# Relation Between the Widom Line and the Dynamic Crossover in Bulk Water and in Protein Hydration Water

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## ABSTRACT

We investigate, for two water models displaying a liquid-liquid critical point, the relation between changes in dynamic and thermodynamic anomalies arising from the presence of the liquid-liquid critical point. We find a correlation between the dynamic fragility transition and the locus of specific heat maxima $C_P^{\max}$ ("Widom line") emanating from the critical point. Our findings are consistent with a possible relation between the previously hypothesized liquid-liquid phase transition and the transition in the dynamics recently observed in neutron scattering experiments on confined water. More generally, we argue that this connection between $C_P^{\max}$ and dynamic crossover is not limited to the case of water, a hydrogen bonded network liquid, but is a more general feature of crossing the Widom line. Specifically, we also study the Jagla potential, a spherically symmetric two-scale potential known to possess a liquid-liquid critical point, in which the competition between two liquid structures is generated by repulsive and attractive ramp interactions. Using molecular dynamics simulations, we also investigate the relation between the dynamic transitions of biomolecules (lysozyme and DNA) and the dynamic and thermodynamic properties of hydration water. We find that the dynamic transition of the macromolecules, sometimes called a "protein glass transition", occurs at the temperature of dynamic crossover in the diffusivity of hydration water, and also coincides with the maxima of the isobaric specific heat $C_P$ and the temperature derivative of the orientational order parameter. We relate these findings to the hypothesis of a liquid-liquid critical point in water. Our simulations are consistent with the possibility that the protein glass transition results from a change in the behavior of hydration water, specifically from crossing the Widom line.

## INTRODUCTION: THE WIDOM LINE

By definition, in a first order phase transitions, thermodynamic state functions such as density $\rho$ and enthalpy $H$ discontinuously change as we cool the system along a path crossing the equilibrium coexistence line [Figure 1(a), path $\beta$]. In a real experiment, this discontinuous change may not occur at the coexistence line since a substance can remain in a supercooled metastable phase until a limit of stability (a spinodal) is reached [1] [Figure 1(b), path $\beta$]. If the system is cooled isobarically along a path above the liquid-gas critical pressure $P_c$ [Figure 1(b), path $\alpha$], the state functions continuously change from the values characteristic of a high temperature phase (gas) to those characteristic of a low temperature phase (liquid). The thermodynamic response functions which are the derivatives of the state functions with respect to temperature [e.g., isobaric heat capacity $C_P \equiv (\partial H/\partial T)_P$] have maxima at temperatures denoted by $T_{\max}(P)$. Remarkably these maxima are still prominent far above the critical pressure [5–9], and the values of the response functions at $T_{\max}(P)$ (e.g., $C_P^{\max}$) diverge as the critical point is approached. The lines of the maxima for different response functions asymptotically approach one another as the

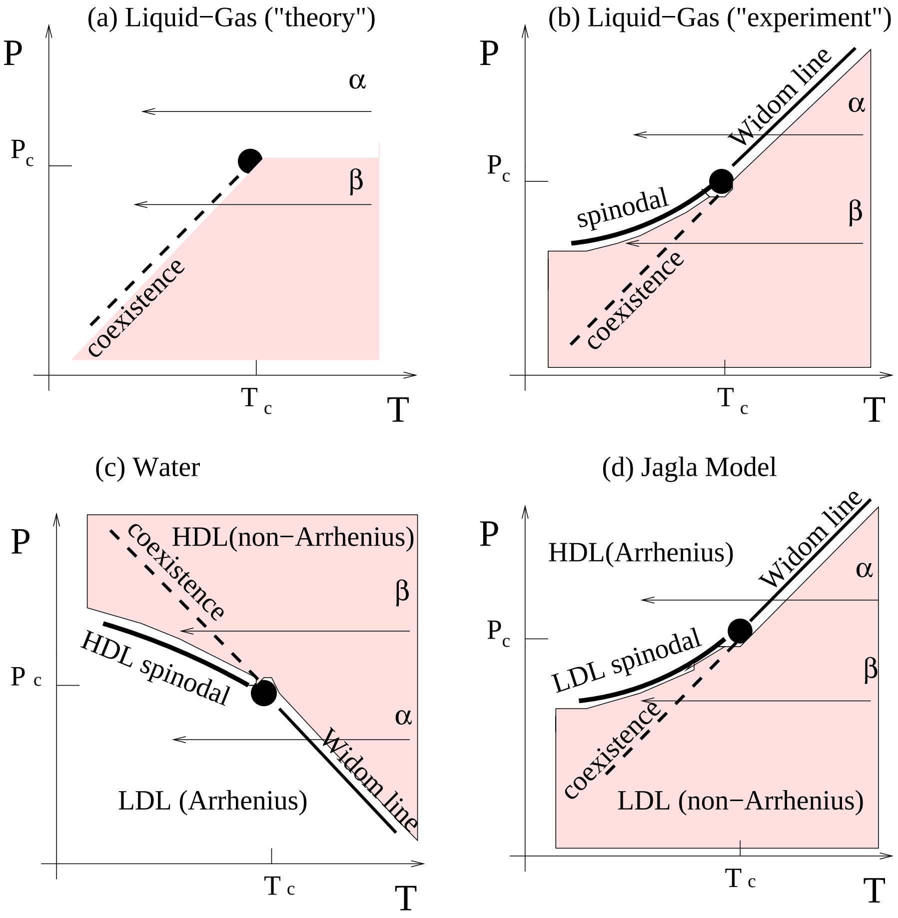

**Figure 1.** (a) Schematic phase diagram for the critical region associated with a liquid-gas critical point. Shown are the two features displaying mathematical singularities, the critical point (closed circles) and the liquid-gas coexistence (bold dashed curve). (b) Same as (a) with the addition of the gas-liquid spinodal and the Widom line. Along the Widom line, thermodynamic response functions have extrema in their $T$ dependence. The path $\alpha$ denotes a path along which the Widom line is crossed. Path $\beta$ denotes a path meeting the coexistence line. (c) A hypothetical phase diagram for water of possible relevance to the recent neutron scattering experiments by Chen et al. [27,28] on confined water. The liquid-liquid coexistence, which has a negative sloped coexistence line, generates a Widom line which extends below the critical point, suggesting that water may exhibit a dynamic crossover (non-Arrhenius-to-Arrhenius) transition for $P < P_c$ (path $\alpha$), while no dynamic changes will occur above the critical point (path $\beta$). (d) A sketch of the $P - T$ phase diagram for the two-scale Jagla model. For the Jagla potential, as well as for the double-step potential [29], the liquid-liquid phase transition line has a positive slope. Upon cooling at constant pressure above the critical point (path $\alpha$), the liquid changes from a low density state (characterized by a non-glassy Arrhenius dynamics) to a high density state (characterized by glassy Arrhenius dynamics with much larger activation energy) as the path crosses the Widom line. Upon cooling at constant pressure below the critical point (path $\beta$), the liquid remains in the LDL phase as long as path $\beta$ does not cross the LDL spinodal line. Thus one does not expect any change in the dynamic behavior along the path $\beta$, except upon approaching to glass transition where one can expect the non-Arrhenius behavior characterized by the Vogel-Fulcher-Tamman (VFT) fit.

critical point is approached, since all response functions become expressible in terms of the correlation length. This asymptotic line is sometimes called the Widom line, and is often regarded as an extension of the coexistence line into the "one-phase regime."

Water's anomalies have been hypothesized to be related to the existence of a line of a first order liquid-liquid phase transition terminating at a liquid-liquid critical point [2–4], located below the homogeneous nucleation line in the deep supercooled region of the phase diagram—sometimes called the "no-man's land" because it is difficult to make direct measurements on the *bulk* liquid phase [3]. In supercooled water, the liquid-liquid coexistence line and the Widom line have negative slopes. Thus, if the system is cooled at constant pressure $P_0$, computer simulations suggest that for $P_0 < P_c$ [Figure 1(c), path $\alpha$] experimentally-measured quantities will change dramatically but continuously in the vicinity of the Widom line (with huge fluctuations as measured by, e.g., $C_P$) from those resembling the high density liquid (HDL) to those resembling the low density liquid (LDL). For $P_0 > P_c$ [Figure 1(c), path $\beta$], experimentally-measured quantities will change discontinuously if the coexistence line is actually seen. However, the coexistence line can be difficult to detect in a pure system due to metastability, and changes will occur only when the spinodal is approached where the HDL phase is no longer stable. The changes in behavior may include not only static quantities like response functions [5–9] but also dynamic quantities like diffusivity.

In the case of water, a significant change in dynamical properties has been suggested to take place in deeply supercooled states [10–13]. Unlike other network forming materials [14], water behaves as a non-Arrhenius liquid in the experimentally accessible window [4,15,16]. Based on analogies with other network forming liquids and with the thermodynamic properties of the amorphous forms of water, it has been suggested that, at ambient pressure, liquid water should show a dynamic crossover from non-Arrhenius behavior at high $T$ to Arrhenius behavior at low $T$ [12–21]. Using Adam-Gibbs theory [22], the dynamic crossover in water was related to the $C_P^{\max}$ line [10,23]. Also, a dynamic crossover has been associated with the liquid-liquid phase transition in simulations of silicon and silica [24,25]. Recently a dynamic crossover in *confined* water was studied experimentally [26–28,30] since nucleation can be avoided in confined geometries. In this work, we interpret recent experiments on water [27,28,30] as arising from the presence of the hypothesized liquid-liquid critical point, which gives rise to a Widom line and an associated fragility transition [Figure 1(c), path $\alpha$].

## RESULTS FOR BULK WATER

Using molecular dynamics (MD) simulations [31], Xu et al. [32] studied three models, each of which has a liquid-liquid critical point. Two of the models (the TIP5P [33] and the ST2 [34]) treat water as a multiple site rigid body, interacting via electrostatic site-site interactions complemented by a Lennard-Jones potential. The third model is the spherical "two-scale" Jagla potential with attractive and repulsive ramps which has been studied in the context of liquid-liquid phase transitions and liquid anomalies [9,18–20,35,36]. For all three models, Xu et al. evaluated the loci of maxima of the relevant response functions, compressibility and specific heat, which coincide close to the critical point and give rise to the Widom line. They found evidence that, for all three potentials, the dynamic crossover occurs just when the Widom line is crossed (Figure 2).

These findings are consistent with the possibility that the observed dynamic crossover along path $\alpha$ is related to the behavior of $C_P$, suggesting that enthalpy or entropy fluctuations may have a strong influence on the dynamic properties [9,10,25]. Indeed, as the thermodynamic properties change from the high-temperature side of the Widom line to the low-temperature side, $(\partial S/\partial T)_P = C_P/T > 0$ implies that the entropy must decrease. The entropy decrease is most

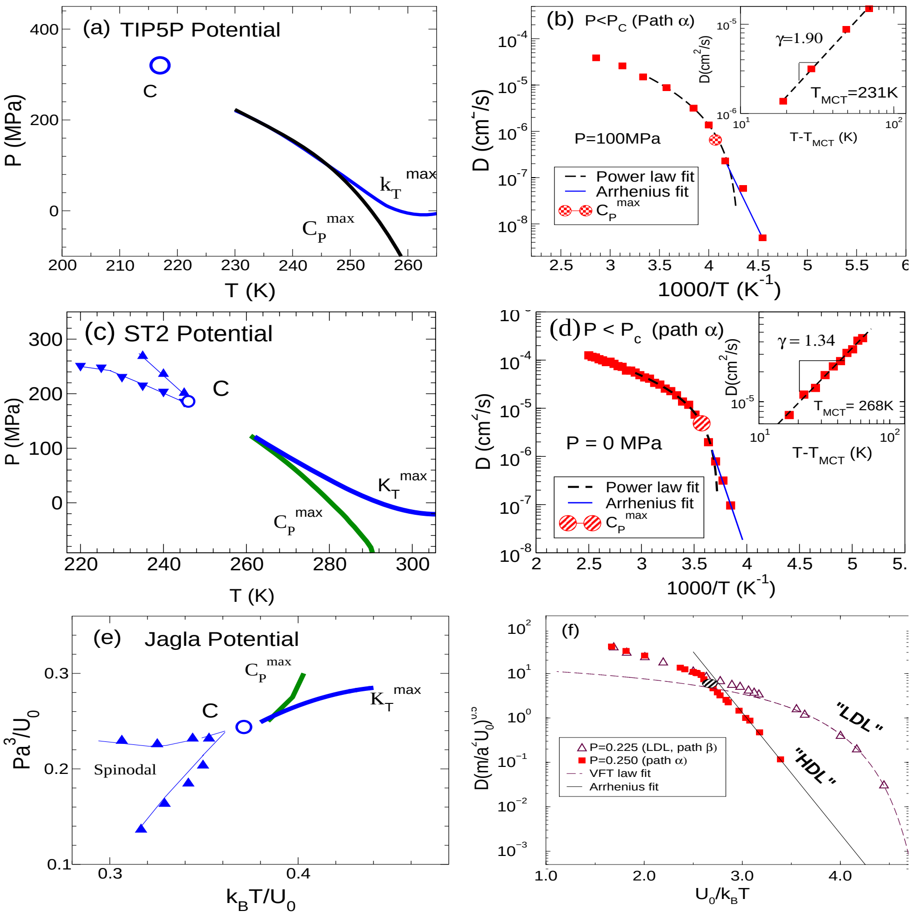

**Figure 2.** (a) Relevant part of the phase diagram for the TIP5P potential, showing the liquid-liquid critical point $C$ at $P_c = 320$ MPa and $T_c = 217$ K, the line of maximum of isobaric specific heat $C_P^{\max}$ and the line of maximum of isothermal compressibility $K_T^{\max}$. (b) $D$ as a function of $T$ for $P = 100$ MPa (path $\alpha$). At high temperatures, $D$ behaves like that of a non-Arrhenius liquid and can be fit by $D \sim (T - T_{MCT})^{\gamma}$ (also shown in the inset) where $T_{MCT} = 220$ K and $\gamma = 1.942$, while at low temperatures the dynamic behavior changes to that of a liquid where $D$ is Arrhenius. (c) The same for the ST2 potential. The liquid-liquid critical point $C$ is located at $P_c = 246$ MPa and $T_c = 146$ K. (d) $D$ as a function of $T$ for $P = 0$ Mpa (path $\alpha$). At high temperatures, $D$ behaves like that of a non-Arrhenius liquid and can be fit by $D \sim (T - T_{MCT})^{\gamma}$ (also shown in the inset) where $T_{MCT} = 239$ K and $\gamma = 1.57$, while at low temperatures the dynamic behavior changes to that of a liquid where $D$ is Arrhenius. (e) Phase diagram for the Jagla potential in the vicinity of the liquid-liquid phase transition. Shown are the liquid-liquid critical point $C$ located at $P_c = 0.24$ and $T_c = 0.37$, the line of isobaric specific heat maximum $C_P^{\max}$, the line of isothermal compressibility $K_T^{\max}$, and spinodal lines. (f) $D$ as a function of $T$ for $P = 0.250$ (squares, path $\alpha$) and $P = 0.225$ (triangles, path $\beta$). Along path $\alpha$, one can see a sharp crossover from the high temperature Arrhenius behavior $D \approx \exp(-1.53/T)$ with lower activation energy to a low temperature Arrhenius behavior $D \approx \exp(-6.3/T)$ with high activation energy, which is a characteristic of the HDL. Along path $\beta$, there is no sharp changes near the critical point, because the liquid remains in the LDL phase. However, near the glass transition, LDL exhibits a non-Arrhenius behavior characterized by the VFT fit at very low temperature.

pronounced at the Widom line when $C_P = C_P^{\max}$. Since the configurational part of the entropy, $S_{\rm conf}$, makes the major contribution to $S$, we expect that $S_{\rm conf}$ also decreases sharply on crossing the Widom line.

According to Adam-Gibbs theory [22], $D \sim \exp(-A/TS_{\rm conf})$. Hence, we expect that $D$ sharply decreases upon cooling at the Widom line. If $S_{\rm conf}$ does not change appreciably with $T$, then the Adam-Gibbs equation predicts an Arrhenius behavior of $D$. For both water and the Jagla model, crossing the Widom line is associated with the change in the behavior of the diffusivity. (i) In the case of water, $D$ changes from non-Arrhenius to Arrhenius behavior, while the structural and thermodynamic properties change from those resembling HDL to those resembling LDL, due to the *negative* slope of the Widom line. (ii) For the Jagla potential, $D$ changes from Arrhenius to non-Arrhenius while the structural and thermodynamic properties change from those resembling LDL to those resembling HDL, due to the *positive* slope of the Widom line.

Thus these results for bulk water are consistent with the experimental observation in confined water of (i) a fragility transition for $P < P_c$ [27,28], and (ii) a peak in $C_P$ upon cooling water at atmospheric pressure [37], so this work offers a plausible interpretation of the results of Ref. 28 as supporting the existence of a hypothesized liquid-liquid critical point.

## GLASS TRANSITION IN BIOMOLECULES

Next we explore the hypothesis [38] that the observed glass transition in biomolecules [39–52] is related to the liquid-liquid phase transition using molecular dynamics (MD) simulations. Specifically, Kumar et al. [38] studied the dynamic and thermodynamic behavior of lysozyme and DNA in hydration TIP5P water, by means of the software package GROMACS [53] for (i) an orthorhombic form of hen egg-white lysozyme [54] and (ii) a Dickerson dodecamer DNA [55] at constant pressure $P = 1$ atm, several constant temperatures $T$, and constant number of water molecules $N$ (NPT ensemble).

The simulation results for the mean square fluctuations $\langle x^2 \rangle$ of both protein and DNA are shown in Figure 3(a). Kumar et al. calculated the mean square fluctuations $\langle x^2 \rangle$ of the biomolecules from the equilibrated configurations, first for each atom over 1 ns, and then averaged over the total number of atoms in the biomolecule. We find that $\langle x^2 \rangle$ changes its functional form below $T_{\rm p} \approx 245$ K, for *both* lysozyme [Figure 3(a)] and DNA [Figure 3(b)].

Kumar et al. next calculated $C_P$ by numerical differentiation of the total enthalpy of the system (protein and water) by fitting the simulation data for enthalpy with a fifth order polynomial, and then taking the derivative with respect to $T$. Figures 4(a) and 4(b) display maxima of $C_P(T)$ at $T_{\rm W} \approx 250 \pm 10$ K for both biomolecules.

Further, to describe the quantitative changes in structure of hydration water, Kumar et al. calculated the local tetrahedral order parameter $Q$ [56] for hydration water surrounding lysozyme and DNA. Figures 4(c) and 4(d) show that the rate of increase of $Q$ has a maximum at $245 \pm 10$ K for lysozyme and DNA hydration water respectively; the same temperatures of the crossover in the behavior of mean square fluctuations.

Upon cooling, the diffusivity of hydration water exhibits a dynamic crossover from non-Arrhenius to Arrhenius behavior at the crossover temperature $T_\times \approx 245 \pm 10$ K [Figure 4(e)]. The coincidence of $T_\times$ with $T_{\rm p}$ within the error bars indicates that the behavior of the protein is strongly coupled with the behavior of the surrounding solvent, in agreement with recent experiments [39]. Note that $T_\times$ is much higher than the glass transition temperature, estimated for TIP5P as $T_g = 215$K [58]. Thus this crossover is not likely to be related to the glass transition in water.

The fact that $T_{\rm p} \approx T_\times \approx T_{\rm W}$ is evidence of the correlation between the changes in protein

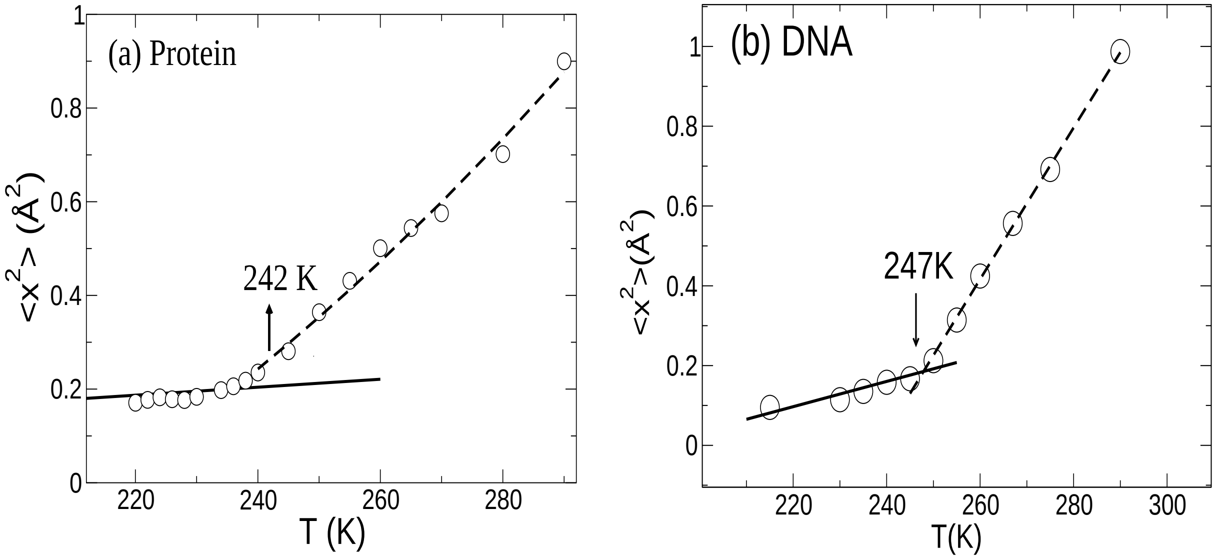

**Figure 3.** Mean square fluctuation of (a) lysozyme, and (b) DNA showing that there is a transition around $T_{\rm p} \approx 242 \pm 10$ K for lysozyme and around $T_{\rm p} \approx 247 \pm 10$ K for DNA. For very low $T$ one would expect a linear increase of $\langle x^2 \rangle$ with $T$, as a consequence of harmonic approximation for the motion of residues. At high T, the motion becomes non-harmonic and we fit the data by a polynomial. We determine the dynamic crossover temperature $T_{\rm p}$ from the crossing of the linear fit for low T and the polynomial fit for high T. We determine the error bars by changing the number of data points in the two fitting ranges.

fluctuations [Figure 3(a)] and the hydration water thermodynamics [Figure 4(a)]. Thus these results are consistent with the possibility that the protein glass transition is related to the Widom line (and hence to the hypothesized liquid-liquid critical point). Crossing the Widom line corresponds to a continuous but rapid transition of the properties of water from those resembling the properties of a local HDL structure for $T > T_{\rm W}(P)$ to those resembling the properties of a local LDL structure for $T < T_{\rm W}(P)$ [32,28]. A consequence is the expectation that the fluctuations of the protein residues in predominantly LDL-like water (more ordered and more rigid) just below the Widom line should be smaller than the fluctuations in predominantly HDL-like water (less ordered and less rigid) just above the Widom line.

The quantitative agreement of the results for both DNA and lysozyme [Figures 3 and 4] suggests that it is indeed the changes in the properties of hydration water that are responsible for the changes in dynamics of the protein and DNA biomolecules. Our results are in qualitative agreement with recent experiments on hydrated protein and DNA [59] which found the crossover in side-chain fluctuations at $T_{\rm p} \approx 225$ K .

## OUTLOOK

It is possible that other phenomena that appear to occur on crossing the Widom line are in fact not coincidences, but are related to the changes in local structure that occur when the system changes from the "HDL-like" side to the "LDL-like" side. In this work we concentrated on reviewing the evidence for changes in dynamic transport properties, such as diffusion constant and relaxation time. Additional examples include: (1) Breakdown of the Stokes-Einstein relation for $T < T_W(P)$ [60–62], (2) Systematic changes in the static structure factor $S(q)$ and the corresponding pair correlation function $g(r)$ revealing that for $T < T_W(P)$ the system more

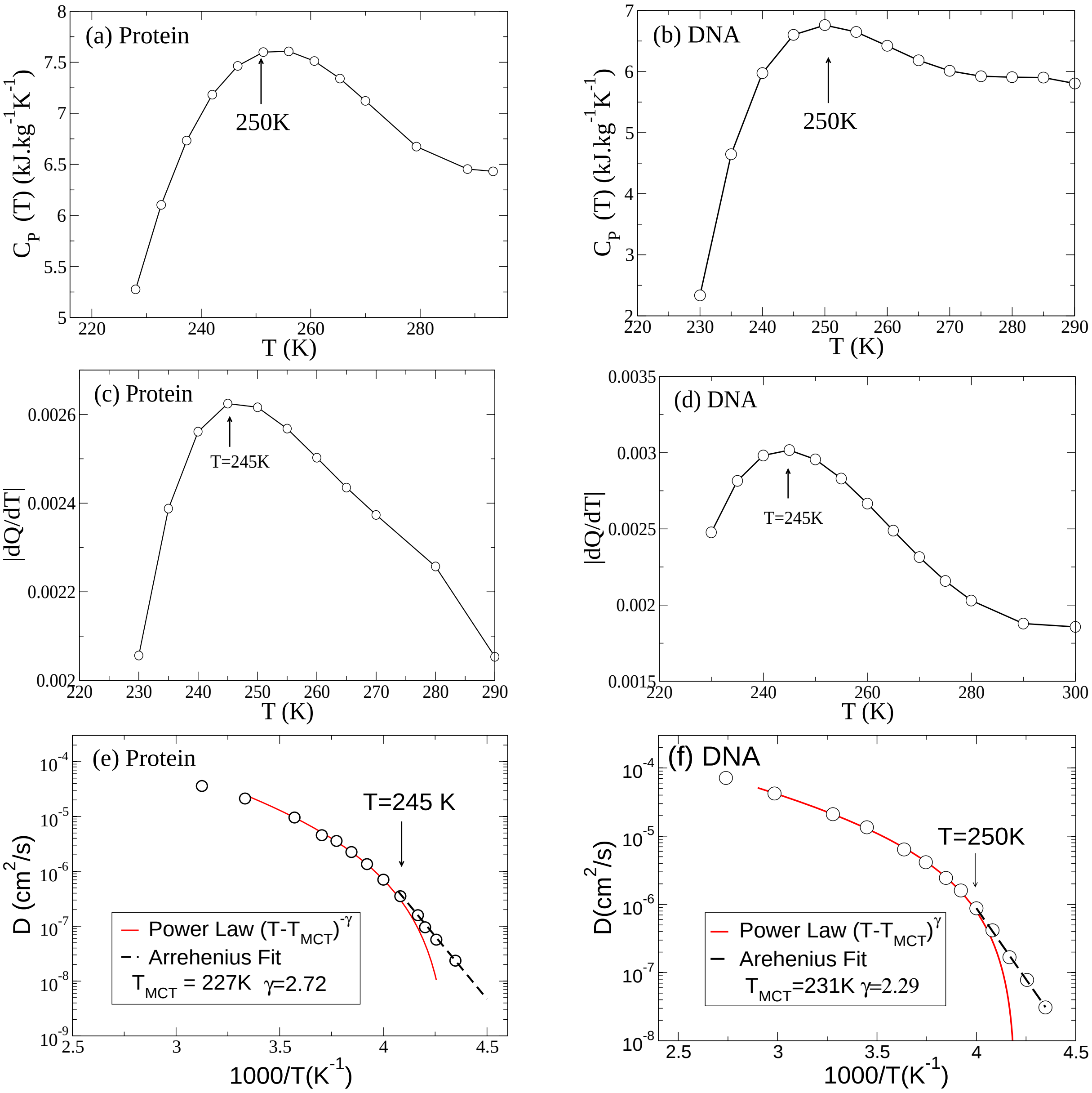

**Figure 4.** The specific heat of the combined system (a) lysozyme and water, and (b) DNA and water, display maxima at $250 \pm 10$ K and $250 \pm 12$ K respectively, which are coincident within the error bars with the temperature $T_{\rm p}$ where the crossover in the behavior of $\langle x^2 \rangle$ is observed in Figure 3. Derivative with respect to temperature of the local tetrahedral order parameter $Q$ for (c) lysozyme and (d) DNA hydration water. A maximum in $|dQ/dT|$ at Widom line temperature suggests that the rate of change of local tetrahedrality of hydration water has a maximum at the Widom line. Diffusion constant of hydration water surrounding (e) lysozyme, and (f) DNA shows a dynamic transition from a power law behavior to an Arrhenius behavior at $T_\times \approx 245 \pm 10$ K for lysozyme and $T_\times \approx 250 \pm 10$ K for DNA, around the same temperatures where the behavior of $\langle x^2 \rangle$ has a crossover, and $C_P$ and $|dQ/dT|$ have maxima.

resembles the structure of LDL than HDL, (3) Appearance for $T < T_W(P)$ of a shoulder in the dynamic structure factor $S(q,\omega)$ at a frequency $\omega \approx 60$ cm$^{-1} \approx 2$ THz, and (4) rapid increase in hydrogen bonding degree for $T < T_W(P)$ [63,64]. It is important to know how general a given phenomenon is, such as crossing the Widom line which by definition is present whenever there is a critical point. Using data on other liquids which have local tetrahedral symmetry, such as silicon and silica, which appear to also display a liquid-liquid critical point and hence must possess a Widom line emanating from this point into the one-phase region. For example, after this work was completed, we learned of interesting new work on silicon, which also interprets structural changes as arising from crossing the Widom line of silicon [65]. It might be interesting to test the effect of the Widom line on simple model systems that display a liquid-liquid critical point, such as two-scale symmetric potentials of the sort recently studied by Xu and collaborators [9].

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## REFERENCES

1. P.G. Debenedetti and H.E. Stanley, “The Physics of Supercooled and Glassy Water,” *Physics Today* **56** [issue 6], 40–46 (2003).
2. P.H. Poole, F. Sciortino, U. Essmann, and H.E. Stanley, “Phase Behavior of Metastable Water,” *Nature* **360**, 324–328 (1992).
3. O. Mishima and H.E. Stanley, “Decompression-Induced Melting of Ice IV and the Liquid-Liquid Transition in Water,” *Nature* **392**, 164-168 (1998).
4. P.G. Debenedetti, *J. Phys.: Condens. Matter* **15**, R1669–R1726 (2003).
5. M.A. Anisimov J.V. Sengers, and J.M.H. Levelt Sengers in ”Aqueous System at Elevated Temperatures and Pressures: Physical Chemistry in Water, Steam and Hydrothermal Solutions,” eds. D.A. Palmer, R. Fernandez-Prini, and A.H. Harvey, (Elsevier, Amsterdam 2004), pp. 29–71.
6. J.M.H. Levelt, in ”Measurements of the compressibility of argon in the gaseous and liquid phase”, *Ph.D. Thesis* (University of Amsterdam, Van Gorkum and Co., Assen, 1958).
7. A. Michels, J.M.H. Levelt, and G. Wolkers, *Physica* **24**, 769–794 (1958).
8. A. Michels, J.M.H. Levelt, and W. de Graaff, *Physica* **24**, 659–671 (1958).
9. L. Xu, S.V. Buldyrev, C.A. Angell, and H.E. Stanley, “Thermodynamics and Dynamics of the Two-Scale Spherically Symmetric Jagla Ramp Model of Anomalous Liquids,” *Phys. Rev. E* **74**, 031108 (2006).
10. F.W. Starr, C.A. Angell, and H.E. Stanley, “Prediction of Entropy and Dynamic Properties of Water below the Homogeneous Nucleation Temperature” *Physica A* **323**, 51–66 (2003).
11. C.A. Angell, *Ann. Rev. Phys. Chem.* **55**, 559–583 (2004).
12. C.A. Angell, *J. Phys. Chem.* **97**, 6339–6341 (1993).
13. P. Kumar, S.V. Buldyrev, F. Starr, N. Giovambattista, and H.E. Stanley, “Thermodynamics, Structure, and Dynamics of Water Confined between Hydrophobic Plates,” *Phys. Rev. E* **72**, 051503 (2005).
14. J. Horbach and W. Kob, *Phys. Rev. B* **60**, 3169–3181 (1999).
15. E.W. Lang and H.D. Lüdemann, *Angew Chem. Intl. Ed. Engl.* **21**, 315-329 (2004).

16. F.X. Prielmeier, E.W. Lang, R.J. Speedy, H.D. Lüdemann, and Ber. Bunsenges, *Phys. Rev. Lett.* **59**, 1128-1131 (1987).
17. K. Ito, C.T. Moynihan, and C.A. Angell, *Nature* **398**, 492-495 (1999).
18. E.A. Jagla, *J. Chem. Phys.* **111**, 8980-8986 (1999).
19. E.A. Jagla, *J. Phys.: Condens. Matter* **11**, 10251-10258 (1999).
20. E.A. Jagla, *Phys. Rev. E* **63**, 061509 (2001).
21. H. Tanaka, *J. Phys.: Condens. Matter* **15**, L703-L711 (2003).
22. G. Adam and J.H. Gibbs, *J. Chem. Phys.* **43**, 139-146 (1965).
23. P.H. Poole, et al., *J. Phys.: Condens. Matter* **17**, L431 (2005).
24. S. Sastry and C.A. Angell, *Nature Materials* **2**, 739-743 (2003).
25. I. Saika-Voivod, P.H. Poole, and F. Sciortino, *Nature* **412**, 514-517 (2001).
26. R. Bergman and J. Swenson, *Nature* **403**, 283–286 (2000).
27. A. Faraone, L. Liu, C.-Y. Mou, C.-W. Yen, and S.-H. Chen, *J. Chem. Phys.* **121**, 10843-10846 (2004).
28. L. Liu, S.-H. Chen, A. Faraone, C.-W. Yen, and C.-Y. Mou, *Phys. Rev. Lett.* **95**, 117802 (2005).
29. G. Franzese, G. Malescio, A. Skibinsky, S.V. Buldyrev, and H.E. Stanley, "Generic mechanism for generating a liquid-liquid phase transition," *Nature* **409**, 692-695 (2001) cond-mat/0102029.
30. F.M. Mallamace, M. Broccio, C. Corsaro, A. Faraone, U. Wanderlingh, L. Liu, C.-Y. Mou, and S.-H. Chen, *J. Chem. Phys.* **124**, 161102 (2006).
31. D.C. Rapaport, in "The Art of Molecular Dynamics Simulation" *(Cambridge University Press, Cambridge)* (1995).
32. L. Xu, P. Kumar, S.V. Buldyrev, S.-H. Chen, P.H. Poole, F. Sciortino, and H.E. Stanley, "Relation between the Widom Line and the Dynamic Crossover in Systems with a Liquid-Liquid Critical Point," *Proc. Natl. Acad. Sci. USA* **102**, 16558–16562 (2005).
33. M.W. Mahoney and W.L. Jorgensen, *J. Chem. Phys.* **112**, 8910-8922 (2000).
34. F.H. Stillinger and A. Rahman, *J. Chem. Phys.* **57**, 1281-1292 (1972).
35. P. Kumar, S.V. Buldyrev, F. Sciortino, E. Zaccarelli, and H.E. Stanley, "Static and Dynamic Anomalies in a Repulsive Spherical Ramp Liquid: Theory and Simulation," *Phys. Rev. E* **72**, 021501 (2005).
36. L. Xu, I. Ehrenberg, S.V. Buldyrev, and H.E. Stanley, "Relationship between the Liquid-Liquid Phase Transition and Dynamic Behavior in the Jagla Model," *J. Phys.: Condensed Matter* **18**, S2239-S2246 (2006).
37. S. Maruyama, K. Wakabayashi, and M. Oguni, *AIP Conf. Proc.* **708**, 675-676 (2004).
38. P. Kumar, Z. Yan, L. Xu, M.G. Mazza, S.V. Buldyrev, S.-H. Chen. S. Sastry, and H.E. Stanley, "Protein Glass Transition and the Liquid-Liquid Critical Point of Water," *Phys. Rev. Lett.* **xx**, xx (2006). http://arxiv.org/abs/cond-mat/0603557.
39. S.-H. Chen, L. Liu, E. Fratini, P. Baglioni, A. Faraone, and E. Mamontov, *Proc. Natl. Acad. Sci. USA*, **103**, 9012 (2006).
40. J.M. Zanotti, M.-C. Bellissent-Funel, and J. Parrello, *Biophys. J.* **76**, 2390 (1999).
41. D. Ringe, G.A. Petsko, *Biophys. Chem.* **105**, 667 (2003).
42. J. Wang, P. Cieplak and P.A. Kollman, *J. Comp. Chem.* **21**, 1049 (2000); E.J. Sorin and V.S. Pande, *Biophys. J.* **88**, 2472 (2005).
43. B.F. Rasmussen, M. Ringe, and G.A. Petsko, *Nature* **357**, 423 (1992).
44. D. Vitkup, D. Ringe, G.A. Petsko, and M. Karplus, *Nat. Struct. Biol.* **7**, 34 (2000).
45. M. Yamada, S. Mossa, H.E. Stanley and F. Sciortino, *Phys. Rev. Lett.* **88**, 195701 (2002).
46. A.P. Sokolov, H. Grimm, A. Kisliuk and A.J. Dianoux, *J. Chem. Phys.* **110**, 7053 (1999).

47. W. Doster, S. Cusack, and W. Petry, *Nature* **338**, 754 (1989).
48. J. Norberg and L. Nilsson, *Proc. Natl. Acad. Sci. USA* **93**, 10173 (1996).
49. M. Tarek and D.J. Tobias, *Phys. Rev. Lett.* **88**, 138101 (2002); *Biophys. J.* **79**, 3244 (2000).
50. H. Hartmann, F. Parak, W. Steigemann, G.A. Petsko, D.R. Ponzi, H. Frauenfelder, *Proc. Natl. Acad. Sci. USA* **79**, 4067 (1982).
51. A.L. Tournier, J. Xu, and J.C. Smith, *Biophys. J.* **85**, 1871 (2003).
52. A.L. Lee and A.J. Wand, *Nature* **411** 501 (2001).
53. E. Lindahl, B. Hess, and D. van der Spoel, *J. Molecular Modeling* **7**, 306 (2001).
54. P.J. Artymiuk, C.C.F. Blake, D.W. Rice, K.S. Wilson, *Acta Crystallogr* **B 38**, 778 (1982).
55. H.R. Drew, R. M. Wing, T. Takano, C. Broka, S. Tanaka, K. Itakura and R.E. Dickerson, *Proc. Natl. Acad. Sci. USA* **78**, 2179 (1981).
56. J.R. Errington and P.G. Debenedetti, *Nature* **409**, 318 (2001).
57. J. Wang, P. Cieplak and P.A. Kollman, *J. Comp. Chem.* **21**, 1049 (2000).
58. I. Brovchenko, A. Geiger, and A. Oleinikova, *J. Chem. Phys.* **123**, 044515 (2005).
59. S.-H. Chen, L. Liu, X. Chu, Y. Zhang, E. Frattini, P. Baglioni, A. Faraone, and E. Mamontov, *Phys. Rev. Lett.* submitted.
60. P. Kumar, "Breakdown of the Stokes-Einstein relation in supercooled water," *Proc. Nat. Acad. Sciences* **103**, 12955-12956 (2006).
61. P. Kumar, S.V. Buldyrev, and H.E. Stanley (preprint).
62. S.-H. Chen et al., "The violation of the Stokes-Einstein relation in supercooled water," *Proc. Nat. Acad. Sciences* **103**, 12974-12978 (2006)
63. P. Kumar, G. Franzese, and H.E. Stanley, "Effects on the Hydrogen Bond Network of Crossing the Widom Line" (preprint).
64. P. Kumar, S.V. Buldyrev, and H.E. Stanley, "Dynamic Crossover and Liquid-Liquid Critical Point in the TIP5P Model of Water," in *Soft Matter under Extreme Pressures: Fundamentals and Emerging Technologies* Editors: Sylwester J. Rzoska, Victor Mazur [Proc. NATO ARW, Odessa, Oct. 2005] (Springer, Berlin, 2006).
65. T. Morishita, "How does tetrahedral structure grow in liquid silicon on supercooling?", *Phys. Rev. Lett.* **97**, 165502 (2006).