First-Order Disorder-to-Order Transition in an Isolated Homopolymer Model

Yaoqi Zhou,[1] Carol K. Hall,[2] and Martin Karplus[1]
[1]*Chemistry Department, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138*
[2]*Department of Chemical Engineering, North Carolina State University, Raleigh, North Carolina 27695-7905*

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The thermodynamic behavior of an isolated freely jointed homonuclear square-well 64mer chain is studied by discontinuous molecular dynamics simulations. It is shown that there are three transitions that can be described as gas-liquid, liquid-solid, and solid-solid polymorphic transitions. The liquid-solid-like transition is a first-order (two-state) disorder-to-order transition. Implications of the results for protein folding are briefly discussed. [S0031-9007(96)01199-4]

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Although isolated homopolymer thermodynamics is dominated by the second-order (except for stiff chains) coil to globule transition (at the Θ point) [1–3], the possible existence of more complex behavior has been suggested by theory [4] and experiments [5,6]. So far, such complex behavior has not been observed in homopolymer simulations except for relatively esoteric lattice chain models [7–9]. In this Letter, we show that a simple off-lattice model of an isolated finite homopolymer chain can have gas-liquid, liquid-solid, and solid-solid polymorphic transitions. Moreover, the liquid-solid-like transformation is found to be a first-order-like transition.

The homopolymer is modeled as a freely jointed square-well chain in which nonbonded beads i and j interact via a square-well potential

$$u_{ij}(r) = \begin{cases} \infty, & r < \sigma\,, \\ -\epsilon, & \sigma < r < \lambda\sigma\,, \\ 0, & r > \lambda\sigma\,. \end{cases} \tag{1}$$

Bonded beads i and $i + 1$ interact via an infinitely deep square-well potential

$$u_{i,i+1}^{\text{bond}}(r) = \begin{cases} \infty, & r < (1-\delta)\sigma\,, \\ 0, & (1-\delta)\sigma < r < (1+\delta)\sigma\,, \\ \infty, & r > (1+\delta)\sigma\,. \end{cases} \tag{2}$$

Here, σ is the bead hard-core diameter, $\lambda\sigma$ is the square-well diameter, and ϵ is the square-well depth. The bond length between two neighboring beads is allowed to vary freely between $(1-\delta)\sigma$ and $(1+\delta)\sigma$ with δ the bond-length-flexibility parameter. A flexible bond length is introduced to decouple multibody collisions into binary collisions between monomer beads or between a monomer bead and a solvent particle in the molecular dynamics simulation [10].

The square-well chain model of length 64 (64mer) with bond-length-flexibility parameter $\delta = 0.1$ is investigated via a discontinuous molecular dynamics (DMD) simulation technique [11]. We use DMD because it is significantly faster than the corresponding Lennard-Jones (LJ) polymer dynamics [12]. The DMD simulation is conducted in the canonical ensemble with the system temperature fixed by Andersen's ghost-solvent method [13]. Details of the simulations will be reported elsewhere [14]. The code was verified by comparing the thermodynamics obtained from simulations with exact results on an isolated flexibly bonded trimer [15]. The 95% confidence limit (student-T test) for averages is obtained based on five independent runs of $(6-1000) \times 10^6$ collisions, of which the first half of the DMD collision events (equilibration) is discarded. We use a square-well diameter $\lambda\sigma = 1.5\sigma$ since the reduced square-well diameter λ for real molecules is around 1.4 based on fitting experimental second-virial coefficients [16].

In this Letter, we describe the thermodynamics. Homopolymer transitions are often characterized by the mean-squared radius of gyration, R_g^2 [2]. However, the radius of gyration may not provide useful information on the possibility of a liquid-solid-like and/or a polymorphic solid-solid transition during which the variation in the radius of gyration of an isolated chain is very small. Liquid-solid-like and/or polymorphic transitions can be investigated via the temperature dependence of thermodynamic properties such as the internal energy E and the heat capacity C_v. The reduced internal energy E^* for an isolated chain is obtained by taking the time average over the equilibrium DMD simulation and the reduced heat capacity C_v^* is obtained from the energy fluctuations according to [17]

$$E^* = \frac{\langle E\rangle_t}{\epsilon}\,, \qquad C_v^* = \frac{C_v}{k_B} = \frac{(\langle E^2\rangle_t - \langle E\rangle_t^2)}{(k_B T)^2}\,, \tag{3}$$

where $\langle\,\rangle_t$ denotes a time average.

In Fig. 1, the reduced heat capacity C_v^* per bead, the reduced internal energy E^* per bead, and the reduced squared radius of gyration R_g^2/σ^2 per bead of an isolated 64mer are shown as functions of reduced temperature ($T^* = k_B T/\epsilon$). These results are obtained via averaging over 3×10^6 to 600×10^6 (depending on T^*) equilibrium collisions per run. For $T^* < 0.35$, it is found necessary to anneal the random initial configuration from high temperature before conducting an equilibrium simulation [14]. For comparison, Monte Carlo (MC) simulation results [14] for an isolated freely jointed 64mer

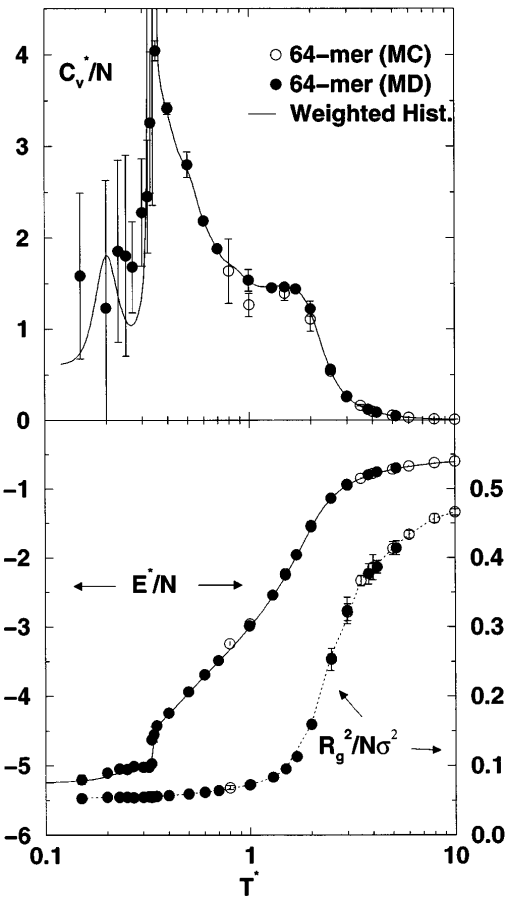

FIG. 1. The reduced heat capacity per bead C_v^*/N, the reduced internal energy per bead E^*/N, and the reduced squared radius of gyration per bead $R_g^2/N\sigma^2$, as a function of reduced temperature T^* for an isolated square-well 64mer. For comparison, the Monte Carlo simulation results [14] for an isolated square-well 64mer with fixed bond length are also shown; the square-well diameter $\lambda\sigma = 1.5\sigma$ was used. Error bars are less than the size of the points except as shown. The solid lines are obtained from a weighted histogram technique [36]. Dashed line for R_g^2 serves only as a guide for the eye.

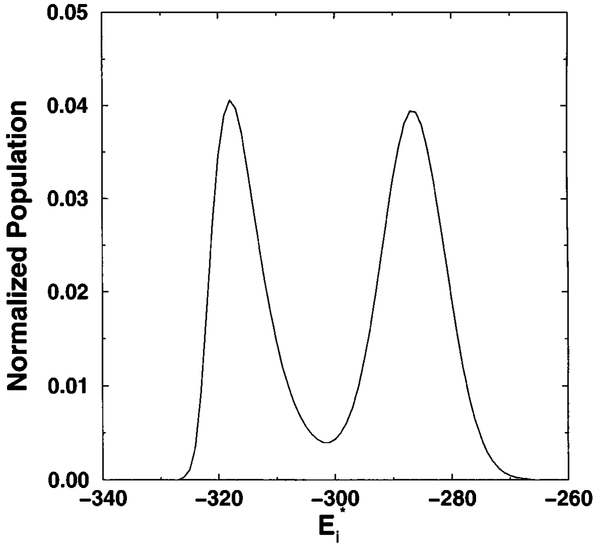

FIG. 2. The population of different energy level E_i at the transition temperature $T_c^* = 0.336$ obtained via the weighted histogram technique [36]. Other parameters as in Fig. 1.

with fixed bond length are also shown for $0.8 < T^* < 10$. The sigmoidal shape of the $R_g^2/N\sigma^2$ vs temperature curve indicates the presence of a collapse transition with a Θ temperature of $T_\Theta^* \approx 3$ [14,18]. The collapse transition is also indicated by a heat capacity vs temperature peak at $T^* = 1.5$ which is a very weak peak (or plateau) in the DMD results and a stronger peak in MC results. As the temperature decreases further, $R_g^2/N\sigma^2$ becomes nearly constant (around 0.05) and there is no indication of any other transition. However, a first-order transition is indicated by the appearance of a "discontinuity" [19] at $T^* = 0.336$ in E^*. This discontinuity $[E^*(T^* = 0.34) - E^*(T^* = 0.32) \approx 0.5N]$ is accompanied by a very large ("infinite") peak in the heat capacity ($C_v^* \sim 30N$ at $T^* = 0.33$ and 0.34 in certain runs). The first-order transition is verified by the appearance of two separate peaks in the energy population (Fig. 2) and the existence of two stable states with different internal energies at the transition temperature $T_c^* = 0.336$ [14].

To examine the nature of the first-order transition, we calculate the root-mean-square bead-distance fluctuation [20] which is defined as

$$\Delta = \frac{2}{N(N-1)} \sum_{i<j} \frac{\sqrt{(\langle r_{ij}^2\rangle_{cf} - \langle r_{ij}\rangle_{cf}^2)}}{\langle r_{ij}\rangle_{cf}} . \qquad (4)$$

[Δ as defined here contains a negligible contribution from bonded beads ($\sim 2\delta/N = 0.003$).] The value of Δ drops from 0.28 at $T^* = 0.34$ to 0.05 at $T^* = 0.32$. Since $\Delta < 0.1$ indicates a solid phase (Lindemann rule) [21,22], the first-order transition observed is a disorder-to-order transition, similar to the liquid-solid transition in an infinite system. The liquid-solid-like transition in the homopolymer is confirmed by other quantities such as radial and angle distribution functions [14].

The "solid" structure of the 64mer at $T^* = 0.32$ is a rather well-ordered three-dimensional lattice which mixes hexagonal and cubic lattice symmetry (see Fig. 3). This occurs because there is an accidental degeneracy for $\lambda = 1.5$ with the beads arranged in a square having the same energy as the beads arranged in hexagon. The simple lattice structure undergoes a continuous polymorphic solid-solid transition (Fig. 1) into a more spherically shaped structure which has less symmetry but a lower energy as the temperature decreases further. This polymorphic transition may be categorized as a displacive polymorphic transition [23], in which the low-temperature structure is more ordered (with a lower entropy) but has a lower symmetry than the high-temperature structure.

Thus, the isolated square-well 64mer can exhibit three thermodynamic transitions. The first one is the well-

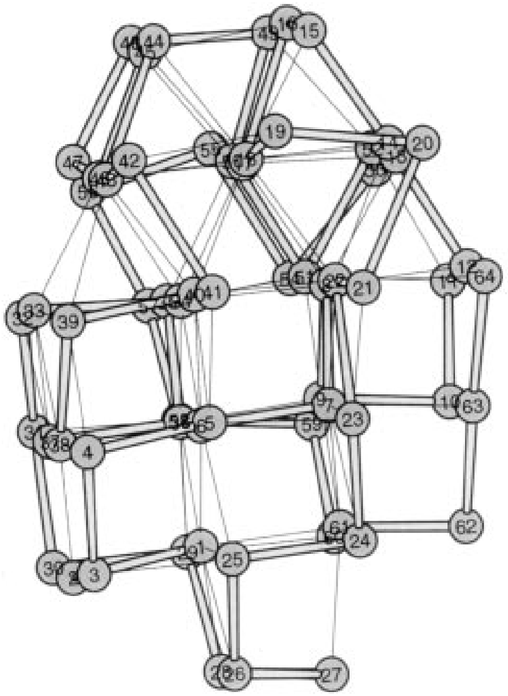

FIG. 3. A typical snapshot of the 64mer at $T^* = 0.32$. The diameter of beads (0.16) is smaller than the actual diameter (1) for a clear view. (This structure is drawn by ASGL, a program developed by A. Šali.)

known collapse transition which is similar to a gas-liquid transition [24]; the collapse transition and the gas-liquid transition both involve significant volume changes. The second transition is a liquid-solid-like disorder-order transition and the third transition is a polymorphic transition from a compact lattice to a compact ordered globule. Consequently, an isolated homopolymer can exist in at least four states: a random coil ("gas"), a disordered compact chain or disordered molten globule ("liquid"), a lattice ("solid I"), and an ordered globule ("solid II").

One question about the complex homopolymer phase diagram presented here is whether it is caused by the discontinuous feature of the square-well potential. We cannot give a direct answer because the DMD simulation is required to obtain well-converged results for the thermodynamics. However, the critical phenomena predicted for a fluid composed of particles interacting with a square-well potential [25] are as realistic as those predicted for a fluid composed of particles interacting with a LJ potential. Also an analogous complex phase diagram is found in simulations of LJ clusters [26,27]. The present results for square-well homopolymers may well be found in more realistic homopolymer models and even in real polymers.

It is of interest to compare the homopolymer thermodynamics with protein folding. It has been shown experimentally [28] that as a function of temperature (or other solution conditions, e.g., pH), a single protein molecule can exist in a denatured state (random coil), a collapsed globule state (which may have some order), and the unique native state; the latter has solidlike properties [29] and has been described as an aperiodic crystal by Schrödinger [30]; i.e., there is no long-range order in the unique structure, although short-range structural regularities (e.g., α-helices) are found and have been well characterized [31]. The gas to liquidlike collapse transition in the homopolymer corresponds to the hydrophobic collapse to a disordered globule found in at least some proteins [32] and observed as the first step in some lattice simulations of protein folding [33]. The liquid-to-solid transition in the homopolymer can be identified with the collapsed globule to native state transition in the protein. Both are finite-system first-order-like transitions in the sense that two states are involved with a low probability region in between [32]. With this identification, the major difference between a protein and the homopolymer studied here would be that the former has a solidlike ground state that is unique due to the heterogeneity introduced by the amino acid side chains, while the latter has a multiplicity of essentially equivalent solidlike states and exhibits a polymorphism [34], which is very unusual in proteins [35], if it exists at all.

The phase behavior of proteins and homopolymers appears to be qualitatively similar. As in the protein molten globule [28], the radius of gyration in the liquid state of the 64mer is only about 15% larger than that in the solidlike states. The "liquid" state is stable over a wide temperature range (T^* from 0.33 to $\sim$1; see Fig. 1). In terms of the physical temperature, a homopolymer whose liquid-to-solid transition occurs at 300 K does not unfold into a random coil until 900 K. This corresponds to the fact that protein thermal denaturation in the accessible temperature range produces collapsed species [28].

In future publications, we shall present the details of this work and its extension to the kinetics of homopolymers. DMD simulations of analogous heteropolymer systems with unique proteinlike ground states are in progress.

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[1] P. J. Flory, *Principles of Polymer Chemistry* (Cornell Univ. Press, Ithaca, London, 1953).
[2] P. G. de Gennes, *Scaling Concepts in Polymer Physics* (Cornell Univ. Press, Ithaca, 1979).
[3] H. S. Chan and K. A. Dill, Annu. Rev. Biophys. Biophys. Chem. **20**, 447 (1991).
[4] I. M. Lifshitz, A. Y. Grosberg, and A. R. Khokhlov, Rev. Mod. Phys. **50**, 683 (1978).
[5] B. Chu, Q. Ying, and A. Y. Grosberg, Macromolecules **28**, 180 (1995).
[6] E. I. Tiktopulo *et al.*, Macromolecules **28**, 7519 (1995).
[7] E. Orlandini, F. Seno, A. L. Stella, and M. Tesi, Phys. Rev. Lett. **68**, 488 (1992).
[8] R. Bradley, Phys. Rev. E **48**, R4195 (1993).
[9] Y. A. Kuznetsov, E. Timoshenko, and K. A. Dawson, J. Chem. Phys. **104**, 336 (1996).
[10] A. Bellemans, J. Orban, and D. V. Belle, Mol. Phys. **39**, 781 (1980).
[11] M. P. Allen and D. J. Tildesley, *Computer Simulation of Liquids* (Oxford University Press, Oxford, 1987), p. 348.
[12] J. Liu, T. L. Bowman II, and J. R. Elliott, Jr., Ind. Eng. Chem. Res. **33**, 957 (1994).
[13] H. C. Andersen, J. Chem. Phys. **72**, 2384 (1980).
[14] Y. Zhou, M. Karplus, J. M. Wichert, and C. K. Hall (to be published).
[15] Y. Zhou and M. Karplus, Mol. Phys. (to be published).
[16] A. E. Sherwood and J. M. Prausnitz, J. Chem. Phys. **41**, 429 (1964).
[17] H. L. Friedman, *A Course in Statistical Mechanics* (Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1985).
[18] J. Wichert and C. K. Hall, Macromolecules **27**, 2744 (1994).
[19] For a finite system, a discontinuity reflects a smooth transition in a very narrow temperature range.
[20] R. S. Berry, T. L. Beck, H. L. Davis, and J. Jellinek, Adv. Chem. Phys. **70B**, 75 (1988).
[21] F. A. Lindemann, Phys. Z. **11**, 609 (1910).
[22] L. Cartz, Proc. Phys. Soc. London Sect. B **68**, 957 (1955).
[23] M. J. Buerger, in *Phase Transformations in Solids*, edited by R. Smoluchowski, J. E. Meyer, and W. A. Weyl (John Wiley & Sons, Inc., New York, 1951).
[24] O. B. Ptitsyn, A. K. Kron, and Y. Y. Eizner, J. Polym. Sci. C **16**, 3509 (1968).
[25] L. Vega *et al.*, J. Chem. Phys. **96**, 2296 (1992).
[26] D. D. Frantz, J. Chem. Phys. **102**, 3747 (1995).
[27] R. E. Kunz and R. S. Berry, Phys. Rev. Lett. **71**, 3987 (1993).
[28] O. B. Ptitsyn, Adv. Protein Chem. **47**, 83 (1995).
[29] F. M. Richards and W. A. Lim, Q. Rev. Biophys. **26**, 423 (1993).
[30] E. Schrödinger, *What Is Life?: The Physical Aspect of the Living Cells* (Cambridge Univ. Press, Cambridge, New York, 1944).
[31] G. E. Schulz and R. H. Schirmer, *Principles of Protein Structure* (Springer-Verlag, New York, 1979).
[32] K. A. Dill and D. Stigter, Adv. Protein Chem. **46**, 59 (1995).
[33] A. Šali, E. I. Shakhnovich, and M. Karplus, Nature (London) **369**, 248 (1994).
[34] The existence of polymorphism in the homopolymer may depend on the square-well diameter and the chain length. See Ref. [14].
[35] D. Westaway *et al.*, Proc. Natl. Acad. Sci. U.S.A. **91**, 6418 (1994).
[36] A. M. Ferrenberg and R. H. Swendsen, Phys. Rev. Lett. **63**, 1195 (1989).