Solvation of Alanine Dipeptide: a Quantum Mechanical Treatment

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The self-consistent reaction field model is used with an *ab initio* wavefunction to predict the structure and energetics of conformers of the alanine dipeptide in aqueous solution; the predictions are in good agreement with the limited experimental data available and with molecular dynamics simulations.

A central problem in modelling biopolymers is the effect of solvent on conformer preferences and energetics. This is traditionally studied using simulation methods [Monte Carlo (MC) or Molecular Dynamics (MD)] employing effective intra- and inter-molecular potentials.[1] The conformational energy surface of the alanine dipeptide (Fig. 1), which contains many of the structural features of the protein backbone, and may thus be considered a suitable model of larger globular proteins, has been studied using MC[2] and MD methods,[3,4] and also investigated using a statistical mechanical integral equation theory.[5]

An extensive quantum mechanical study of an alanine dipeptide analogue (Fig. 1 with the two terminal methyl groups replaced by hydrogen atoms) has been reported,[6] identifying the stationary points on the potential energy surface. Such isolated molecule studies are only strictly relevant to the gas phase and perhaps to species in non-polar solvents. They are particularly useful in deriving intramolecular force field parameters for use in MC and MD models of solvation which include explicit solvent molecules. Alternatively, the solvent may be modelled as a dielectric continuum following the Onsager reaction field approach as developed by Kirkwood.[7] The resulting solvent–solute electrostatic interactions may be readily incorporated into self-consistent field molecular orbital (SCF-MO) methods allowing 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.[7]

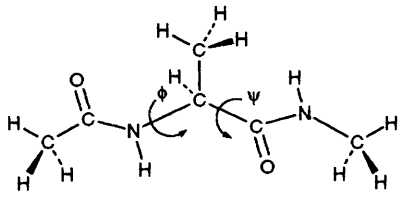

Fig. 1 Structure of alanine dipeptide and definition of ϕ and ψ angles

We here describe the application of the SCRF method to the study of the conformational preferences of the alanine dipeptide in water, as an alternative to the use of MC or MD simulation studies.

We use the SCRF method as described by Rivail *et al.*[8] 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 centre multipole expansion (up to $l = 7$). The solvent (water) is considered to be a uniform dielectric, with a relative permittivity ε of 78.0. The calculations were performed within an *ab initio* MO framework using a 6-31G** basis set, and the SCRF code of Rivail implemented in the GAUSSIAN 90 program.[9]

Calculations were first carried out on the isolated (gas phase) molecule in order to identify the structures and energetics of the minima on the potential energy surface. Seven such energy minima were located (and characterized by evaluation of the harmonic force constants) corresponding to the four internally hydrogen bonded structures ($C7_{eq}$, $C7_{ax}$, α_R, α_l) and the three extended structures (C5, β, β_2). In Table 1 we show the relative energies of these structures and their conformations as characterized by the Ramachandran angles[10] (ϕ, ψ). These results are broadly in line with those for the model alanine dipeptide, lacking terminal methyl groups,[6]

Table 1 Conformations (degrees) and energetics (kcal mol^{-1}; 1 cal = 4.184 J) of alanine dipeptide in gas phase

Conformation	ϕ	ψ	Energy	μ/Debye
$C7_{eq}$	−85.8	79.0	0.00[a]	2.87
$C7_{ax}$	76.0	−55.4	2.82	3.91
C5	−157.2	159.8	0.40	2.56
α_R	−60.7	−40.7	4.35	6.59
α_L	67.0	30.2	4.76	6.26
β	−57.6	134.4	4.90	2.36
β_2	−130.9	22.3	2.58	4.94

[a] Zero of energy = −492.885305 a.u.

Table 2 Conformations (degrees) and energetics (kcal mol^{-1}) of alanine dipeptide in water, using the SCRF model

Conformation	ϕ	ψ	Energy
$C7_{eq}$	−73.3	75.0	0.00[a]
$C7_{ax}$	75.0	−73.5	0.18
α_L	68.4	39.3	1.34
β	−118.2	133.2	−5.25
β_2	−112.0	2.5	−5.68

[a] Zero of energy = −492.903047 a.u.

Table 3 Comparison of predictions of the relative free energies (kcal mol^{-1}) of alanine dipeptide conformations in water

Conformation[a]	Ref. 4	Ref. 5	This work
$\beta(P_{II})$	0.0	0.0	0.0
$\beta_2(\alpha_R)$	0.2	1.6	−0.4
α_L	4.0	0.9	6.6
$C7_{ax}$	3.5	0.7	5.4

[a] We compare our β conformation with the P_{II} of Pettitt and Karplus,[5] and our β_2 conformation with the α_R of Tobias and Brooks[4] and Pettitt and Karplus.[5]

with the most stable structures being the $C7_{eq}$ and C5. This is in agreement with experimental CD and NMR results of Madison and Kopple[11] who have shown that the $C7_{eq}$ conformation dominates in non-polar solvents.

Starting with these seven conformations, geometry optimization was performed within the SCRF formalism in order to identify the corresponding minima on the potential energy surface of the solvated dipeptide. Only five stationary points were located, with the gas phase C5 and α_R structures collapsing into the β and β_2 structures respectively, in aqueous solution. The structures and relative energies of these five conformations are shown in Table 2. There are considerable changes in the structures (particularly of the β and β_2 conformations) and of their relative energies when compared to the gas phase calculations. In particular, the stabilities of the intramolecular hydrogen-bonded and the extended conformers are reversed. Of the conformations we identify in aqueous solution, β is in the polyproline II-like (P_{II}) region of the (ϕ, ψ) map, whilst β_2 is close to the α_R region.[11] We use these similarities to compare our predicted energetics with MD and integral equation results (Table 3). Our results are extremely close to the MD results,[4] but deviate considerably from the integral equation results of Pettitt and Karplus,[5] which may arise from inaccuracies in their gas phase energy surface. Our predictions are also in agreement with the qualitative conclusions of Madison and Kopple[11] who suggest that the C7 conformation, dominant in non-polar solvents, is replaced by α-helical and P_{II} conformations in polar solvents.

The value of continuum models to treat solvation by water, where hydrogen bonding is important, may be questioned. However, since the main component of the hydrogen bond arises from electrostatic interactions, which are represented by the continuum, the effect is well reproduced by the model.[12] Indeed, in the case of water, the continuum model leads to an interaction energy with the continuum in good agreement with experiment.[13]

In conclusion, the first quantum mechanical treatment of dipeptide solvation, presented in this paper, shows that this new approach may be as accurate as more time-consuming MD treatments and thus might be used to derive force field parameters needed to model peptides in solution without the explicit consideration of solvent molecules.

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References

1 C. L. Brooks, III, M. Karplus and B. M. Pettit, *Proteins: A Theoretical Perspective of Dynamics, Structure and Thermodynamics*, Wiley, New York, 1988, *Advances in Chemical Physics*, vol. 71.
2 M. Mezei, P. K. Mehrotra and D. L. Beveridge, *J. Am. Chem. Soc.*, 1985, **107**, 2239.
3 P. J. Rossky and M. Karplus, *J. Am. Chem. Soc.*, 1979, **101**, 1913.
4 D. J. Tobias and C. L. Brooks, III, *J. Phys. Chem.*, 1992, **96**, 3864.
5 B. M. Pettitt and M. Karplus, *Chem. Phys. Lett.*, 1985, **121**, 194.
6 T. Head-Gordon, M. Head-Gordon, M. J. Frisch, C. L. Brooks, III, and J. A. Pople, *J. Am. Chem. Soc.*, 1991, **113**, 5989.
7 M. W. Wong, K. B. Wiberg and M. J. Frisch, *J. Am. Chem. Soc.*, 1992, **114**, 1645; S. Woodcock, D. V. S. Green, M. A. Vincent, I. H. Hillier, M. F. Guest and P. Sherwood, *J. Chem. Soc., Perkin. Trans. 2*, 1992, 2151.
8 J. L. Rivail and B. Terryn, *J. Chim. Phys.*, 1982, **79**, 2; D. Rinaldi *Comput. Chem.*, 1982, **6**, 155, D. Rinaldi, J. L. Rivail and N. Rguini, *J. Comput. Chem.*, 1992, **13**, 675.
9 GAUSSIAN 90, Revision J: M. J. Frisch, M. Head-Gordon, G. W. Trucks, J. B. Foresman, H. B. Schlegel, K. Raghavachari, M. Robb, J. S. Binkley, C. Gonzalez, D. J. Defrees, D. J. Fox, R. A. Whiteside, R. Seeger, C. F. Melius, J. Baker, R. L. Martin, L. R. Kahn, J. J. P. Stewart, S. Topiol and J. A. Pople, Gaussian Inc., Pittsburgh, PA 15213, 1990.
10 C. Ramakrishnan and G. N. Ramachandran, *J. Biophys.*, 1965, **5**, 909.
11 V. Madison and K. D. Kopple, *J. Am. Chem. Soc.*, 1980, **102**, 4855.
12 E. Sanchez Marcos, B. Terryn and J. L. Rivail, *J. Phys. Chem.*, 1985, **89**, 4695.
13 J. Bertran, M. F. Ruiz-López, D. Rinaldi and J. L. Rivail, *Theor. Chim. Acta*, 1992, **84**, 181.