Physica Scripta. Vol. T118, 196–198, 2005

Theoretical Study of the Thermodynamics of a Solvated Peptide: Contryphan Vn

M. D'Alessandro[1,2,*], M. D'Abramo[1,2], M. Paci[2] and A. Amadei[2]

[1]Dipartimento di Chimica, Università di Roma "La Sapienza" P.le Aldo Moro 5, 00185 Roma, Italy
[2]Dipartimento di Scienze e Tecnologie Chimiche Università di Roma "Tor Vergata" via della Ricerca Scientifica 1, 00133 Roma, Italy

Received October 18, 2003; revised version received July 27, 2004; accepted August 13, 2004

PACS numbers: 65.40.Gr, 82.20.−w, 87.15.Aa, 87.15.He, 87.15.La

Abstract

In recent papers we combined molecular dynamics (MD) simulations with the quasi Gaussian entropy (QGE) theory, in order to model the statistical mechanics and thermodynamics of simple solute molecules in water. In this paper we apply this approach to a more complex solute in water: a 9 residues peptide, Contryphan Vn. Results show that this approach can provide an accurate theoretical description of this complex solute-solvent system over a wide range of temperature.

1. Introduction

In very recent papers [1, 2] we extended the QGE theory, in combination with molecular dynamics (MD) simulations, to obtain a complete description of the thermodynamics of diluted polar and apolar simple solutes in water.

It would be of great importance in theoretical physical chemistry the use of a largely analytical method providing the thermodynamics of simulated liquid mixtures and solutions at relatively low computational costs, regardless of the complexity of the molecules involved. In this work we investigate the applicability of the method and its accuracy for a more complex solute: the Contryphan Vn, a cyclic peptide of 9 residues, which is a bioactive component of the venom of Conus Ventricosus, a marine snail of Mediterranean sea.

2. Theory

In this section we summarize the essential derivations of the QGE theory necessary for treating partial molecular properties and to combine this approach with MD data. A detailed description of the theory can be found in the previous papers [1, 2].

Let Q and Q_{ref} be the canonical partition functions respectively for a fluid state system of one solute and n_s solvent molecules, and that of the reference system at the same temperature and density but without excess (potential) energy $\mathcal{U}'$ (hence without any unaccessible configuration).We can express the excess (Helmholtz) free energy per solute molecule as [3, 4, 5, 6]

$$A' = A - A_{ref} = -kT\ln(Q/Q_{ref}) = kT\ln\langle e^{\beta\mathcal{U}'}\rangle - kT\ln\epsilon \quad (1)$$

where ϵ is the fraction of available configurational space [6]. The entropic term due to a possible confinement of the system in configurational space, $k\ln\epsilon$, is usually associated with hard-body excluded volume [3]. The ensemble average in Eq. (1) can also be expressed as

$$\langle e^{\beta\mathcal{U}'}\rangle = \int \rho(\mathcal{U}')e^{\beta\mathcal{U}'}\,d\mathcal{U}' \quad (2)$$

where $\rho(\mathcal{U}')$ is the probability distribution function of the excess energy $\mathcal{U}'$. We showed in previous papers [6] that one of the simplest distribution, the Gamma distribution, yields a fully physically acceptable theoretical model (Gamma state) providing an excellent description of the fluid state thermodynamics over a wide range of temperature and density, including solute-solvent systems. We can rewrite the excess free energy as

$$A'(T) = n_s a'_s + a' \quad (3)$$

where a'_s is the partial molecular excess (Helmholtz) free energy of the solvent and a' is the partial molecular excess (Helmohltz) free energy of the solute. Assuming that A' can be well modeled by a single Gamma state [3], we have

$$U' = U'_0 + (T - T_0)\frac{c'_{V0}T_0}{T(1-\delta_0)+\delta_0 T_0}, \quad (4)$$

$$A' = U'_0 - T_0 C'_{V0}\Lambda(T) - kT\ln\epsilon, \quad (5)$$

$$\Lambda(T) = \frac{1}{\delta_0} + \frac{T}{T_0\delta_0^2}\ln\{1-\delta(T)\}, \quad (6)$$

$$\delta(T) = \frac{T_0\delta_0}{T(1-\delta_0)+T_0\delta_0}. \quad (7)$$

with $U'_0 = U'(T_0)$ and $C'_{V0} = C'_V(T_0)$ the excess internal energy and heat capacity of the system at the reference temperature T_0 and δ_0 a dimensionless intensive property [3] independent of the temperature, that in our case (high dilution) is determined by the solvent. The Gamma state expressions [3] would then provide any thermodynamic property of the system. Assuming a Gamma state behavior for the solute-solvent system as well as for the pure solvent one, from the previous equations we can obtain the solute partial molecular properties via the excess chemical potential [1, 2]

$$\mu' = \Delta A' = u'_0 - c'_{V0}T_0\Lambda(T) - kT\ln\bar{\epsilon} + p'v \quad (8)$$

where u'_0 and c'_{V0} correspond to the partial molecular excess internal energy and heat capacity of the solute, evaluated at the reference temperature T_0, $-kT\ln\bar{\epsilon}$ is the corresponding partial molecular excess free energy due to the confinement, p' is the excess pressure (given by the solvent at high solute dilution) and v is the solute partial molecular volume. Finally $\Delta A'$ is the change of the excess free energy between the solute-solvent and the pure solvent systems. Note that the excess free energies of the solute-solvent system as well as of the pure solvent one, were obtained by fitting the average excess (potential) energy in temperature [1], provided by the simulations, with the corresponding Gamma state models (eq. (4)).

*Author to whom the correspondence should be addressed.
E-mail: mdalessa@caspur.it

3. Simulation methods

We performed five different MD simulations over a wide temperature range (300–700 K). The molecule was immersed in a rectangular box filled with 429 water molecules and a chloride ion. The model used for the water molecules was the SPC model [7]. All the simulations were performed using Gromacs software package [8, 9, 10] modified to use the isokinetic temperature coupling [11]. This was done in order to obtain results fully consistent with statistical mechanics [5, 12]. Short range interactions were evaluated within 0.9 nm cut off radius, and LINCS [13] algorithm was used to fix bond lengths. The long range electrostatics was calculated using the Particle Mesh Ewald method [14] with a 4th order cubic interpolation. We also used roto-translational constraints to stop the solute in the simulation box [5]. This procedure, which speeds up the solvent relaxation around the solute, provides the correct statistical mechanics and thermodynamics of the system. A simulation time of about 14 ns at each temperature was analysed. We verified that average potential energies, the only observable from the solute-solvent simulations we need for the parameterization of the Gamma state, were well converged whithin the simulation time length. The time step was 2 fs for all the simulations except at 700 K were we used 1 fs. Equilibration runs were performed before starting the productive simulations. Finally, the pure solvent properties used in the QGE models were obtained by the simulations described in a previous paper [1].

4. Results

We parameterized our theoretical models, described in the theory section, using only the average potential energy (excess internal energy) and pure solvent pressure in the whole temperature range, i.e., by fitting these values with the corresponding QGE theoretical models.

In recent papers, it has been shown, both for the canonical [15] and the isothermal-isobaric ensemble [16], that the use of mixing distributions for gamma state models (multiple Gamma state model) provides a powerful method for describing very complex fluid state systems, such as proteins where the solute configurational space of internal coordinates can be partitioned into many subspaces, each one described by a single gamma state. In this way, protein folding thermodynamics [16] can be correctly described via a specific set of Gamma states. In this context, the Contryphan Vn represents an intermediate complexity level between simple solutes, well described by a single gamma state [1,2], and a protein, requiring a multi-Gamma state model. Interestingly, Contryphan Vn thermodynamics can be accurately described using a single Gamma state model over a large temperature range, showing that for this solvated peptide a multiple Gamma state model is not necessary. If compared with the protein folding behavior [16], this clearly means that no unfolding process occurs for Contryphan Vn, probably because of its small and well structured closed ring, fixed by a stable disulfide bond. From the conformational analysis [17], performed on very long trajectories (200 ns), we observed that during the 300 K to 400 K transition the peptide backbone remains quite rigid, whithout any relevant conformational change. Moreover, it must be noted that we evaluate the thermodynamics of Contryphan Vn along an isochore, not along an isobar as for typical unfolding studies, probably providing a further stabilization of the peptide structure.

Table I. *Parameters of the QGE theoretical models obtained by molecular properties of pure SPC (256 molecules) at 55.32 mol/l, and of a Contryphan VN in SPC box (429 molecules).*

	v l/mol	u'_0 (kJ/mol)	c'_{v0} (KJ/mol K)	δ_0
SPC	0.0181	−41.4	0.046	0.6565
Contryphan	0.9784	−1115.9	1.756	0.6565

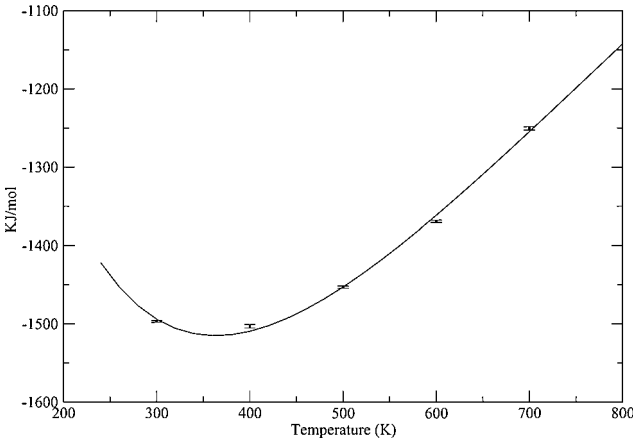

Fig. 1. Isochoric excess internal energy change $(\partial U'/\partial n)_{V,T,n_s}$ due to the Contryphan VN. Solid line: QGE model. Points: simulation data. The error bars for the simulation data correspond to a standard deviation.

The partial molecular properties of the solute are obtained, according to the theory section, via $\mu' = \Delta A'$. Note that in the calculation of μ' is very important to use exactly the same temperatures for the evaluation of the overall excess free energies of the solute-solvent and pure solvent systems. This is because even a slight systematic deviation in these two excess free energies would result in an error of μ'. In table I we summarize the physical parameters which define the Gamma state models for SPC and Contryphan. In figure 1 we show the isochoric energy change due to the solute molecular number $(\partial U'/\partial n)_{V,n_s,T}$. Note that this thermodynamic property coincides with the difference of the average potential energy of the systems with and without the Contryphan (since we simulated only one solute molecule). The theoretical prediction of the gamma state model is, within the

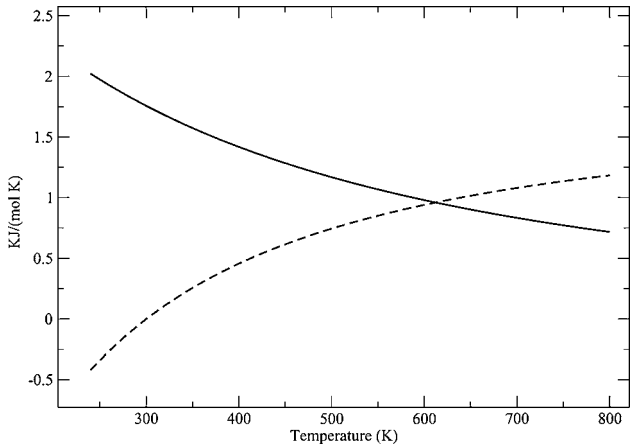

Fig. 2. Partial molar excess heat capacity c'_V (solid line) and entropy change $s'(T) - s'(T_0)$ (dashed line) of Contryphan Vn. Reference is $T_0 = 300$ K.

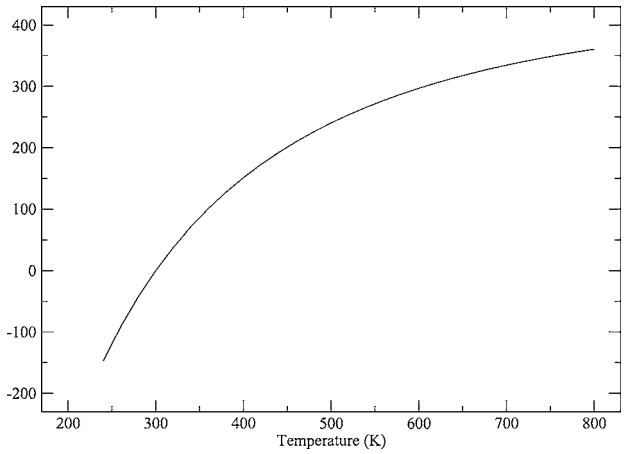

Fig. 3. Excess chemical potential change, $\mu'(T)/(KT) - \mu'(T_0)/(KT_0)$, of Contryphan Vn. Reference is $T_0 = 300$ K.

error bars, excellent. A well defined mimimum, already observed in other dilute solutions [1, 2] occurs at about 380 K suggesting an energetically optimal solvent structure around the solute, at that temperature. In figure 2 we show Contryphan Vn partial molar excess heat capacity and entropy and, finally, in figure 3 its excess chemical potential.

5. Conclusions

In this paper we show that the combined use of the QGE theory with MD simulations can provide the whole thermodynamics of a rather complex solute-solvent system, including all the partial molar properties. We have investigated the 9 residues peptide, Contryphan Vn at high dilution, along the typical liquid water isochore. Unfortunally neither experimental nor computational studies of Contryphan thermodynamics are available and hence no comparison between our and literature data is possible. However, the results shown clearly indicate that this approach provides, at relatively low computational costs, a coherent and accurate description of the thermodynamics of a complex biochemical system such as the solvated peptide studied in this paper.

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