The thermodynamics of water stabilization of Carboxybetaine hydrogels from molecular dynamics simulations

Tod A. Pascal[†‡], Yi He[ζ], Shaoyi Jiang[ζ] and William A. Goddard III*[†‡]

[†]*Materials and Process Simulation Center, California Institute of Technology, Pasadena, California, USA*

[‡]*Graduate School of EEWS(WCU), Korea Advanced Institute of Science and Technology, Daejeon, Korea*

[ζ]*Department of Chemical Engineering, University of Washington, Seattle, Washington, USA*

*Corresponding author: Professor William A Goddard III, wag@wag.caltech.edu

Supporting Information

I. THE 2PT METHOD

From molecular dynamics trajectories in the canonical ensemble, we calculate the velocity autocorrelation function (VACF) as:

$$C(t) = \sum_{j=1}^{N} \sum_{k=1}^{3} m_j \left[\lim_{t \to \infty} \frac{1}{2\tau} \int_{-\tau}^{\tau} v_j^k(t+t') v_j^k(t) dt' \right] \quad 1)$$

where N is the number of atoms and $v_j^k(t)$ is the k-th component of the velocity of atom j at time t. From a Fourier Transform of the VACF, we obtain the total Density of States (DoS):

$$DoS(v) = \lim_{\tau \to \infty} \int_{-\tau}^{\tau} C(t) e^{-2\pi i v t} dt \quad 2)$$

Here *DoS(v)* is the number of modes of the system at frequency *v*, including both vibrational and diffusional components. Indeed, *DoS(0)* measures the diffusion coefficient D0:

$$DoS(0) = \frac{12 m D_0}{kT} \quad 3)$$

where *m* is the mass, *k* is Boltzmann's constant and *T* is the temperature.

A finite DoS(0) would lead to infinite entropy for standard quantum statistical formula[1]. 2PT overcomes this limitation by partitioning *DoS(v)* into two components:

- *DoS_{diff}(v)*: the diffusional component is described as a hard sphere diffusing gas, for which the VACF decays exponentially with time, leading to:

$$DoS_{diff}(v) = \frac{DoS(0)}{1 + \left[\frac{DoS(0) \pi v}{2 N_{diff}} \right]^2} \quad 4)$$

where $N_{diff} = 3Nf$ is the total diffusional degrees of freedom (*f* is the fraction of modes that are diffusive). The diffusional contributions to the thermodynamics, S_{diff}, U_{diff}, A_{diff}, are obtained from the Chapman-Enskog hard sphere theory[2], as explained in Ref[1]. For the systems considered here, we find that *f* ranges from 5% (41p) to 22% (91p). For the sake of comparison, a box of SPC-E waters has *f* of 25%.

- $DoS_{solid}(v)$: goes smoothly to zero as $v \to 0$ (no diffusion), representing a vibrating Debye crystal. Here, we evaluate the partition function Q using the standard harmonic oscillator expressions from statistical mechanics [2]:

$$\ln Q = \int_0^\infty DoS_{solid}(v) \frac{\exp(-\beta h v/2)}{1 - \exp(-\beta h v/2)} dv \quad 5)$$

Since $DoS_{solid}(v) \to 0$ as $v \to 0$, there are no singularities in eqn. (5) at $v = 0$.

The system thermodynamics of the solid component are then obtained by integrating over the $DoS_{solid}(v)$. Thus the standard molar entropy S^0 is:

$$S^0 = k \ln Q + \beta^{-1} \left(\frac{\partial \ln Q}{\partial T} \right)_{N,V}$$

$$= k \left[\int_0^\infty DoS_{solid}(v) \left\{ \frac{\beta h v}{\exp(\beta h v) - 1} - \ln(1 - \exp(-\beta h v)) \right\} dv \right] \quad 6)$$

where $\beta = 1/kT$. The internal energy E^0 is:

$$E^0 = E^{MD} - \int_0^\infty DoS_{solid}(v) h v \left[\frac{1}{2} + \frac{1}{\exp(\beta h v - 1)} \right] dv \quad 7)$$

where E^{MD} is the system energy from MD. E^0 is the reference energy of the system with all vibrations are in their lowest (zero) vibrational level, explicitly including zero-point energies. Finally, the Helmholtz Free energy A^0 is:

$$A^0 = E^0 - \beta^{-1} \ln Q$$

$$= E^0 + \beta^{-1} \int_0^\infty DoS_{solid}(v) \ln \frac{1 - \exp(\beta h v)}{\exp(-\beta h v/2)} dv \quad 8)$$

We have developed a post trajectory code that performs the 2PT calculations. The code is available upon request from the authors (wag@wag.caltech.edu, tpascal@wag.caltech.edu).

II. COMPUTATIONAL METHODS

II.a. Molecular Dynamics simulations

The zwitterionic CBMA hydrogel model was built using an approach similar to that reported by Chiessi, et al. [3]. The polymer chains of the network were built with Accelrys Material Studio (version 3.2). Each of these chains has 15 repeating units in a fully extended conformation and a parallel orientation with respect to the Cartesian axes. The polymer network was then solvated with various amounts of water molecules to obtain hydrogels with various water contents. The all-atom Consistent Valence Force Field (CVFF)[4] was used to describe the interactions in the polymer networks. The partial charges of each atom in the CBMA polymer were calculated using the Jaguar program [5]. These calculations were carried out at the Hartree-Fock (HF) level using the 6-31G** basis set. In this procedure, the electrostatic field at a grid of points was calculated from the HF wave function. Using the grid points outside the VDW radii, atom-centered charges were derived so as to match the HF potential while reproducing the dipole moment from HF. The water molecules are described with the Extended Simple Point Charge (SPC/E) model.[6]

Our MD simulations were performed using the LAMMPS[7,8] simulation engine, which affords the flexibility of using various forcefields in a common framework. Long-range coulombic interactions were calculated using the particle-particle particle-mesh Ewald method[9] (with a precision of 10^{-5} kcal/mol), while the van der Waals interaction were computed with a cubic spline (inner cutoff of 11Å and an outer cutoff of 12Å). We used the spline to guarantee that the energies and forces go smoothly to zero at the outer cutoff, preventing energy drifts that might arise from to inconsistent forces. We also tested the effect of the cutoff by computing the energy of benzene with cutoffs ranging from 8 to 20Å and found converged results at 12Å.

For each system, we used the Continuous Configurational Boltzmann Biased (CCBB) Monte Carlo (MC) method[10,11] to generate a random starting structure of 512 solvent molecules packed to minimize the system interaction energy. To rapidly equilibrate the systems, we used our standard procedure[12-14]: after an initial conjugant gradient minimization to an RMS force of 10^{-4}kcal/mol/Å, the system was slowly heated from 0K to 298K over a period of 100 ps using a Langevin thermostat in the constant temperature, constant volume canonical (NVT) ensemble. The temperature coupling constant was 0.1 ps and the simulation timestep was 1.0 fs.

This equilibration was followed by 20ns of constant-pressure(iso-baric), constant-temperature (NPT) dynamics at 298K and 1 atm. The temperature coupling constant was 0.1 ps while the pressure piston constant was 2.0 ps. The equations of motion used are those of Shinoda et al.[15], which combine the hydrostatic equations of Martyna et al.[16]with the strain energy proposed by Parrinello and Rahman[17]. The time integration schemes closely follow the time-reversible measure-preserving Verlet integrators derived by Tuckerman et al.[18].

Production dynamics was then run for a further 5.0 ns in the NPT ensemble. All data reported in this paper are the statistical averages of two individual MD simulations from two different initial configurations.

II.b. Free energy calculations

During the final 5ns of the production dynamics simulations outlined above, we selected snapshots of the system (coordinates and velocities) every 0.5 ns. Each of the 10 snapshots was then simulated for 20 ps of MD using the Gibbs (constant particle, constant volume, constant temperature – NVT) ensemble. The velocities and coordinates were saved every 4 fs (must be shorter than the fastest vibrational levels, which have periods of ~10 fs for the 3000 cm^{-1} C-H vibrations).

III. Tables

Table S1: Description of CBMA – water systems considered in this study. The quoted average volumes and solvent accessible surface areas are obtained by averaging 1000 structure during the last 4ns of MD.

% water	# num	[a]$<$SASA$>$ Å^2	$<$Volume$>$ Å^3	$<$SASA/V$>$
41	592	17877.5	37481.0	0.477
49	819	20764.6	43960.8	0.472
62	1396	16668.4	61287.4	0.272
71	2120	14987.1	83048.0	0.180
81	3630	15739.8	126859.0	0.124
91	8200	16867.4	248168.0	0.068

[a]Solvent accessible surface area, obtained according to the method of Lee-Richards[19] with a 1.4Å probe radius

Table S2: Thermodynamics of the CBMA hydrogel from 2PT analysis.

% water	A^0 (kJ/mol)		E^0 (kJ/mol)		ZPE (kJ/mol)[a]		E^{md} (kJ/mol)[b]		S^0 (J/mol/K)	
	avg	±	avg	±	avg	±	avg	±	avg	±
41	56630.1	210.4	62712.5	188.4	53815.9	158.0	23716.7	86.9	20274.7	130.6
49	56501.6	161.8	62563.9	151.1	53717.5	141.9	23439.3	78.7	20207.7	120.5
62	56218.3	157.1	62194.7	176.8	53380.9	129.3	23232.1	100.8	19921.3	55.7
71	55948.8	114.9	61900.9	126.9	53341.6	104.8	22912.3	90.9	19840.3	84.8
81	56589.8	182.1	62475.6	171.1	53355.1	169.0	22420.1	57.8	19619.3	101.7
91	56780.1	186.8	62756.5	154.8	53618.2	104.5	23408.7	173.2	19921.2	152.1
dry: 0%										

[a]Zero point energy determined using equation 7.
[b]Total Energy of hydrogel from MD. The per-atom long range electrostatic contributions were obtained by 1000 single point energy calculations using Ewald summations along the 20ps trajectory, as detailed in ref[20].

Table S3: Thermodynamics per molecule of waters in CBMA hydrogel from 2PT analysis

% water	A^0 (kJ/mol)		E^0 (kJ/mol)		Cv (kJ/mol/K)[a]		S^0 (J/mol/K)	
	avg	±	avg	±	avg	±	avg	±
41	-51.74	0.08	-35.99	0.08	35.93	0.04	50.67	0.23
49	-52.03	0.11	-35.73	0.08	35.88	0.06	52.64	0.21
62	-52.57	0.10	-35.17	0.09	35.92	0.07	56.42	0.38
71	-52.81	0.06	-34.94	0.06	35.64	0.04	58.30	0.23
81	-52.94	0.03	-34.80	0.03	35.35	0.05	59.53	0.13
91	-52.86	0.04	-34.77	0.01	34.96	0.05	59.42	0.08
bulk[b]	-53.2	0.03	-34.61	0.02	34.79	0.04	62.76	0.11

[a]Constant volume heat capacity

Table S4: Components of entropy (J/mol/K/molecule) of waters in CBMA hydrogel from 2PT analysis

% water	Diffusional		Librational		Rotational	
	avg	±	avg	±	avg	±
41	0.27	0.17	41.94	0.47	8.46	0.05
49	1.77	0.38	41.98	0.06	8.89	0.06
62	3.10	0.22	43.51	0.24	9.81	0.11
71	7.00	0.41	41.15	0.31	10.15	0.05
81	8.43	0.11	40.72	0.20	10.38	0.03
91	9.07	0.24	39.84	0.35	10.52	0.04
bulk	11.10	0.04	38.99	0.10	10.67	0.03

IV. REFERENCES

(1)   Lin, S. T.; Blanco, M.; Goddard, W. A. *J. Chem. Phys.* **2003**, *119*, 11792.

(2)   McQuarrie, D. A. *Statistical mechanics*; University Science Books: Sausalito (Calif.), 2000.

(3)   Chiessi, E.; Cavalieri, F.; Paradossi, G. *J Phys Chem B* **2007**, *111*, 2820.

(4)   Dauberosguthorpe, P.; Roberts, V. A.; Osguthorpe, D. J.; Wolff, J.; Genest, M.; Hagler, A. T. *Proteins* **1988**, *4*, 31.

(5)   Schrödinger, I. Portland, OR, 1991-2000.

(6)   Berendsen, H. J. C.; Grigera, J. R.; Straatsma, T. P. *J. Phys. Chem.* **1987**, *91*, 6269.

(7)   Plimpton, S. J.; Pollock, R.; Stevens, M. In *Proc of the Eighth SIAM Conference on Parallel Processing for Scientific Computing* Minneapolis, MN 1997.

(8)   Plimpton, S. *J. Comput. Phys.* **1995**, *117*, 1.

(9)   Hockney, R. W.; Eastwood, J. W. *Computer Simulation Using Particles*; Taylor & Francis: New York, 1989.

(10)   Maiti, P. K.; Çağın, T.; Wang, G.; Goddard, W. A. *Macromolecules* **2004**, *37*, 6236.

(11)   Cagin, T.; Wang, G. F.; Martin, R.; Breen, N.; Goddard, W. A. *Nanotechnology* **2000**, *11*, 77.

(12) Maiti, P. K. P., Tod A.; Vaidehi, Nagarajan; Goddard, William A. *J. Nanosci. Nanotechnol.* **2007**, *7*, 1712.

(13) Maiti, P. K.; Pascal, T. A.; Vaidehi, N.; Heo, J.; Goddard, W. A. *Biophys. J.* **2006**, *90*, 1463.

(14) Maiti, P. K.; Pascal, T. A.; Vaidehi, N.; Goddard, W. A. *NUCLEIC ACIDS RES* **2004**, *32*, 6047.

(15) Shinoda, W.; Shiga, M.; Mikami, M. *Physical Review B* **2004**, *69*.

(16) Martyna, G. J.; Tobias, D. J.; Klein, M. L. *J. Chem. Phys.* **1994**, *101*, 4177.

(17) Parrinello, M.; Rahman, A. *Journal of Applied Physics* **1981**, *52*, 7182.

(18) Tuckerman, M. E.; Alejandre, J.; Lopez-Rendon, R.; Jochim, A. L.; Martyna, G. J. *J Phys a-Math Gen* **2006**, *39*, 5629.

(19) Lee, B.; Richards, F. M. *J. Mol. Biol.* **1971**, *55*, 379.

(20) Kumar, H.; Mukherjee, B.; Lin, S. T.; Dasgupta, C.; Sood, A. K.; Maiti, P. K. *J. Chem. Phys.* **2011**, *134*.