

Conformational transitions in random heteropolymer models

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We study the conformational properties of heteropolymers containing two types of monomers A and B , modeled as self-attracting self-avoiding random walks on a regular lattice. Such a model can describe in particular the sequences of hydrophobic and hydrophilic residues in proteins [K. F. Lau and K. A. Dill, *Macromolecules* **22**, 3986 (1989)] and polyampholytes with oppositely charged groups [Y. Kantor and M. Kardar, *Europhys. Lett.* **28**, 169 (1994)]. Treating the sequences of the two types of monomers as quenched random variables, we provide a systematic analysis of possible generalizations of this model. To this end we apply the pruned-enriched Rosenbluth chain-growth algorithm, which allows us to obtain the phase diagrams of extended and compact states coexistence as function of both the temperature and fraction of A and B monomers along the heteropolymer chain.
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I. INTRODUCTION

Many polymers encountered in chemical and biological physics can be considered as long flexible chains of linear architecture. In the good solution regime, where the steric hard-core repulsions between monomers are dominant, a typical polymer chain usually attains a coil-like conformation. In this regime, the size measures of a typical N -monomer chain such as the mean-square end-to-end distance $\langle R_e^2 \rangle$ or the mean-square radius of gyration $\langle R_g^2 \rangle$ obey scaling laws:¹⁻³

$$\langle R_e^2 \rangle \sim \langle R_g^2 \rangle \sim N^{2\nu_{\text{coil}}},$$

with the universal self-avoiding walk exponent $\nu_{\text{coil}} = 0.587597(7)$ in three dimensions.⁴ At temperatures below the so-called Θ -point, the polymer radius shrinks, which causes the collapse transition into the compact globule-like conformation regime. Exactly at the Θ -temperature, the macromolecules in three dimensions behave like an ideal Gaussian chain (up to logarithmic corrections) with size exponent $\nu_{\Theta} = 1/2$.

The conformational properties of long flexible polymer chains in the vicinity of the Θ -point are perfectly captured within the lattice model of self-attracting self-avoiding walks (SASAWs).⁵⁻¹² Here, each monomer is treated as a point particle on a regular lattice, and interactions are restricted to an attractive coupling $\varepsilon_{ij} = -1$ between non-bonded monomers i and j occupying nearest-neighbor sites. This takes solvent effects implicitly into account.

A subject of great interest is the study of conformational transitions of heteropolymer chains, containing monomers of essentially different chemical nature. Typical examples are proteins, consisting of sequences of amino acid residues, connected by peptide bonds. One of the ways to analyze this

problem is via a generalization of the SASAW model by assuming interaction energies ε_{ij} of all pairs of monomers along the chain to be independent identically distributed quenched random variables (so-called random-bond model¹³⁻¹⁵). This in particular allows an analytic description of the thermodynamics of heteropolymers within the random-energy model developed by Derrida¹⁶ for the theory of spin glasses. In Ref. 17, a modification of this model was proposed, where the energies of different states are random variables but may take only discrete values. However, more realistic is the case where the interaction energies are determined by the underlying monomer sequence. For simplicity, we will focus on copolymers, when there are only two distinct types of monomers: N_A monomers of type A and correspondingly $N_B = N - N_A$ monomers of type B . One distinguishes between the “sequence space” (the set of all possible sequences of A and B residues along the chain) and the “conformational space” (the set of all possible internal conformations of a chain due to different bond orientation, taken at fixed sequence of A and B). It is convenient to introduce the parameter $c \equiv N_A/N$ (fraction of A monomers), so that $c = 1$ (0) corresponds to the limiting case of homogeneous chains with all monomers of type A (B). In the following we shall focus on the following five cases:

$$\text{HP model : } \varepsilon_{AA} = -1, \varepsilon_{BB} = \varepsilon_{AB} = 0, \quad (1)$$

$$\text{Symmetrized HP (SHP) model : } \varepsilon_{AA} = \varepsilon_{BB} = -1, \varepsilon_{AB} = 1, \quad (2)$$

$$\text{Polyampholyte (PA) : } \varepsilon_{AA} = \varepsilon_{BB} = 1, \varepsilon_{AB} = -1, \quad (3)$$

$$\text{Polyelectrolyte (PE) : } \varepsilon_{AA} = 1, \varepsilon_{BB} = \varepsilon_{AB} = 0, \quad (4)$$

$$\text{Antisymmetrized (AS) model : } \varepsilon_{AA} = -1, \varepsilon_{BB} = 1, \varepsilon_{AB} = 0. \quad (5)$$

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Case (1) refers to the (minimal) HP model, proposed in Ref. 18 to describe protein folding. In general, the constituents (monomers) of macromolecules in an aqueous environment can be characterized as hydrophilic (polar) or hydrophobic, depending on their chemical structure. Hydrophilic residues (B) tend to form hydrogen bonds with surrounding water molecules, whereas the hydrophobic monomers (A) effectively attract each other and tend to form a dense hydrophobic core. Despite its simplicity, this model (and its off-lattice “AB” model variant) catches the main thermodynamic features of real proteins, allowing to explore the full conformational and sequence spaces of macromolecules by powerful numerical methods, and thus still attracts attention of researchers.^{19–36} The thermodynamics and ground-state search for various HP sequences were analyzed specifically, either representing real proteins (e.g., a 103-mer for cytochrome²¹) or just some model cases (like Fibonacci sequences^{22,26}). The largest sequence explored systematically so far is a 136mer.²³ In general, the ability of the chain to fold into a compact state was found to be dependent both on the composition (the fraction of residues of each type) and on the sequence of residues.

The related case (2) is the standard SHP model for copolymers with monomers that have a tendency to segregate.³⁷ In Ref. 28, the thermodynamic properties of copolymers with correlated sequences were analyzed analytically, using an approach based on the cavity method as used in various frustrated systems. It was shown that heteropolymers possess different dense phases depending upon the temperature, the nature of the monomer interactions, and the sequence correlation.

The situation (3), when the like monomers repel and the opposite ones attract each other, may refer to the model of randomly charged polyampholytes:^{38,39} heteropolymers, comprising both positively and negatively charged monomers. Typical examples of polyampholytes are synthetic copolymers bearing acidic and basic repeat groups. In general, the long-range nature of the electrostatic Coulomb interaction between charged groups produces crucial effects on macromolecule properties and leads to an extremely rich conformational behavior, strongly dependent both on their overall charge Q and the quality of solvent (and thus on temperature T).^{40–48} If positive and negative charges are almost balanced (Q is small), the attractive Coulomb interaction dominates, and the polymer collapses into a globular (sphere-like) state at low temperatures. If the energy of the electrostatic interactions prevails the globular surface energy, which happens when the excess charge Q approaches $Q_c \sim N^{1/2}$, the molecules split into extended necklace-like conformations of small connected globules. In the high-temperature regime but small Q (predominant electrostatic attraction), the PA forms globule-like structures, whereas at the critical value of the excess charge $Q_c \sim N^{1/2}$ the charged polymer attains the shape of a neutral polymer coil. Polyampholytes with considerable disbalance between positive and negative charges ($Q > Q_c$) and thus predominant Coulomb repulsion are expected to attain a stretched rod-like configuration. The simplified PA model with strongly screened (short-range) Coulomb interactions in the form (3) has been studied previously in Ref. 49.

Here, for each c value at fixed total length of the chain, the various possible sequences have been constructed, and quenched sequence averaging for thermodynamic observables was performed. In such a way, the phase diagram of extended and compact state coexistence has been constructed as function of both the temperature and the fraction of residues of each type.

The situation (4) may describe polyelectrolytes:^{38,39} heteropolymers, comprising some fraction of charged monomers of the same sign with strongly screened Coulomb interactions. A transition into the compact state cannot be reached for these systems.

The case (5) could be viewed as an additional generalization of above models, comprising an interplay between different kinds of short-range interactions.

In the present work, we aim to extend the picture, developed in Ref. 49 for the PA model to the whole range of cases (1)–(5); namely, to treat different sequences of A and B monomers at given fixed fraction c (ranging from 0 to 1) as different realizations of quenched disorder, and to obtain observables of interest after performing double conformation and sequence averaging. Thus, we will obtain a systematic picture of conformational transitions from extended into compact state in models (1)–(5) in the form of phase diagrams as function of the fraction c of A monomers and temperature T . In particular, this allows us to compare the properties of HP-like models and models of charged polymer chains with strongly screened Coulomb interaction directly within the same approach.

The layout of the rest of the paper is as follows: in the next Sec. II we briefly describe the pruned-enriched Rosenbluth method, applied in our study. The results obtained are given in Sec. III. We end up by giving conclusions and an outlook in Sec. IV.

II. METHOD

To study the conformational properties of models (1)–(5), we apply the pruned-enriched Rosenbluth method (PERM).¹¹ The chain grows step by step, i.e., the n th monomer is placed at a randomly chosen neighbor site of the last placed ($n - 1$)th monomer ($n \leq N$). The growth is stopped, if the total length of the chain, N , is reached (we consider chains of length up to $N = 100$). The total energy of a chain $E(N)$ is given by

$$E(N) = \sum_{i=1}^N \sum_{j=i+2}^N \varepsilon_{ij} \sigma_{ij}, \quad (6)$$

where each i and j is either of the type A or B , correspondingly ε_{ij} is 1, -1 , or 0 depending on the model, and $\sigma_{ij} = 1$ if monomers i and j are nearest neighbors and zero otherwise. The Rosenbluth weight factor W_n of an n -step trajectory is thus taken to be¹¹

$$W_n = e^{-\frac{E(n)}{k_B T}} \prod_{l=2}^n m_l, \quad (7)$$

where m_l is the number of free lattice sites to place the l th monomer and k_B is the Boltzmann constant. In what follows, we will assume units in which $k_B = 1$.

Pruning and enrichment are performed by choosing thresholds $W_n^<$ and $W_n^>$ depending on the current estimate of the sum of weights $Z_n = \sum_{\text{conf}} W_n^{\text{conf}}$ of the n -monomer chain.^{11,27,50} If the current weight W_n of an n -monomer chain is less than $W_n^<$, the chain is discarded with probability 1/2, whereas if W_n exceeds $W_n^>$, the configuration is doubled (enrichment of the sample with high-weight configurations). We adjust the pruning-enrichment control such that at least 10 chains are generated per each iteration tour and perform 10^6 tours.

When studying random heteropolymers, a double averaging has to be performed to receive the quantitative value for any observable. At first, the conformational averaging of any observable O is performed over an ensemble of possible conformations of a macromolecule with a fixed sequence of A and B monomers for a given fraction of A monomers along the chain:

$$\langle O \rangle = \frac{\sum_{\text{conf}} W_N^{\text{conf}} O}{\sum_{\text{conf}} W_N^{\text{conf}}}, \quad (8)$$

where W_N^{conf} is the weight of an N -monomer chain in a given conformation. The second is the “sequence average” $\overline{\langle \dots \rangle}$, which is carried out over different random sequences of A and B monomers for a given c value:

$$\overline{\langle O \rangle} = \frac{1}{M} \sum_{i=1}^M \langle O \rangle_i. \quad (9)$$

Here, M is the number of different sequences and the index i means that a given quantity is calculated for sequence i . Note that the number M of all possible sequences of an N -monomer chain at fixed fraction c of A monomers, $N_A = cN$, is given by

$$M = \frac{N!}{(cN)!(N - (cN))!},$$

which becomes incredibly large with growing of N , especially with c close to 0.5. In our calculations, we consider up to $M = 2500$ random sequences at given fraction c ; this, however, leads to reasonable results as is shown by comparison with some phenomenological predictions (see below). Note that the case of so-called “quenched disorder” is considered, where the average over different sequences is taken after the configurational average has been performed.

III. RESULTS

Estimates for the averaged energy of heteropolymer models (1)–(5) can be obtained based on the following considerations. Let us introduce the averaged number of nearest-neighbor contacts $p(d)$ for any monomer of a chain, which in d dimensions can be estimated from the empirical relation:

$$z(d) = 2d - 1 - p(d), \quad (10)$$

where $z(d)$ is the connectivity constant (averaged number of possibilities to make the next step in a growing SAW trajectory). For an idealized Gaussian chain, when the trajectory is allowed to cross itself, for the case of a regular d -dimensional lattice one has $z(d) = 2d$. Taking into account self-avoidance effect, one first of all forbids the “turning back” of the trajectory at each step, which reduces the connectivity constant to the value $2d - 1$. Finally, another factor which reduces the connectivity constant at each step due to the self-avoidance effect, is the number of nearest sites, already visited by the trajectory (number of contacts with nearest neighbors $p(d)$). Having a heterogeneous polymer chain in $d = 3$ with fixed fraction c (so that $N_A = N \cdot c$, $N_B = N \cdot (1 - c)$), we can estimate the number of AA nearest-neighbor contacts:

$$n_{AA} = \frac{1}{2} N_A p(d=3)c = \frac{1}{2} N p(d=3)c^2, \quad (11)$$

the number of BB nearest-neighbor contacts:

$$n_{BB} = \frac{1}{2} N_B p(d=3)(1-c) = \frac{1}{2} N p(d=3)(1-c)^2 \quad (12)$$

and the number of AB nearest-neighbor contacts:

$$n_{AB} = N_A p(d=3)(1-c) = N p(d=3)c(1-c). \quad (13)$$

Thus, for the total energies of models (1)–(5) we have correspondingly:

$$E_{HP} = -n_{AA} = -\frac{1}{2} N p(d=3)c^2, \quad (14)$$

$$\begin{aligned} E_{SHP} &= -n_{AA} - n_{BB} + n_{AB} \\ &= -2N p(d=3) \left(c^2 - c + \frac{1}{4} \right), \end{aligned} \quad (15)$$

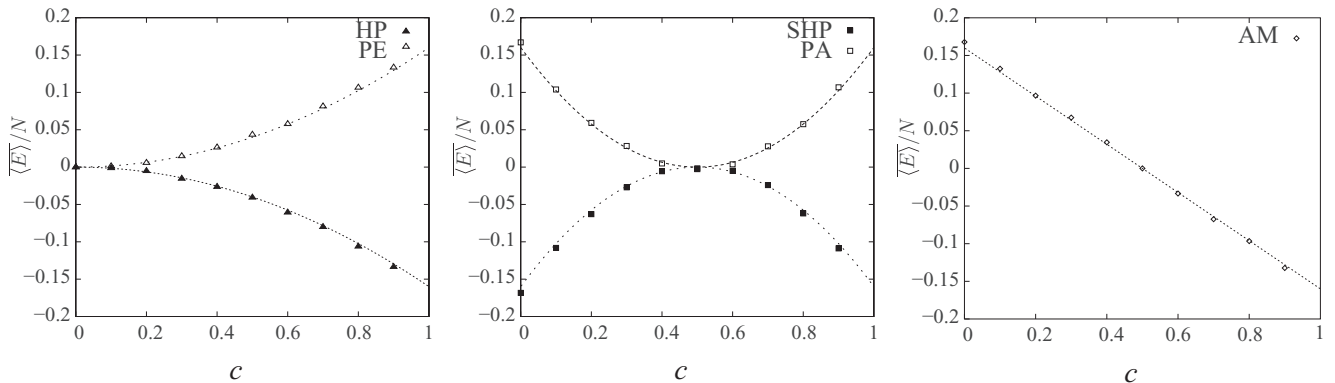


FIG. 1. The averaged energy per monomer of an $N = 100$ -monomer heterogeneous chain in the high-temperature regime with various types of intramonomer interaction as function of fraction c of A monomers. Lines are the corresponding results of empirical estimations (14)–(18).

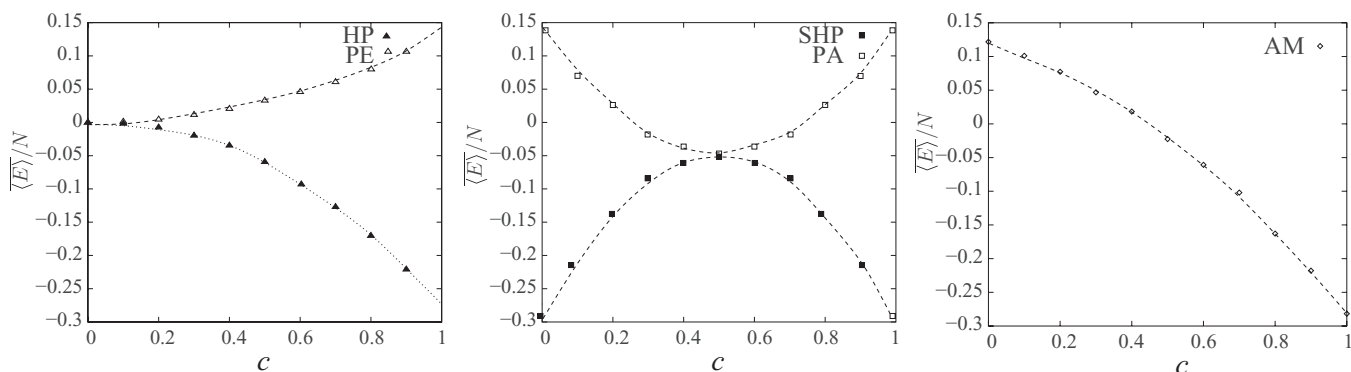


FIG. 2. The averaged energy per monomer of an $N = 100$ -monomer heterogeneous chain with various types of intramonomer interaction as function of fraction c of A monomers at temperature $T = 4.0$. Lines are guides to the eye.

$$E_{PA} = n_{AA} + n_{BB} - n_{AB} = 2Np(d=3) \left(c^2 - c + \frac{1}{4} \right), \quad (16)$$

$$E_{PE} = n_{AA} = \frac{1}{2}Np(d=3)c^2, \quad (17)$$

$$E_{AS} = -n_{AA} + n_{BB} = Np(d=3) \left(\frac{1}{2} - c \right). \quad (18)$$

In the high-temperature regime, the steric self-avoidance effect between monomers plays the only role in determining the conformational properties of polymers. Thus taken the known value $z(d=3) = 4.68404(9)^{51}$ (which gives $p(d=3) = 0.31596(9)$ according to (10)), we can obtain numerical estimates for (14)–(18). These expressions perfectly agree with results of our numerical simulations, see Fig. 1 where the corresponding energies per monomer are presented.

When the temperature decreases, the interactions between monomers become essential, and the p -values for each model will depend on the fraction c and temperature T . As an example, we present our simulation results for the corresponding energies per monomer at $T = 4.0$ in Fig. 2. Though for all models the polymer chains are expected to be

still in an extended state (coil regime) at this temperature, the typical conformations they attain at given c are governed by that nearest-neighbor contact value which minimizes the total energy. Indeed, for the PE model the most preferable configurations would be those with a small value of nearest-neighbor contacts, whereas for the HP model the largest possible value of p will minimize the total energy. The values of p for all the models at various c -values can be estimated on the basis of data presented in Fig. 2 applying expressions (14)–(18).

In Fig. 3, we present our results for the averaged energies of the $N = 100$ -monomer heterogeneous chain as function of temperature at two representative fixed fractions $c = 0.7$ and $c = 0.2$. At $c = 0.7$, the energy of the HP, SHP, PA, and AS models decreases monotonically as temperature is lowered and sharply decreases within a short temperature interval, indicating the transition from an extended state (coil regime) to a compact state. For the PE model, however, one observes only a monotonic decrease of energy, which gradually tends to zero when the temperature decreases, and thus no transition occurs. Moreover, within the frames of this model, decreasing the energy means decreasing the averaged number of nearest-neighbor contacts, and thus expanding the chain. Thus, unlike the other models, in this case the averaged size of the heteropolymer chain increases when the temperature decreases.

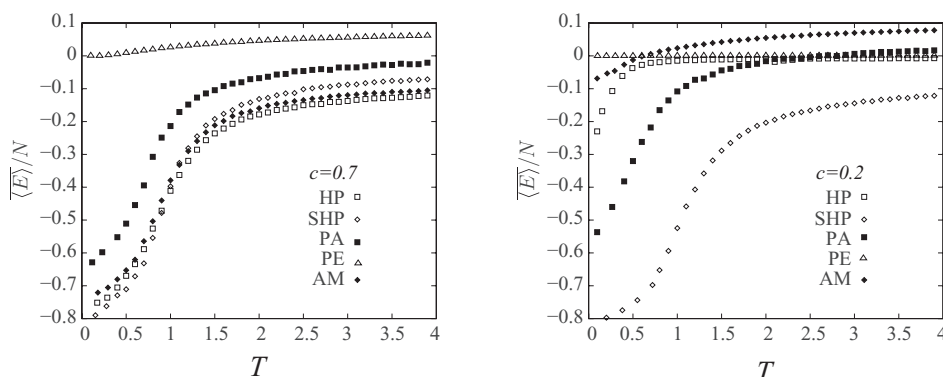


FIG. 3. Averaged energy per one monomer of the heterogeneous polymer chain with various types of monomer-monomer interactions as function of temperature at fixed fraction of A monomers $c = 0.7$ and $c = 0.2$.

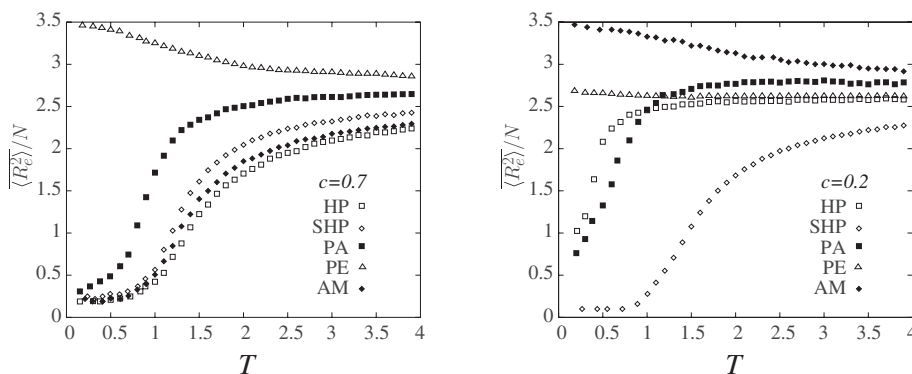


FIG. 4. Averaged end-to-end distance of the heterogeneous polymer chain with various types of monomer-monomer interactions as function of temperature at fixed fraction of A monomers $c = 0.7$ and $c = 0.2$.

Similar results are found at fixed fraction of A monomers $c = 0.2$. In this case, the AS model consists mainly of monomers, which repel each other, and thus behaves like the PE model: conformations with a minimum number of nearest-neighbor contacts are energetically preferable, which leads to expanding the chain size with decreasing the temperature. Note also that at small concentration of attractive monomers, the chains can attain the compact state only when they are long enough and have enough attractive nearest-neighbor contacts to overcome the conformational entropy.

In Fig. 4, our results for the averaged end-to-end distance of the $N = 100$ -monomer heterogeneous chain as function of temperature are given at the same two representative fractions of A monomers $c = 0.7$ and $c = 0.2$. These results confirm our discussions above. For the case $c = 0.7$, one notices a decrease of the polymer chain size when the temperature decreases (HP, SHP, PA, and AS models), which becomes crucial close to the transition temperature into the compact state. However, for the PE model, the polymer chain is expanding its size when the temperature decreases due to repulsion between monomers, and the polymer chain remains in an extended state at any temperature. At $c = 0.2$, the size of the polymer chain in the AS model increases even stronger than that of a polyelectrolyte due to the considerably larger amount of mutually repelling monomers; in both cases the polymer chain remains in an extended state at any temperature.

To obtain a quantitative description of conformational transitions from extended to compact states in models (1)–(5), we study the ratio $\langle R_e^2 \rangle / N$ for various N and fixed fraction c as function of temperature (Fig. 5). Assuming that the collapse of heteropolymers is through the Θ -transition similar to homogeneous polymers, we expect $\langle R_e^2 \rangle \sim N$ at the Θ -point, and thus the curves intersect in the vicinity of the transition temperature (the larger N , the steeper the curves). Despite the slight dependence of the intersection points on N , we can locate the crossover temperature. If at some T and c values the curves do not intersect, there is no phase transition and the polymer is in an extended state at any temperature.

As a result, we obtain the phase diagrams, presented in Fig. 6. Note that for the PE model of polyelectrolytes the polymer chain is always in an extended state at any temperature and fraction c of A monomers, thus we do not construct any phase diagram for this model. In the limiting case $c = 1$, the HP, SHP, and AS models describe homogeneous polymer chains with nearest-neighbor attractions (for the SHP model also $c = 0$) with known value of transition temperature $T_\Theta = 3.717(3)$.¹¹ For the SHP model, the Θ -transition is present always at any fraction c , whereas the other models remain in the extended state when the concentration of attracting monomers is too small to cause a transition into the compact state. The results for the PA model are in a good agreement with those obtained previously in Ref. 49.

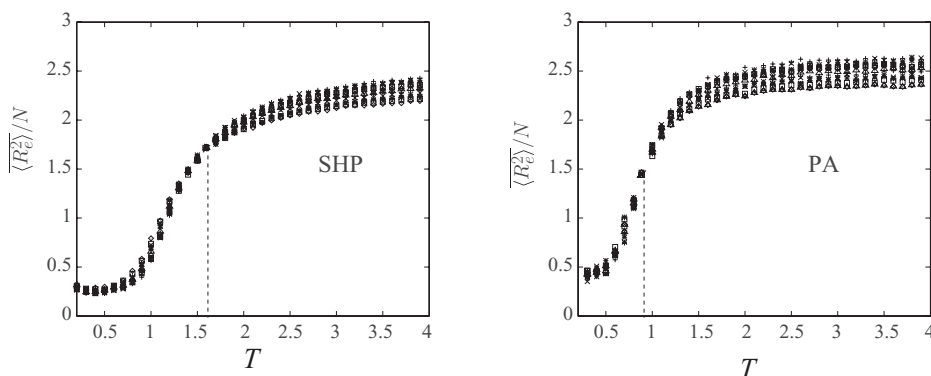


FIG. 5. Averaged end-to-end distance of a heterogeneous polymer chain divided by number of monomers as function of temperature at fraction of A monomers $c = 0.7$ at various values of N from 68 up to 100.

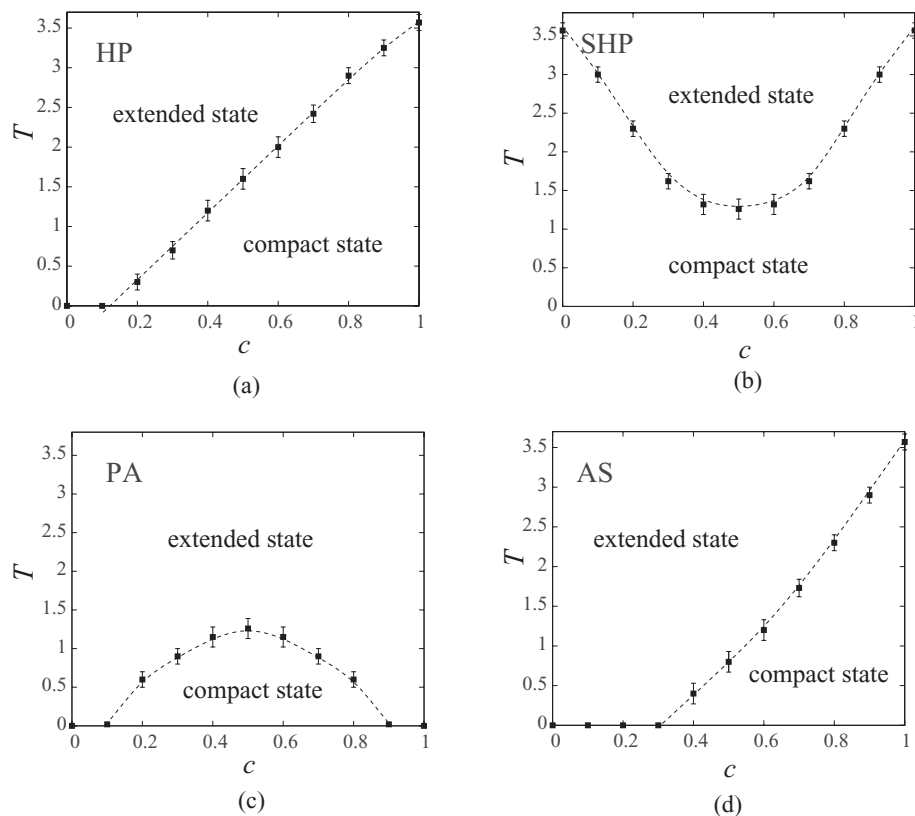


FIG. 6. Phase diagrams of heterogeneous polymer chains in T - c space: HP (a), SHP (b), PA (c), AS (d). The PE model always stays in the extended state and does not exhibit any phase transition.

IV. CONCLUSIONS

We studied the conformational properties of heteropolymers in $d = 3$ dimensions within the frames of a lattice model containing N_A monomers of type A and $N_B = N - N_A$ monomers of type B . Restricting ourselves to only short-range interactions between any pair of monomers residing on neighboring lattice sites that are not connected by a covalent bond, we considered several generalizations (1)–(5) of this model. In particular, case (1) refers to the (minimal) HP model¹⁸ with hydrophobic (A) and hydrophilic (B) monomers, case (2) is the standard SHP model for copolymers with monomers that have a tendency to segregate,³⁷ and the PA and PE models of cases (3) and (4) stand correspondingly for polyampholytes⁴⁹ and polyelectrolytes^{38,39} with strongly screened Coulomb interactions, respectively. The AS model of case (5) can be considered as additional generalization of above models, comprising an interplay between different kinds of short-range interactions.

In the present work, we extended the picture, developed in Ref. 49 for the PA model to the whole range of cases (1)–(5); namely, we treat different sequences of A and B monomers at given fixed fraction c of A monomers (ranging from 0 to 1) as different realizations of quenched disorder, and obtained observables of interest after performing double conformation and sequence averaging. Applying the pruned-enriched Rosenbluth chain-growth algorithm (PERM) we analyzed numerically the peculiarities of transitions from the extended into the compact state as a function of the fraction

$c \equiv N_A/N$ of A monomers for all the heteropolymer chain models, and obtained the diagrams of phase coexistence in c - T space.

For the PE model, unlike the other cases, the polymer chain is expanding its size as the temperature decreases due to repulsion between monomers, and the polymer chain remains in an extended state at any temperature. In the SHP model, the Θ -transition is present always at any value of the fraction c of A monomers, whereas the other models remain in an extended state when the concentration of attracting monomers is too small to cause a transition into the compact state. Note also that at small concentration of attractive monomers, the chains can attain the compact state only when they are long enough and have enough attractive nearest-neighbor contacts to overcome the conformational entropy. In the limiting case $c = 1$, the HP, SHP, and AS models describe homogeneous polymer chains with nearest-neighbor attractions (for the SHP model also $c = 0$) with known value of the transition temperature $T_\Theta = 3.717(3)$.¹¹

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