipeptide in aqueous solution.[17] For most biological applications the effect of a polar solvent, such as water, is an essential problem in studies of the structural, thermodynamic, and dynamic properties of biopolymers.[18] There have been several studies of the thermodynamics of the conformational equilibria of alanine and glycine dipeptide in aqueous solution using classical computer simulations (Monte Carlo (MC) and molecular dynamics (MD)) and statistical mechanical integral equation theories.[19-25] Mezei et al.[20] used MC simulations to calculate the relative solvation thermodynamics of the $C7_{ax}$, α_R, and β ($\Phi \sim -80°$, $\Psi \sim 150°$) conformations of AD. The full Φ, Ψ free energy surface for AD has been predicted in water by Pettitt and Karplus[5b,22] using statistical mechanical integral equation theory, the extended RISM theory, and by Anderson and Hermans[23] who employed MD simulations with specialized sampling methods to construct the conformational probability distribution from which they derived the free energy surface.

In addition, Lau and Pettitt[24] have determined the intramolecular potential of mean force for GD in aqueous solution and have determined the free energy surface as a function of Φ and Ψ and have compared this with the vacuum surface. They also performed a parallel study on AD.

For AD, all three studies[20,22,23] agree qualitatively in that they all show that there is a marked solvent effect on the conformational equilibria. In general, it is observed that the aqueous solvent decreases the free energy difference between conformations that differ by large energies on the vacuum surface and lowers the barriers separating these conformations. Indeed, the results of Anderson and Hermans[23] for the AD Φ, Ψ probability distribution in water match the observed protein distribution quite well. In a recent paper, Tobias and Brooks[25] have reported molecular dynamics simulations with holonomic backbone dihedral angle constraints and thermodynamic perturbation theory to calculate the free energy profiles along paths connecting four important conformations of the dipeptide in the gas phase and in water. They predict that the extended β conformation is the most stable in the gas phase and in water, the $C7_{ax}$ conformation being 2.4 and 3.6 kcal/mol higher in energy in the gas phase and in water, respectively. The greatest effect of solvent was observed for the right- and left-handed α helical conformations, α_R and α_L, which are less stable than the β conformation by 9.1 and 11.6 kcal/mol, respectively, in the gas phase. However, in aqueous solution they are less stable than the β conformation by 0.2 and 4.1 kcal/mol, respectively.

Recently Shang and Head-Gordon[26] have reported molecular orbital calculations of the full conformational space of α-(formylamino)ethanamide (GDA) and (*S*)-α-(formylamino)propanamide (ADA) in the presence of a reaction field representation of water. They found secondary structures of right- and left-handed helices, in contrast to recent gas-phase results, indicating that the origin of helical stabilization in dipeptides is strictly due to environment. However, they have expressed concern over the limitations of the reaction field model they have used, multipole expansion limited to the dipole ($l = 1$) level and the use of a spherical cavity. This is most spectacularly illustrated by the stabilization afforded to the intramolecular hydrogen bonded conformers C5 and C7(s), which are not seen experimentally.[17]

In this paper, we study the structure and energetics of the low-energy conformers of alanine and glycine dipeptide for the free molecule and in water using *ab initio* methods. Our goals are first to characterize the low-energy conformations in the gas phase. Here we study the actual AD and GD structures, with the approximation of replacing terminal methyl groups with hydrogen atoms removed. We next investigate the value of continuum methods, implemented within an *ab initio* MO framework in predicting the structure and energetics of AD and GD in aqueous solution. We use implementations of the reaction field method which go beyond the dipole level and solute cavities which are based upon more realistic physical shapes. Here we compare our results both with experiment and with computer simulation (MC, MD) data. Such continuum calculations are generally not as computationally intensive as simulations studies, and they have the additional benefit of including solute polarization effects. The drawback of such methods may be that they do not consider solvent–solute interactions explicitly. Thus, subtle hydrogen-bonding effects between the solute and the solvent may not be considered properly.

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Theoretical Methods

All *ab initio* calculations were carried out using the Gaussian 90[27] and GAMESS[28,29] molecular orbital packages run on the Cray YMP/8I of the Rutherford Appleton Laboratory, the Cray YMP's of the Pittsburgh and San Diego Supercomputer Centres, and on Hewlett-Packard 700 series workstations.

Free Molecule Calculations. One of us has previously reported the structures and energetics of four of the low-energy conformers of AD[14] optimized at the HF/6-31G**[30] level. In this paper we have located a further three low-energy conformers of AD and a total of four low-energy conformers of GD at the same level of theory. All seven AD conformers and four GD conformers were characterized as minima by calculation of the analytical second derivatives. Single-point MP2 calculations were performed on the 6-31G** optimized structures, using Dunning's[31] triple-ζ plus polarization (TZVP) basis set. The exponents of the polarization functions for this TZVP basis set were 0.72 (d on C), 1.0 (p on H), 0.98 (d on N), and 1.28 (d on O). The zero-point, thermal, and entropic contributions to the free energy were calculated using the rigid-rotor/harmonic-oscillator approximation[32] at the HF/6-31G**//HF/6-31G** level. Optimizations were considered converged when the largest force was less than 0.000 45 hartree/bohr and the rms of the forces was less than 0.0003 hartree/bohr.

Calculation of Solvation Energies. Solvation effects may be estimated either by simulation studies (MC or MD) in which the solvent molecules are explicitly considered or alternatively by models which consider the solvent as a dielectric continuum, following the Onsager reaction field approach as developed by Kirkwood.[33] In this latter model the resulting solvent–solute electrostatic interactions may be readily incorporated into self-consistent field molecular orbital (SCF-MO) methods and allows solute properties, such as structures and energetics, to be predicted. This self-consistent reaction field (SCRF) approach has been shown to yield quantitative predictions of the effect of solvent on a range of properties.[34]

We have employed two continuum models in which the solute is modeled in a cavity surrounded by solvent characterized by a relative permitivity (ϵ). The first is the SCRF model developed by Tapia and Goscinski[35] and by Rivail and co-workers.[36] Here the solute occupies an ellipsoidal cavity whose dimensions are determined by the solute van der Waals surface. The charge distribution of the solute is described by a single-center multipole expansion, up to $l = 7$. The solvent, water, is considered to be a uniform dielectric, with dielectric constant, $\epsilon = 78.0$. The calculation of solvation energies used the 6-31G** basis set and was carried out using the SCRF code of Rivail implemented in Gaussian 90. Initially the free molecule-optimized structures of GD and AD obtained at the HF/6-31G** level were used. Further calculations were carried out in which the GD and AD conformers were optimized within the SCRF framework also at the HF/6-31G** level. Although these structures were identified as stationary points from calculation of the energy gradients, we have not evaluated second derivatives of the energy, so that we cannot unequivocally characterize the structures as energy minima.

An alternative approach of improving upon the widely used dipole approximation for the solute charge distribution and upon the use of a spherical cavity is the polarizable continuum model (PCM) of Tomasi and co-workers.[37] This method involves the generation of a solvent cavity from spheres centered at each atom in the molecule and the calculation of virtual point charges on the cavity surface representing the polarization of the solvent. The magnitude of these charges is proportional to the derivative of the solute electrostatic potential at each point calculated from the molecular wave function. The point charges may then be included in the one-electron Hamiltonian, thus inducing polarization of the solute. An iterative calculation is carried out until the wave function and the surface charges are self-consistent. This method has been implemented in the program GAMESS.[29]

The degree of solvation predicted by both the SCRF and the PCM models is critically dependent upon cavity size. In the SCRF method the cavity is defined by an ellipsoidal cavity whose dimensions are determined by the solute van der Waals surface. For the PCM model, the individual sphere radii naturally depend upon atom type, but should also vary with formal atomic charge, and are expected to be basis set dependent. Appropriate parameters have been developed by Aguilar and del Valle[38] to allow the atomic radii to be calculated in terms of Mulliken charge and basis set.

We have estimated the electrostatic contribution to the solvation free energy of the GD and AD conformers using the PCM model and a 6-31G** basis. Initially, the gas-phase-optimized geometries, obtained at HF/6-31G** level, were used. We have also calculated the solvation free energy using the SCRF-optimized structures of the GD and AD conformers, employing atomic radii obtained from free molecule calculations of these structures. In the case of the PCM calculations, we have estimated the dispersion contributions to the solvation energy within the philosophy of the model as formulated by Floris and Tomasi[39] and evaluated the cavitation energy following the procedure of Huron and Claverie.[40] We have not calculated the vibrational frequencies of the solvent-optimized structures. Thus, free energies were calculated using the zero-point, thermal, and entropic corrections calculated for the corresponding free molecule structure.

Table 1. Calculated Relative Energies of Conformers of Free Molecules of α-(Formylamino)propanamide and 1-(Acetylamino)-*N*-methylpropanamide

theory	$C7_{eq}$	$C7_{ax}$	C5	α_R	α_L	β	β_2
α-(Formylamino)propanamide[12]							
HF/6-31+G*[a]	0.00[b]	2.56	0.19	–	4.73	–	2.24
HF/6-31+G**[c]	0.00[d]	2.53	0.14	–	4.82	–	2.29
MP2/6-31+G**[e]	0.00[f]	2.19	1.13	–	4.46	–	2.67
1-(Acetylamino)-*N*-methylpropanamide							
HF/6-31G**[g]	0.00[h]	2.82	0.40	4.35	4.76	4.90	2.58
HF/TZVP[i]	0.00[j]	2.93	0.19	4.19	5.03	4.75	2.61
MP2/TZVP[k]	0.00[l]	2.05	1.47	3.91	4.42	4.08	3.25

All values in kcal/mol. [a,c,e] HF/6-31+G* optimized geometries. [g,i,k] HF/6-31G** optimized geometries. [b] Zero of energy –414.799 097 3. [d] Zero of energy –414.818 800 4. [f] Zero of energy –416.067 459 5. [h] Zero of energy –492.885 304 8. [j] Zero of energy –493.026 287 1. [l] Zero of energy –494.637 381 5 au.

Free-Molecule Results

In Table 1 we compare the relative free-molecule energies of the conformers of AD from this work with those of Head-Gordon et al.[12] for the model alanine dipeptide analogue (ADA), where it is seen that the ordering of the conformers is the same. This is maintained through HF/TZVP//HF/6-31G** and MP2/TZVP//HF/6-31G** with respect to the HF/6-31+G**//HF/6-31+G*, and MP2/6-31+G**//HF/6-31+G* values. We report in Table 2 the values of the optimized free molecule angles Φ and Ψ at the HF/6-31G** level. A comparison with those of Head-Gordon et al.[12] reveals an interesting difference in the values for the β_2 conformation. We obtain $\Phi = -130.9°$ and $\Psi = 22.3°$ while Head-Gordon et al.[12] obtain $\Phi = -110.4°$ and $\Psi = 12.0°$. For the other conformations, the largest difference in the Φ and Ψ angles is less than 5°. A further difference is the number of minima predicted for ADA[12] and AD. We find minima corresponding to α_R and β conformations which are not reported by Head-Gordon et al.[12] We have not searched for the high-energy conformation, α, reported by these workers. These differences may be attributed to the basis set used in our

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Table 2. Conformations and Relative Energies of Free Molecules of 1-(Acetylamino)-*N*-methylpropanamide

conformation	Φ	Ψ	E (HF/6-31G**)	E (MP2/TZP)	G (HF/6-31G**)[a]	G (MP2/TZVP)[a]	μ (D)
$C7_{eq}$	−85.8	79.0	0.00	0.00	0.00	0.00	2.87
$C7_{ax}$	76.0	−55.4	2.82	2.05	3.02	2.25	3.91
C5	−157.2	159.8	0.40	1.47	−0.35	0.71	2.56
α_R	−60.7	−40.7	4.35	3.91	4.50	4.06	6.59
α_L	67.0	30.2	4.76	4.42	5.15	4.81	6.26
β	−57.6	134.4	4.90	4.08	5.36	4.54	2.36
β_2	−130.9	22.3	2.58	3.25	1.88	2.55	4.94

All values in kcal/mol. [a] Zero point, thermal, and entropic corrections calculated at HF/6-31G**//HF/6-31G**. G (MP2/TZVP) obtained at HF/6-31G** optimized geometry. μ is the dipole moment in Debyes calculated at HF/6-31G**//HF/6-31G**.

Table 3. *Ab Initio* Structural Parameters (HF/6-31G**//HF/6-31G**) of Free Molecules of 1-(Acetylamino)-*N*-methylpropanamide

parameter[a]	$C7_{eq}$	$C7_{ax}$	C5	α_R	α_L	β	β_2
Φ	−85.8	76.0	−157.2	−60.7	67.0	−57.6	−130.9
Ψ	79.0	−55.4	159.8	−40.7	30.2	134.4	22.3
W_1	180.0	174.0	179.9	−169.2	165.7	173.2	−167.5
W_2	−174.4	−177.8	179.5	175.4	−176.5	−176.0	172.4
R_{C4-C6}	1.511	1.513	1.512	1.513	1.513	1.510	1.513
R_{C6-N7}	1.349	1.348	1.348	1.361	1.364	1.361	1.365
R_{C6-O5}	1.207	1.207	1.204	1.198	1.198	1.201	1.198
R_{N7-C9}	1.457	1.463	1.442	1.454	1.460	1.453	1.453
R_{C9-C11}	1.521	1.531	1.535	1.528	1.527	1.528	1.527
R_{C9-C12}	1.535	1.535	1.526	1.530	1.534	1.539	1.532
$R_{C12-O13}$	1.203	1.204	1.204	1.200	1.200	1.202	1.202
$R_{C12-N17}$	1.345	1.340	1.345	1.352	1.348	1.348	1.346
$R_{N17-C19}$	1.446	1.446	1.448	1.448	1.447	1.449	1.447
R_{N7-H8}	0.993	0.992	0.994	0.994	0.994	0.994	0.995
$R_{N17-H18}$	0.996	0.996	0.992	0.993	0.991	0.992	0.992
Θ_{C4C6N7}	116.3	115.7	115.9	115.5	115.3	115.4	115.0
Θ_{C6N7C9}	122.9	127.1	122.0	121.8	122.5	120.4	122.3
$\Theta_{N7C9C12}$	109.8	114.3	107.4	113.8	113.4	109.3	112.6
$\Theta_{C9C12N17}$	114.6	117.4	115.6	116.5	116.4	118.0	116.7
$\Theta_{C12N17C19}$	121.2	120.9	121.7	120.4	120.5	120.0	121.1
R_{H18-O5}	2.23	2.04					
$\Theta_{N17H18O5}$	139.3	146.2	93.5	92.1	97.5	89.9	119.8

[a] See Figure 1 for atom labeling. Φ, Ψ, W, Θ are in degrees, R values are in angstroms.

calculations, 6-31G** as opposed to 6-31+G*, or they may be due to the difference between AD and ADA, the terminal methyl groups being absent in the latter. We note that, as pointed out by one of the referees, the number of minima in compounds of this nature may vary with the basis set used. The magnitude of the residual forces could be improved upon by tightening the convergence criteria to say <0.0001 hartree/bohr as the potential energy surface is quite flat, and therefore the angles quoted in the tables are only semiquantitative. However, we would like to reiterate that all minima reported here have been characterized as stationary points on the potential energy surface by calculation of the analytical second derivatives, no imaginary frequencies being found.

As far as the effects of electron correlation are concerned, we have not performed geometry optimization at the MP2 level, since for GD and AD the number of basis functions at 6-31G**, 185 and 210, respectively, renders such calculations extremely computationally expensive. We note that, while Frey et al.[41] have performed SCF and MP2 optimizations on three conformers of glycine and two of ADA, they found that although optimization at MP2 changed the magnitude of the separation between the conformers it did not change the ordering. While the conclusions might change with MP2 optimization and larger basis sets, it would not be possible to evaluate whether the structures obtained were true minima by calculation of the analytical second derivatives at the MP2 level, for AD at 6-31G** the frequency calculation would require a minimum of 7 Gb of disk using the "STINGY" or "VERYSTINGY" options in Gaussian 92 and multiple transformations of the atomic integrals.

In Table 2 we have reported the relative free energies of the AD conformers calculated at the HF/6-31G** and MP2/TZVP levels of theory, and in Table 3, the corresponding structural parameters. We use the term gas phase to refer to free-molecule calculations which have been corrected to 298 K by addition of zero point, thermal, and entropic corrections calculated at the optimized geometry.[32] Comparison of these results with those of Tobias and Brooks[25] reveals differences in the ordering and in the magnitude of the separation between the conformers, as summarized in Table 4. The *ab initio* results predict the $C7_{ax}$ structure to be significantly lower in energy than the β conformer, while Tobias and Brooks,[25] using a CHARMM force field, predict the β conformer to be more stable. The molecular mechanics results similarly seriously overestimate the stability of the β conformer compared to the α_R and α_L structures when compared to our *ab initio* results. In this comparison we note that the molecular dynamics calculations refer to energy differences between structures with standard (Φ, Ψ) angles, while our results refer to minimum-energy structures.

Table 4. Relative Free Energies of Conformations of 1-(Acetylamino)-*N*-methylpropanamide in the Gas Phase[a]

conformation	Tobias and Brooks[25]	MP2/TZVP (this work)
β	0.0	0.0
α_R	9.1	−0.5
α_L	11.6	0.3
$C7_{ax}$	2.4	−2.3

[a] All values in kcal/mol.

In Table 5 we report the relative energies of the optimized free molecule structures of the GD conformers from this work and compare them with those of Head-Gordon et al.[12] for the glycine dipeptide analogue (GDA). We identify four minima at the HF/6-31G**//HF/6-31G** level, whereas Head-Gordon et al.[12] identify two for GDA using a similar basis (HF/6-31+G*). As for AD this difference may be due to the fact that Head-Gordon

(41) Frey, R. F.; Coffin, J.; Newton, S. Q.; Ramek, M.; Cheng, V. K. W.; Momany, F. A.; Schafer, L. *J. Am. Chem. Soc.* **1992**, *114*, 5369.

Table 5. Calculated Relative Energies of Conformers of Free Molecules of α-(Formylamino)ethanamide and 1-(Acetylamino)-*N*-methylethanamide

theory	C7	C5	α_R	β_2, α_L
α-(Formylamino)ethanamide[12]				
HF/6-31+G*[a]	0.58	0.00[b]	–	–
HF/6-31+G**[c]	0.60	0.00[d]	–	–
MP2/6-31+G**[e]	0.00[f]	1.11	–	–
1-(Acetylamino)-*N*-methylethanamide				
HF/6-31G**[g]	0.27	0.00[h]	4.30	2.17
HF/TZVP[i]	0.49	0.00[j]	4.60	4.75
MP2/TZVP[k]	0.00[l]	1.99	3.95	4.08

All values in kcal/mol. [a,c,e] HF/6-31+G* optimized geometries. [g,i,k] HF/6-31G** optimized geometries. [b] Zero of energy −375.762 297 2. [d] Zero of energy −375.779 057 6. [f] Zero of energy −376.878 277 7. [h] Zero of energy −453.844 334 1. [j] Zero of energy −453.978 031 3. [l] Zero of energy −455.434 724 7 au.

et al.[12] report results for α-(formylamino)ethanamide (GDA), rather than be attributed to the somewhat different basis sets employed. (For GD, with a chiral α-carbon, the α_L and β_2 structures are equivalent.)

Comparison of the HF/6-31G**//HF/6-31G** and HF/6-31+G*//HF/6-31+G* results for the C7 and C5 conformations reveals the same ordering. Inclusion of correlation (MP2) and the use of a TZVP basis inverts the order, with C7 now the lowest energy structure of GD. A similar effect is seen for GDA, but the energy difference is somewhat smaller. We report the free molecule optimized Φ and Ψ values for the GD conformers in Table 6 along with the relative free energies calculated at the HF/6-31G** and MP2/TZVP levels of theory and in Table 7 show the corresponding structural parameters.

Aqueous Solution Results

In addition to comparing the two approaches to the calculation of the electrostatic contribution ΔG_{el} to the solvation free energy, namely the SCRF and PCM, we shall consider the effect of using either free molecule optimized geometries or those optimized including the reaction field, as well as the contribution of dispersion and cavitation energies $\Delta G_{cav+disp}$ to the total free energy of solvation. All solvation calculations are carried out at the HF/6-31G** level, and we have used zero-point, thermal, and entropic corrections evaluated at free-molecule geometries and calculated at this level to evaluate total relative free energies ΔG_{rel} in aqueous solution.

We begin by describing the results of the PCM and SCRF methods as applied to the free-molecule optimized conformers of AD. In Table 8, we present the PCM results for the electrostatic ΔG_{el} and cavitation and dispersion contributions $\Delta G_{cav+disp}$ to the solvation free energies and the total relative free energies. It can be seen that the dominant contribution to the relative solvation energies is the electrostatic term. We find that the magnitude of the calculated electrostatic contribution to the solvation energy is generally in line with the calculated dipole moments (Table 2), with the α_R and α_L structures having the largest values. In contrast to the free-molecule situation (Table 2), we find that the conformer, C5, is the most stable in aqueous solution followed by $C7_{eq} < \beta_2 < \alpha_R < \alpha_L < C7_{ax} < \beta$. This contrasts with the experimental findings[17] which suggests that in aqueous solution AD adopts the α_R and β conformations. However, Richardson[42] has shown that a plot of the main chain dihedral angles, Φ and Ψ, experimentally determined for approximately 1000 non-glycine residues in eight proteins whose structures have been refined at high resolution, includes heavy clusters in the regions Φ, −60 → −180° and Ψ, 90 → 180° corresponding to the β and C5 region and in the region Φ, −60 → −80° and Ψ, −40 → −60° corresponding to the α_R region. It is also noteworthy that there are rather frequent occurrences of residues between the α_R and β regions.

(42) Richardson, J. S. *Adv. Protein Chem.* **1981**, *34*, 167.

Therefore, while our findings are not totally consistent with experiment,[17] they do appear to identify conformations of AD which would be accessible to proteins, in particular, identification of the β_2 conformer as being of importance in the aqueous phase.

In Table 9, we present the SCRF results for the electrostatic contribution to the solvation free energies for the free molecule-optimized AD conformers and the total relative free energies. The results are in line with the PCM results with the electrostatic contribution to the solvation energies generally following the calculated dipole moments. However, this correlation is not strictly adhered to; for example, the solvation energies of β_2 and α_L do not follow the calculated dipole moments. Inspection of the contributions from individual l values clearly shows the importance of terms beyond $l = 1$. This shows the inadequacy of more simple treatments in which a spherical solvent cavity and the dipole approximation for the solute charge distribution are used. Again, the resultant order, $\beta_2 < C5 < C7_{eq} < \alpha_R < C7_{ax} < \alpha_L < \beta$, differs from that found in the free molecule. These results are, however, for the free molecule-optimized structures.

We now investigate the effect of geometry optimization within the SCRF formalism. In Table 10, we present the SCRF optimized values of the angles Φ and Ψ for AD along with the free molecule-optimized values. It is noteworthy that C5 and α_R conformations could not be located in aqueous solution. It can be seen that for the $C7_{eq}$, $C7_{ax}$, α_L, and β_2 conformations Φ and Ψ do not change appreciably, the maximum deviation being ~20°, while for the β conformation Φ changes by ~60°. The α_R conformation collapses to the β_2 conformation while the C5 conformation optimizes to the β conformation. It can be seen in Table 11, which reports the structural parameters for the solvent optimized conformations of AD, that in comparison with the free molecule optimized structures, Table 3, the C=O bond lengths are lengthened quite significantly due to solvent polarization. In general the other bond lengths of the conformers do not change as markedly.

The SCRF results for the electrostatic contribution to the solvation free energies for the solvent optimized AD conformers and the total relative free energies are given in Table 12. When compared with the prediction using the free molecule-optimized structures, the major difference is the increased solvation energy of all the structures relative to $C7_{eq}$. The predicted ordering of the conformers, $\beta_2 < \beta < C_{7eq} < C_{7ax} < \alpha_L$, now compares quite favorably with the findings of Tobias and Brooks[25] with the exception that the order of the β and β_2 (α_R) conformations is reversed. Comparison with the experimental results[17] is favorable as in aqueous solution it is thought that AD adopts either the β or α_R conformation. We view our β_2 conformation as a modified form of the α_R conformation.

We have used the PCM to predict the electrostatic contribution to the solvation free energies for the SCRF-optimized AD conformers along with the total free energies (Table 13). The changes found when using the solvent-determined structures are similar to those arising from the use of the SCRF model. In particular the solvation energy of the β conformation is significantly increased leading to the order $\beta < \beta_2 < C7_{ax} < C7_{eq} < \alpha_L$. This order is the same ordering as found by Tobias and Brooks[25] using MD simulations.

In view of the similarity in the PCM and SCRF predictions we compare our results with those derived from MD and MC simulations using our SCRF-optimized calculations to calculate the solvation free energies and the relative free energies of the various AD conformations in water (Table 14). It can be seen that the SCRF results for the relative free energies agree very well with the MD results of Tobias and Brooks[25] considering the small β, β_2 energy separation predicted by both models. However, our results deviate somewhat more from the integral equation results of Pettitt and Karplus,[5b,22] which may arise from inaccuracies in their gas-phase energy surface. Comparison of

Table 6. Conformations and Relative Energies of Free Molecules of 1-(Acetylamino)-*N*-methylethanamide

conformation	Φ	Ψ	*E* (HF/6-31G**)	*E* (MP2/TZP)	*G* (HF/6-31G**)[a]	*G* (MP2/TZVP)[a]	μ (D)
C7	−85.5	72.0	0.00[b]	0.00[c]	0.00[d]	0.00[e]	3.91
C5	180.9	180.5	−0.27	1.99	−1.60	0.66	2.56
α_R	−60.7	−40.7	4.03	3.95	4.76	4.68	6.59
β_2	−116.2	19.9	1.90	3.25	1.63	2.98	4.94

All values in kcal/mol. [a] Zero point, thermal, and entropic corrections calculated at HF/6-31G**//HF/6-31G**. [b] Zero of energy −453.844 334 1. [c] Zero of energy −455.434 724 7. [d] Zero of energy −453.713 820 9. [e] Zero of energy −455.304 211 5 au. *G* (MP2/TZVP) obtained at HF/6-31G** optimized geometry. μ is the dipole moment in Debyes calculated at HF/6-31G**//HF/6-31G**.

Table 7. *Ab Initio* Structural Parameters (HF/6-31G**//HF/6-31G**) of Free Molecules of 1-(Acetylamino)-*N*-methylethanamide[a]

parameter	C7	C5	α_R	β_2, α_L	β_2 (sol)
Φ	−85.5	−179.1	−60.7	116.2	−119.0
Ψ	72.0	−179.5	−40.7	−19.9	19.6
W_1	−179.4	178.9	−169.6	169.7	−169.2
W_2	−177.0	−177.9	175.4	−173.1	177.0
R_{C4-C6}	1.511	1.512	1.512	1.513	1.511
R_{C6-N7}	1.348	1.347	1.362	1.363	1.346
R_{C6-O5}	1.206	1.203	1.197	1.198	1.221
R_{N7-C9}	1.450	1.434	1.449	1.445	1.446
R_{C9-C12}	1.528	1.520	1.525	1.523	1.527
$R_{C12-O13}$	1.203	1.203	1.198	1.202	1.214
$R_{C12-N17}$	1.343	1.345	1.352	1.345	1.333
$R_{N17-C19}$	1.446	1.448	1.448	1.447	1.456
R_{N7-H8}	0.992	0.994	0.993	0.994	0.996
$R_{N17-H18}$	0.996	0.993	0.993	0.992	0.992
Θ_{C4C6N7}	116.5	116.1	115.5	115.0	114.8
Θ_{C6N7C9}	122.5	121.2	121.4	122.6	125.5
$\Theta_{N7C9C12}$	112.9	109.2	115.4	116.0	117.3
$\Theta_{C9C12N17}$	115.2	115.0	116.1	117.0	117.6
$\Theta_{C12N17C19}$	121.3	121.8	120.5	121.3	124.8
R_{H18-O5}	2.20				
$\Theta_{N17H18O5}$	140.9	91.9	91.8	120.7	115.7

[a] See Figure 1 for numbering. Φ, Ψ, *W*, Θ are in degrees. *R* values are in anstroms.

Table 8. Electrostatic Contribution ΔG_{el} to Solvation Free Energies at HF/6-31G** Level of 1-(Acetylamino)-*N*-methylpropanamide at Free Molecule-Optimized Geometries, Calculated by the PCM Model, and Total Relative Free Energies[a]

conformation	ΔG_{el}	ΔG_{el}(rel)	ΔG(gas phase)	ΔG(cav+disp)	ΔG(rel)
$C7_{eq}$	−17.85	0.00	0.00	0.00	0.00
$C7_{ax}$	−17.84	0.01	3.02	−0.06	2.97
C5	−19.03	−1.18	−0.35	0.80	−0.73
α_R	−20.96	−3.11	4.50	0.20	1.59
α_L	−20.24	−2.39	5.15	−0.21	2.55
β	−18.54	−0.69	5.36	0.15	4.82
β_2	−19.53	−1.68	1.88	0.45	0.65

[a] All values in kcal/mol.

Table 9. Electrostatic Contribution ΔG_{el} to Solvation Free Energies at HF/6-31G** Level of 1-(Acetylamino)-*N*-methylpropanamide at Free Molecule-Optimized Geometries, Calculated by the SCRF Model, and Total Relative Free Energies[a]

conformation	ΔG_{el}	ΔG_{el}(rel)	ΔG(gas phase)	ΔG(cav+disp)	ΔG(rel)
$C7_{eq}$	−11.14	0.00	0.00	0.00	0.00
$C7_{ax}$	−12.41	−1.27	3.02	−0.06	1.69
C5	−11.70	−0.56	−0.35	0.80	−0.11
α_R	−15.74	−4.60	4.50	0.20	0.10
α_L	−12.56	−1.42	5.15	−0.21	3.52
β	−10.97	0.17	5.36	0.15	5.68
β_2	−16.45	−5.31	1.88	0.45	−2.98

[a] All values in kcal/mol.

our calculated relative solvation free energies with those of Tobias and Brooks[25] shows that the ordering is slightly different and the separations are somewhat smaller. With respect to the results of Pettitt and Karplus[5b,22] we also find that our results deviate somewhat in the ordering of the conformers.

Having described the results of our solvation calculations on AD, we now turn our attention to the conformers of GD. In Table 15 we present the PCM results for the free-molecule

Table 10. Conformations of 1-(Acetylamino)-*N*-methylpropanamide Optimized for Free Molecule and in Solution, Using the SCRF Model[a]

conformation	Φ	Ψ	Φ(sol)	Ψ(sol)
$C7_{eq}$	−85.8	79.0	−73.4	75.1
$C7_{ax}$	76.0	−55.4	74.9	−73.4
C5	−157.2	159.8	–	–
α_R	−60.7	−40.7	–	–
α_L	67.0	30.2	68.4	39.3
β	−57.6	134.4	−118.2	133.1
β_2	−130.9	22.3	−112.1	22.5

[a] All values of Φ and Ψ are in degrees. Φ and Ψ refer to the HF/6-31G** free molecule-optimized conformers. Φ(sol) and Ψ(sol) refer to the HF/6-31G** solvent-optimized geometries.

Table 11. *Ab Initio* Structural Parameters (HF/6-31G**//HF/6-31G**) of 1-(Acetylamino)-*N*-methylpropanamide (SCRF, l = 7, ϵ = 79.0)[a]

parameter	$C7_{eq}$	$C7_{ax}$	α_L	β	β_2
Φ	−73.4	74.9	68.5	−118.2	−112.1
Ψ	75.1	−73.4	39.3	133.1	22.5
W_1	177.9	177.9	172.2	173.2	−170.8
W_2	−179.5	178.7	172.8	−178.7	175.4
R_{C4-C6}	1.513	1.513	1.511	1.512	1.511
R_{C6-N7}	1.346	1.346	1.350	1.339	1.343
R_{C6-O5}	1.213	1.213	1.213	1.222	1.226
R_{N7-C9}	1.462	1.462	1.458	1.452	1.456
R_{C9-C11}	1.532	1.533	1.525	1.536	1.534
R_{C9-C12}	1.540	1.540	1.537	1.534	1.539
$R_{C12-O13}$	1.221	1.220	1.208	1.214	1.211
$R_{C12-N17}$	1.330	1.330	1.341	1.333	1.336
$R_{N17-C19}$	1.452	1.452	1.450	1.455	1.456
R_{N7-H8}	0.993	0.993	0.996	0.994	0.997
$R_{N17-H18}$	0.996	0.996	0.992	0.992	0.991
Θ_{C4C6N7}	115.4	115.6	114.6	114.6	114.1
Θ_{C6N7C9}	127.4	127.5	125.9	127.2	127.6
$\Theta_{N7C9C12}$	111.7	111.5	113.2	111.7	114.8
$\Theta_{C9C12N17}$	116.3	116.3	115.3	116.6	118.2
$\Theta_{C12N17C19}$	124.5	124.4	123.7	123.5	123.9
R_{H18-O5}	2.12	2.11			
$\Theta_{N17H18O5}$	140.6	141.9	87.2	97.3	111.5

[a] Φ, Ψ, *W*, and Θ are in degrees. *R* values are in angstroms.

Table 12. Electrostatic Contribution ΔG_{el} to Solvation Free Energies at HF/6-31G** Level of 1-(Acetylamino)-*N*-methylpropanamide Solvent-Optimized Geometries, Calculated by the SCRF Model, and Total Relative Free Energies

conformation	ΔG_{el}	ΔG_{el}-(rel)	ΔG-(free molecule)[a]	ΔG-(cav+disp)	ΔG-(rel)
$C7_{eq}$	−15.35	0.00	0.00	0.00	0.00
$C7_{ax}$	−14.97	0.38	0.00	−0.31	0.07
α_L	−16.69	−1.34	3.06	0.17	1.89
β	−19.53	−4.18	−0.60	0.69	−4.27
β_2	−22.08	−6.73	0.35	0.94	−5.44

All values in kcal/mol. [a] Computed as the energy difference between the solvent-optimized structures, with zero point and statistical corrections for the corresponding free molecule-optimized structure.

optimized structures. We find that the ordering of the conformers is C5 < C7 < β_2 (= α_L) < α_R. This ordering is somewhat surprising when compared to the findings of Lau and Pettitt[24] who found the order to be P_{II} < C_5 ~ C7 < α_R ~ α_L, where P_{II} is described by Φ and Ψ angles of −57 and −168°, respectively.

Table 13. Electrostatic Contribution ΔG_{el} to Solvation Free Energies at HF/6-31G** Level of 1-(Acetylamino)-*N*-methylpropanamide Solvent-Optimized Geometries, Calculated by the PCM Model, and Total Relative Free Energies

conformation	ΔG_{el}	ΔG-(rel)	ΔG-(free molecule)[a]	ΔG-(cav+disp)	ΔG-(rel)
$C7_{eq}$	−18.91	0.00	0.00	0.00	0.00
$C7_{ax}$	−19.26	−0.35	0.00	−0.31	−0.66
α_L	−21.45	−2.54	3.06	0.17	0.69
β	−22.59	−3.68	−0.60	0.69	−3.59
β_2	−21.67	−2.76	0.35	0.94	−1.47

All values in kcal/mol. [a] Computed as the energy difference between the solvent-optimized structures, with zero point and statistical corrections for the corresponding free molecule-optimized structure.

Table 14. Comparison of Theoretical Results for the Relative Solvation Free Energies and Relative Free Energies of Various 1-(Acetylamino)-*N*-methylpropanamide Conformations in Water

	Pettitt and Karplus		Tobias and Brooks		this work	
conformation[a]	ΔG(sol)	ΔG(rel)	ΔG(sol)	ΔG(rel)	ΔG_{el}	ΔG(rel)
$\beta(P_{II})$	0.0	0.0	0.0	0.0	0.0	0.0
$\beta_2(\alpha_R)$	1.2	1.6	8.8	0.2	−2.6	−1.2
α_L	0.0	0.9	10.1	4.0	2.8	6.2
$C7_{ax}$	8.9	0.7	18.8	3.5	4.6	4.3

[a] We compare our β conformation with the P_{II} of Pettit and Karplus[5b,22] and our β_2 conformation with the α_R of Tobias and Brooks[25] and Pettit and Karplus.[5b,22] All values are in kcal/mol.

Table 15. Electrostatic Contribution ΔG_{el} to Solvation Free Energies at HF/6-31G** Level of 1-(Acetylamino)-*N*-methylethanamide Free Molecule-Optimized Geometries, Calculated by the PCM Model, and Total Relative Free Energies

conformation	ΔG_{el}	ΔG_{el}-(rel)	ΔG-(free molecule)[a]	ΔG-(cav+disp)	ΔG-(rel)
C7	−17.94	0.00	0.00	0.00	0.00
C5	−19.45	−1.51	−1.60	0.54	−2.57
α_R	−20.79	−2.85	4.76	0.28	2.19
β_2	−19.98	−2.04	1.63	0.52	0.11

All values in kcal/mol. [a] Computed as the energy difference between the free molecule-optimized structures, with zero point and statistical corrections.

In Table 16, we present the SCRF results for the electrostatic contribution ΔG_{el} to the solvation free energies for the free molecule-optimized GD conformers and the total relative free energies. The ordering of the conformers, $\beta_2 = \alpha_L < C5 < C7 < \alpha_R$, is somewhat different to that found with the PCM method. Upon optimization of the free molecule conformers within the SCRF method we obtained only two structures, modified β_2 and α_L conformers, which were equal in energy. These conformers are in the heavily populated region of the Ramachandran plot of Richardson,[42] suggesting that the SCRF method is capable of identifying important conformers of GD. We have reported the structural parameters of the solvent optimized β_2 conformation in Table 7.

We finally address the question of convergence of the multipolar expansion used in the SCRF method. Examination of the contributions of the multipole terms to the polarization energy

Table 16. Electrostatic Contribution ΔG_{el} to Solvation Free Energies at HF/6-31G** Level of 1-(Acetylamino)-*N*-methylethanamide Free Molecule-Optimized Geometries, Calculated by the SCRF Model, and Total Relative Free Energies

conformation	ΔG_{el}	ΔG_{el}-(rel)	ΔG-(free molecule)[a]	ΔG-(cav+disp)	ΔG-(rel)
C7	−12.64	0.00	0.00	0.00	0.00
C5	−10.31	2.33	−1.60	0.54	−0.73
α_R	−16.63	−3.99	4.76	0.28	1.05
β_2	−17.79	−5.15	1.63	0.52	−3.00

All values in kcal/mol. [a] Computed as the energy difference between the free molecule-optimized structures, with zero point and statistical corrections.

for the SCRF optimized conformers of AD and GD shows that truncation at $l = 1$ is inadequate and that $l = 7$ is the smallest term, being less than 1 kcal mol^{-1} except for the β_2 structure of AD.

Conclusions

Our investigation of the conformational preference for models of the alanine and glycine dipeptides in vacuum and in a reaction field model of solvent shows that the incorporation of the solvent environment is critical to the stabilization of the helical minima for small peptides. We have not only calculated the electrostatic contribution to the solvation free energies of the conformers but also the total relative free energies which has enabled direct comparison of our results with those obtained from MD simulations. It is clear that optimization of the conformers within the reaction field is a prerequisite to obtaining a correct description of the available conformers and their energetics. Unlike Shang and Head-Gordon,[26] we have found for AD that the helical conformers are significantly stabilized in solution with respect to the intramolecular hydrogen-bonded conformers, so that our results more closely model the experimental[17] and MD simulation results. It may be that the combination of a more realistic cavity shape and the extension of the multipole expansion past the $l = 1$ case is responsible for the destabilization of the C5 and C7(s) conformers. Furthermore, for GD we find only one conformer upon optimization whereas Shang and Head-Gordon[26] found several minima.

We believe that the solvation models used in this study are of utility to answering the question of how solvation affects molecular conformation. There are still a large number of uncertainties in the methodology, the most significant being the description of the cavity size and shape. We see these methods as being complementary to MD and MC simulations. Extension of these methods to include molecular water would benefit such studies as intermolecular hydrogen-bonded interactions could be explicitly considered.

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