Hydrogen Bonding Sequence Directed Coil-Globule Transition in Water Soluble Thermoresponsive Polymers

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The origin of the coil-globule transition for water-soluble thermoresponsive polymers frequently used in nanomaterials remains elusive. Using polypropylene oxide as an example we demonstrate by means of atomistic molecular dynamics simulations that temperature-induced increase in the sequence length of monomers that are not hydrogen bonded to water drives the coil-globule transition. Longer chains statistically exhibit longer sequences which serve as nucleation sites for hydrophobic cluster formation, facilitating chain collapse at lower temperature in agreement with experimental data.

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Introduction.—The behavior of thermoresponsive amphiphilic polymers in an aqueous environment continues to attract the attention of researchers due to both fundamental interest and important applications in smart materials and temperature-triggered biomedical nanomaterials [1–3]. The solubility of these amphiphilic polymers depends on hydrogen bonding with water, which decreases with increasing temperature in favor of water-water hydrogen bonding leading to phase separation and, in dilute solution, the coil-globule transition. Several analytical models, including one by one of us, were developed to describe hydrogen bonding and phase separation of these polymers [4–7]. There have been a few attempts to describe the coil-globule transition of these polymers by considering additional excluded volume related to hydrogen bonding in simulations [8] or in a modified Flory model of the chain collapse [9]. Despite these efforts the origin and mechanism of the temperature induced collapse of these amphiphilic polymers remain much less clear compared to the coil-globule transition in traditional (nonhydrogen bonded) polymers [10–15] or protein cold denaturation, which occurs near the freezing point of water and is attributed to different water structuring around hydrophobic units [16–18]. The most studied amphiphilic polymer that loses hydrogen bonds with water upon temperature increase and undergoes a coil-globule transition at experimentally accessible temperatures is poly(N-isopropylacrylamide) (PNIPAM) [19–24]. Formation of intramolecular hydrogen bonds is considered to be the main mechanism for the coil-globule transition for PNIPAM [19–23] and poly(2-dimethylaminoethyl methacrylate) (PDMAEMA) [25]. Other thermosensitive polymers, such as polypropylene oxide (PPO) considered here or poly(N-vinylcaprolactam) (PVCL), are not capable of intramolecular hydrogen bonding, but still undergo the coil-globule transition in an experimentally relevant range of temperatures [26–29]. The mechanism of the conformational transition remains unknown. Another feature which remains unclear is the molecular weight dependence of the coil-globule transition, as has been experimentally observed for PPO [28], while there are mixed reports for PVCL and PNIPAM [24,26,30]. Experimental characterization of the relationship between hydrogen bonding and the coil- globule transition is difficult, as the degree of hydrogen bonding between water and polymer is not readily experimentally accessible. Additionally, depending on the molecular weight the transition often occurs at temperatures and/or polymer concentrations that make it difficult to draw conclusions on the molecular mechanism of the transition. Computer simulations at the atomistic level, such as we employ in this study, can provide insights into the molecular reorganization of water and concomitant changes in the hydrogen bonding pattern accompanying the conformational transition of a polymer from the expanded to collapsed state upon temperature increase and therefore provide valuable insights for theoretical model development and experimental material design.

In this Letter, using polypropylene oxide (PPO) as an example we investigate via atomistic molecular dynamics (MD) simulations the temperature-induced coil-globule transition (Fig. 1). So far the temperature-induced coil-globule transition of PPO in water has not been studied by molecular dynamic simulations although constant temperature simulations have been performed [31–34]. We compare the transition temperature determined in simulations to experimental data and investigate the effect of hydrogen bond sequences formed between PPO and water and correlate these changes with the overall chain conformation for two molecular weights of PPO. This analysis uncovers the underlying mechanism of the coil-globule transition of PPO and the origin of the molecular weight effect. This mechanism is expected to be generally applicable for a

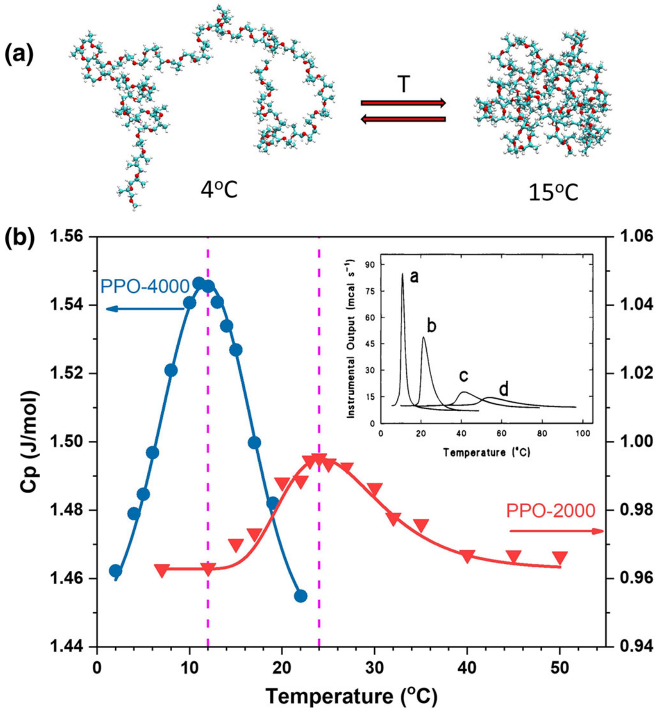

FIG. 1. (a) MD simulation snapshots of PPO-4000 in expanded (4 °C) and collapsed (15 °C) conformations. Carbon atoms are shown in cyan, oxygen in red, and hydrogen in white. Water is not shown for clarity. (b) The relative heat capacity ΔC_p for PPO-4000 (blue circles) and PPO-2000 (red triangles) aqueous solutions as functions of temperature. Curves are shown as guides for the eyes. (Inset) Experimental calorimetric traces for aqueous solutions of PPO of molecular weight a. 4000, b. 2000, c. 1000, and d. 725 [28].

large class of water soluble thermoresponsive amphiphilic polymers that find applications in a range of smart nanomaterials.

Model.—All MD simulations were performed using the GPU version of GROMACS 4.6.5 [35] with the OPLS all atom force field [36]. To compare the transition temperature with experimental data we studied methyl-terminated poly (propylene oxide) containing 69 repeat units (PPO-4000) and 35 repeat units (PPO-2000) in dilute solution of simple point charge extended model (SPC/E) water [37]. The specifics of the model and simulation protocol are described in the Supplemental Material [38]. The simulations were performed with NPT ensemble at a pressure of 1 bar in a $(9 \times 9 \times 9)$ nm^3 periodic box. The bonds were constrained using the LINCS algorithm. The temperature coupling was done using the v-rescale thermostat with coupling constant of 1 ps. Pressure coupling was carried out using the Berendsen barostat for the initial 30 ns of equilibration time and continued with the Parinello-Rahman barostat for 600 or 800 ns of a production run with coupling constant of 1 ps. The integration time step for simulations was 2 fs. Electrostatic interactions was calculated using particle-mesh Ewald (PME) summation. The hydrogen bonds between PPO and water were characterized using geometrical criteria: donor-acceptor distance $(r_{\mathrm{DA}}) \leq 3.5$ Å and hydrogen-donor-acceptor angle $\leq 30°$ [39,40]. The constant pressure specific heat capacity (C_p) of the system was calculated using the total energy fluctuations of the system: [41,42] $C_p = \langle \delta E^2 \rangle_{\mathrm{NPT}} / k_b T^2$ where $\langle \delta E^2 \rangle = \langle E^2 \rangle - \langle E \rangle^2$, E is the total energy of the system, k_b is the Boltzmann constant, and T is the temperature. All visualizations were done using visual molecular dynamics (VMD) [43].

Results.—To understand the origin of coil-globule transition of water-soluble responsive polymers, we performed atomistic MD simulations for PPO-4000 and PPO-2000 in aqueous solutions and observed a noticeable change of the polymer conformation from an expanded coil at low temperature to a compact globule at high temperature, as shown in Fig. 1(a). These temperature-induced conformational changes of PPO are reflected in the change of the relative specific heat capacity $\Delta C_p = C_{P_{\mathrm{PPO}}} - C_{P_{\mathrm{water}}}$ which is defined as the difference between specific heat capacity of the PPO solution and the specific heat capacity of the solvent at a given temperature. The relative specific heat capacities (ΔCp) for PPO-4000 and PPO-2000 in aqueous solutions are shown in Fig. 1(b) as functions of temperature. As is seen, ΔCp first increases with an increase of temperature, reaches a maximum, which corresponds to the coil-globule transition temperature, and then decreases at higher temperature. The maximum of ΔCp for PPO-4000 system occurs at about 12 °C and for PPO-2000 at about 23 °C, both in excellent agreement with the results of the experimental calorimetry measurements by Armstrong *et al.* [28] [Fig. 1(b), inset]. We note that both experimental observations and our results show a strong molecular weight dependence of the PPO coil-globule transition temperature in aqueous solutions.

Temperature-induced changes in polymer conformation can be conveniently characterized via the radius of gyration. As shown in Fig. 2(a) the average radius of gyration, R_g, changes rather sharply and in a step-function-like manner at the transition temperatures, $T_{\mathrm{tr}} = 12$ °C for PPO-4000 and $T_{\mathrm{tr}} = 23$ °C for PPO-2000, as expected based on the heat capacity data (Fig. 1). At low temperature in the expanded state $R_g \approx 1.60$ nm for PPO-4000 and 1.28 nm for PPO-2000, while in the collapsed state R_g decreases to 1.05 and 0.86 nm, respectively. As polymer solvation decreases due to the loss of hydrogen bonds with water, it is informative to correlate the changes in the radius of gyration and hence polymer conformation with the average degree of hydrogen bonding between PPO and water. Figure 2(b) shows the temperature dependence of the average number of hydrogen bonds between water and PPO calculated per repeat unit of PPO. At low temperature there are about 0.80–0.83 hydrogen bonds with water per repeat unit of PPO, which translates into about 1.8–1.9 waters in the hydration shell per repeat unit of PPO

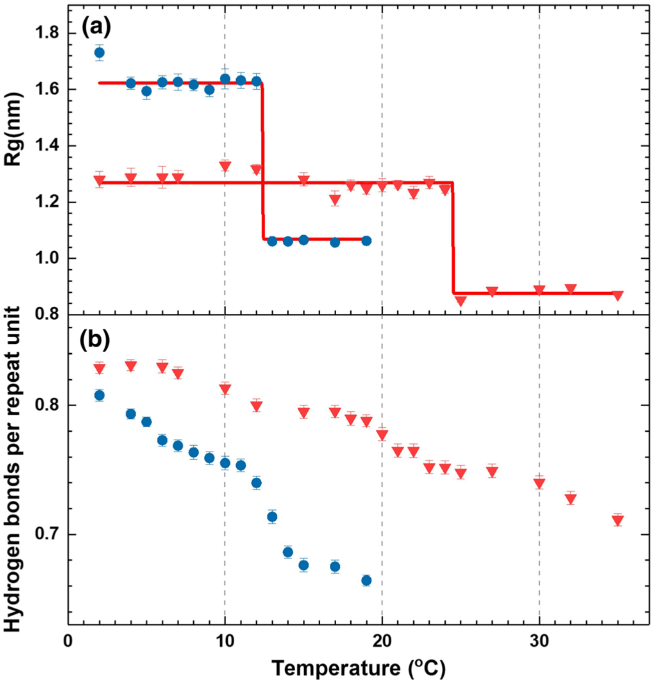

FIG. 2. Temperature dependence of (a) the average radius of gyration and (b) the average number of hydrogen bonds with water per oxygen of PPO-4000 (blue circles) and PPO-2000 (red triangles) in aqueous solution. Error bars are standard errors.

(see Fig. S1 of the Supplemental Material [38]) in agreement with experimental data [44]. As is seen, for both chain lengths the average number of hydrogen bonds decreases with temperature, as expected. It is worthwhile to note that the decrease in the average number of hydrogen bonds per repeat unit is more pronounced for PPO-4000 compared to PPO-2000. We note that the molecular weight effect on polymer hydration per repeat unit is not anticipated by analytical models [4,6], except for an end-group contribution [7], which is not the case here. Near the transition temperature the decrease in hydrogen bonding is also stronger for PPO-4000, while for PPO-2000 a much smaller change in hydrogen bonding can be detected, which is consistent with the more shallow peak in ΔCp in Fig. 1(b). For both polymers the change in hydrogen bonding with temperature is continuous and certainly not as abrupt as the change in R_g, indicating that the correlation between hydrogen bonding and R_g is rather subtle.

To understand the molecular mechanism of the conformational transition, it is useful to inspect the distribution of hydrogen bonded (H) water-soluble and nonhydrogen bonded (O) more hydrophobic repeat units along the chain, i.e., the "effective primary structure" of the amphiphilic chain. A typical sequence of H and O units obtained at $T = 7$ C is shown in Fig. 3(a) for PPO-2000 and PPO-4000. As is seen, in both cases the majority of nonhydrogen bonded (NHB) monomers are single monomers somewhat randomly distributed along the chain. At the same time, one can also find a few groups of two or even three consecutive NHB units, as is especially evident for the longer PPO chain. Statistical analysis confirms this observation: at a given temperature ($T = 7$ C below the conformational transition) single NHB units are dominant and scale with

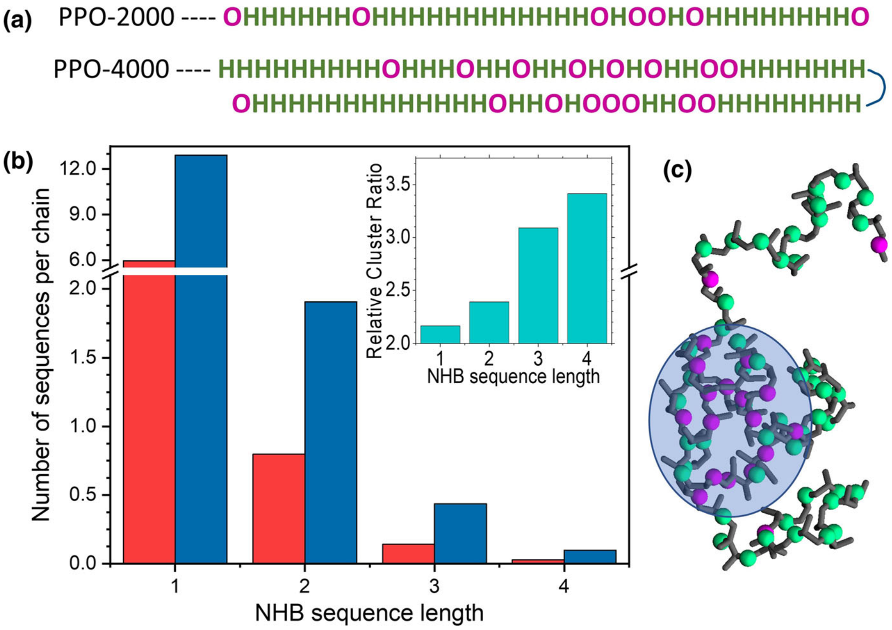

FIG. 3. (a) Typical sequence of hydrogen bonded (H) and nonhydrogen bonded (O) repeat units along the chain, (b) the average number of consecutive NHB monomers in PPO-2000 (red) and PPO-4000 (blue) and the ratio of NHB sequences for PPO-4000 to that for PPO-2000 (inset) at $T = 7$ °C. (c) Computer simulation snapshot of PPO-4000 conformation showing hydrogen bonded (green) and NHB (magenta) monomers and a cluster of NHB monomers.

chain length, i.e., about 12 and 6 for PPO-4000 and PPO-2000, respectively. Clusters of two, three, or four consecutive NHB monomers are less abundant and occur with a higher frequency for the longer PPO chain: e.g., sequence of 3 NHB repeat units is 3 times more likely to occur in PPO-4000 than PPO-2000. This observation, on a first sight surprising, has a clear statistical origin. Indeed, if we consider the chain "primary structure" as a sequence of independent Bernoulli trials with the probability to have a hydrogen bond p, then the longer the chain, i.e., a larger number of trials, the higher is the chance of an occurrence of a longer sequence of hydrogen bonded with water (…HHHHH…) or NHB (…OOO…) units [45]. In other words, the expected value for a chain of length N (i.e., the number of trials), $E(N)$, required to produce a sequence of m consecutive NHB units is $E(N) = [(1-p)^{-m} - 1]/p$, [46]. Thus, to observe a sequence of three NHB units ($m = 3$) for $p = 0.8$ [p being the average number of hydrogen bonds per monomer, Fig. 2(b)], the chain should be 155 units long, while for a sequence of two units ($m = 2$), a much shorter chain is needed $N = 31$, which is consistent with our observations that sequences of two NHB units occur for both PPO-2000 and (twice for) PPO-4000 [Fig. 3(a)]. With an increase of temperature, the average fraction of hydrogen bonds decreases and accordingly the occurrence of sequences of NHB monomers increases (Fig. S2 of Supplemental Material [38]). Thus, for $p = 0.7$, to have three consecutive NHB units a chain of 53 repeat units is required, which routinely occurs at higher T for PPO-4000, but rarely for PPO-2000.

In Fig. 4(a) the temperature dependence of the average length of the longest sequence of NHB monomers is shown for PPO chains of two different lengths. As is seen for PPO-4000, the longest NHB sequence increases from about 2.5 to 3.5 as temperature increases from 2 to 20 C, while for PPO-2000 the longest NHB sequence length is smaller and changes from about 2 to 2.5 in the temperature range 10 to 35 C. The results obtained in our simulations (solid symbols) are compared in Fig. 4(a) with statistical predictions (open symbols) for the longest run $R_{\max}$ in an independent Bernoulli process of N trials [47]:

$$R_{\max} \approx \log_{1-p} Np, \tag{1}$$

where p is the probability to form a hydrogen bond [for which we used data shown in Fig. 2(b)]. As is seen for both chain lengths studied there is an excellent agreement with statistical predictions indicating that the observed sequences of NHB units have a purely statistical nature. Analytical prediction for the average number of hydrogen bonds can also be successfully employed in Eq. (1) to yield $R_{\max}$ (Fig. S3 of Supplemental Material [38]) for one, but not both chain lengths simultaneously. While the longest sequence of NHB units is not so large, its effect on PPO conformational behavior is noticeable especially for longer chains. Indeed, the longer NHB sequences are relatively long lived and have a tendency to accumulate other NHB monomers at neighboring sites, as is seen in Fig. 3(a) and Fig. S4 of the Supplemental Material [38]. As an example, a sequence of 3 or more NHB units generates a group of NHB units along the chain twice of its size (Fig. S5 of Supplemental Material [38]). Such NHB groups persist for a noticeably longer time >1 ns (Fig. S6 of Supplemental Material [38]) than the typical lifetime of a water hydrogen bond 8–25 ps [39,40,48]. With a temperature increase the size of such groups of NHB units increases together with its fraction among all NHB monomers [Figs. 4(a), Figs. S5, S7, of the Supplemental Material [38]]. This leads to a stronger decrease in the average degree of hydrogen bonding for longer PPO chains, as we see in Fig. 2, effectively a feedback loop. Furthermore, having a persistent group of hydrophobic NHB units within a section of a chain results in rearrangement of the local chain conformation thereby bringing together additional NHB units in

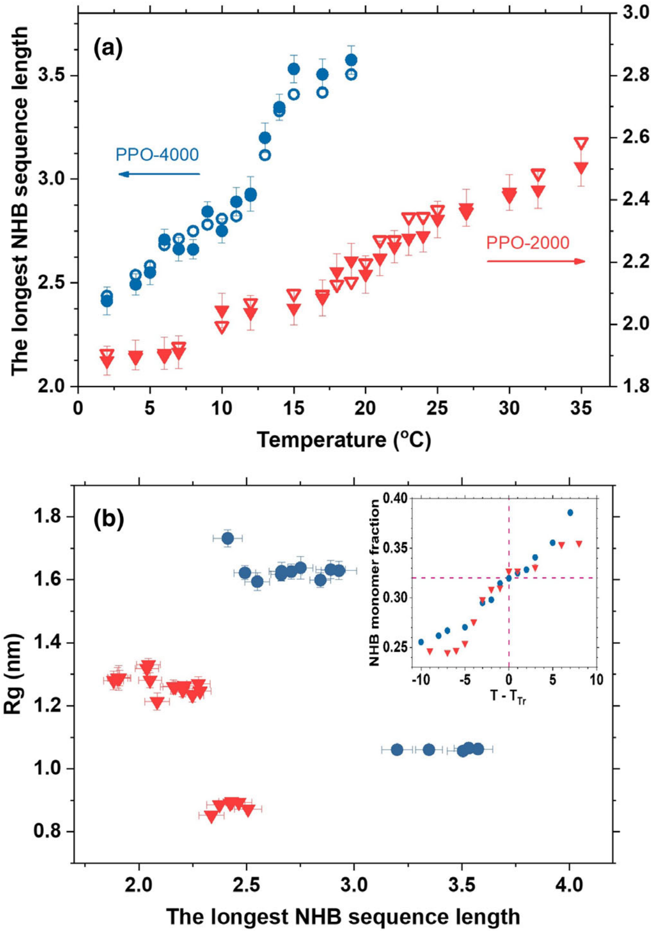

FIG. 4. (a) The average value of the longest sequence of NHB units obtained from simulations (solid symbols) and calculated using Eq. (1) (open symbols), (b) radius of gyration vs longest sequence of NHB units for PPO-4000 (blue circles) and PPO-2000 (red triangles). The inset shows the average fraction of NHB monomers as a function of the shifted temperature, $T - T_{\mathrm{tr}}$.

the physical vicinity, i.e., forming a cluster of hydrophobic NHB units, as shown in Fig. 3(c). Formation of such clusters can be favorable to minimize water interaction with hydrophobic NHB groups and can considerably facilitate the conformational transition to a collapsed state. As has been discussed in the literature, especially in relation to protein folding, both the number and distribution of hydrophobic units along the chain play an important role in the coil-globule transition [49–52]. Indeed, it has been shown that a "proteinlike" primary structure with grouped sequences of hydrophobic (or self-attracting) units makes the folding of macromolecules into compact structure easier and for polymers for which the solubility decreases with a temperature decrease, the transition for proteinlike chains occurs at higher temperature than for random or alternating heteropolymers [53–55]. Obviously having sequences of hydrophobic units makes it easier to form a cluster, which works as a nucleation site for folding [56,57]. A similar mechanism can be in play in the case of PPO chains, which can be viewed as a heteropolymer [Fig. 3(a)] with a mobile and temperature dependent primary structure of hydrogen bonded (H) monomers being well solvated by water and NHB units (O) being essentially hydrophobic. As the longest NHB sequence is the origin of clustering acting as a nucleation site for the coil-globule transition, it is informative to correlate the average radius of gyration with the longest sequence of NHB units. As is seen in Fig. 4(b) there is an obvious interconnection. For PPO-4000 an expanded state corresponds to a longest NHB sequence below 3 and the collapsed state to 3 and above. For the shorter PPO-2000 only shorter NHB sequences can be formed and as a consequence the transition is more shallow and occurs at higher temperature when the maximum sequence length reaches about 2.3, i.e., the 3 NHB sequence (OOO) occurs in a chain at least $1/3$ of the time. Furthermore, comparing the overall average fraction of NHB monomers for long and short PPO chains [Fig. 4(b), inset], one can notice that in both cases the transition occurs when NHB fraction exceeds 30%, but this level of hydrophobicity is reached at different temperatures, as the longer NHB sequences formed in longer chains facilitate both the decrease in hydrogen bonding and clustering which serves as nucleation site for the transition.

Our analysis of the temperature-induced coil-globule transition of PPO reveals that reduction of the average number of repeat units hydrogen bonded with water does not directly correlate with the conformational changes, but rather affects the primary structure, i.e., the distribution of nonhydrogen bonded hydrophobic units along the chain. The longest sequences of NHB units are accurately predicted by a statistical (probability) Bernoullian analysis and are found to be long lived. Together with additional neighboring NHB units they form a cluster that acts as a nucleation site for the collapsed state. Although for both chain lengths the transition to collapsed state occurs when the fraction of NHB units exceeds 30%, longer chains that are more likely to form longer sequences of NHB units reach this limit at a lower temperature compared to shorter chains that can form only short sequences. Accordingly short chains remain in an expanded conformation up to a considerably higher temperature, in agreement with experimental observations [28,29]. This mechanism of coil-globule conformational transition driven by a statistical distribution of NHB units along the chain is expected to be valid for the broad class of amphiphilic thermoresponsive polymers for which solubility is achieved via hydrogen bonding with water and therefore can be an important factor in responsive nanomaterial design.

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