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Letter

Grafting Density Governs the Thermoresponsive Behavior of P(OEGMA-*co*-RMA) Statistical Copolymers

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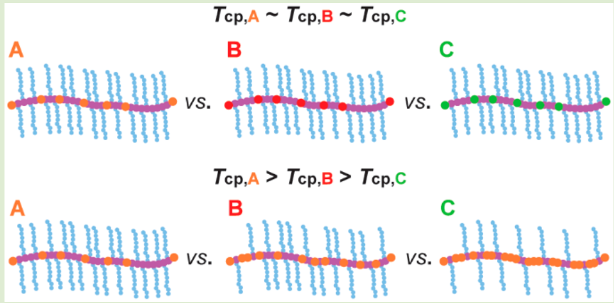
ABSTRACT: Thermoresponsive copolymers that exhibit a lower critical solution temperature (LCST) have been exploited to prepare stimuli-responsive materials for a broad range of applications. It is well understood that the LCST of such copolymers can be controlled by tuning molecular weight or through copolymerization of two known thermoresponsive monomers. However, no general methodology has been established to relate polymer properties to their temperature response in solution. Herein, we sought to develop a predictive relationship between polymer hydrophobicity and cloud point temperature (T_{CP}). A series of statistical copolymers were synthesized based on hydrophilic oligoethylene glycol monomethyl ether methacrylate (OEGMA) and hydrophobic alkyl methacrylate monomers and their hydrophobicity was compared using surface area-normalized partition coefficients (log P_{oct}/SA). However, while some insight was gained by comparing T_{CP} and hydrophobicity values, further statistical analysis on both experimental and literature data showed that the molar percentage of comonomer (i.e., grafting density) was the strongest influencer of T_{CP}, regardless of the comonomer used. The lack of dependence of T_{CP} on comonomer chemistry implies that a broad range of functional, thermoresponsive materials can be prepared based on OEGMA by simply tuning grafting density.



The motivation to design polymers to respond to environmental triggers such as light, ultrasound, pH, redox state, or temperature has led to significant advances in the field of stimuli-responsive materials.[1−5] These developments have underwritten their application as biosensors,[6] coating materials,[7] or drug delivery systems.[8] Temperature has been most widely studied because of the simplicity of its external application and the availability of methods for tuning polymer thermoresponsiveness.[9] Such thermoresponsive polymers typically display two distinct behaviors in solution, known as the upper critical solution temperature (UCST) and lower critical solution temperature (LCST), representing the critical points above and below which the polymer and solvent are completely miscible.[10] Polymers that exhibit an LCST transition are soluble below a critical temperature, above which they undergo a phase transition and demix as a result of increased entropy (for further details, see the following representative references).[8,11] The LCST transition is particularly attractive for biological applications due to the relatively low temperatures required to elicit response.[12]

There are several ways to control the LCST of a polymer solution and thus achieve a phase transition at a desired temperature.[13−18] The LCST can be tuned via changing polymer molecular weight (MW) or solution concentration or by varying the composition of a copolymer based on two or more monomers (i.e., P(oligoethylene glycol monomethyl ether methacrylate-*co*-diethylene glycol methacrylate), P(OEGMA-*co*-DEGMA), Figure 1).[19−22] For example, Gibson and co-workers studied the thermoresponsive behavior of a series of P(*N*-vinylpiperidone) homopolymers with molecular weights ranging from 4.5 to 83 kDa. The authors showed that the cloud point (T_{CP}) of P(*N*-vinylpiperidone) decreased from 99 to 67 °C with increasing polymer MW.[14] Lecommandoux and co-workers investigated the possibility of manipulating the LCST through copolymerization of 2-isopropyl-2-oxazoline (hydrophobic) with 2-methyl-2-oxazoline (hydrophilic). The T_{CP} of the resulting copolymer increased by 21 °C compared with the P(2-isopropyl-2-oxazoline) homopolymer due to an overall increase in hydrophilicity.[23] However, the scope of monomers known to yield LCST-responsive materials upon copolymerization is currently limited, complicating the design of new and functional polymers with bespoke transition temperatures.

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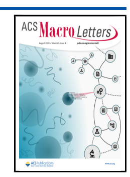

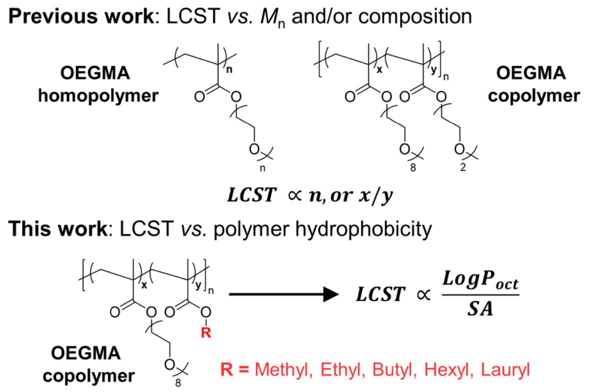

Figure 1. Previous studies have focused on the influence of MW or composition on LCST. Herein, we investigate how hydrophobicity influences thermoresponsive behavior.

We have had recent success correlating polymer properties such as solubility and self-assembly behavior to descriptors of their hydrophobicity. In particular, the classification of small molecule hydrophobicity using octanol−water partition coefficients (log P_{oct}) has proven exceptionally successful when leveraged to describe polymer phenomena. For example, we demonstrated that surface area-normalized log P_{oct} (log P_{oct}/SA) values provided predictive information to guide the selection of corona- and core-forming monomers for polymerization-induced self-assembly (PISA) using either reversible addition−fragmentation chain transfer (RAFT) polymerization or ring-opening metathesis polymerization (ROMP).[24,25] Log P_{oct}/SA was also used effectively as a tool to optimize solvent selection for crystallization-driven self-assembly (CDSA) of P(L-lactic acid) (PLLA)-based block copolymers.[26] In order to further benefit from the advantages of using this computational tool to dramatically reduce experimental workload, we postulated that it could be exploited to relate polymer chemical structure to T_{CP}.

Herein, we synthesized a series of copolymers of OEGMA and various alkyl methacrylates (RMA, R = methyl, ethyl, *n*-butyl, *n*-hexyl, and *n*-dodecyl (lauryl)) and studied their LCST response. Polymer cloud point temperature (T_{CP}), the temperature at which polymers undergo a solubility-to-insolubility transition,[14] was used as a proxy for the LCST. We then attempted to correlate T_{CP} to copolymer hydrophobicity via log P_{oct}/SA to predict T_{CP} of new polymers. Surprisingly, we found log P_{oct}/SA to be a secondary descriptor of T_{CP} for OEGMA copolymers compared to mol % of comonomer. Indeed, copolymer molar composition (which can be viewed through the lens of grafting density) correlated strongly for both copolymers synthesized in this study and for related copolymers identified from previous literature reports. These discoveries highlight the importance of copolymer topology in determining thermal properties and suggest a route to prepare a wide variety of functional, brush-like copolymers with precisely defined T_{CP} values.

In the vast majority of studies regarding the manipulation of the LCST through copolymerization, two monomers known to produce homopolymers with LCSTs are copolymerized to produce statistical copolymers possessing intermediate LCSTs (Figure 1). Luzon, Ramirez-Jiménez, Porsch, Bebis, and Lutz have all reported thermoresponsive copolymers based on OEGMA and DEGMA, where T_{CP} decreased as a linear function of the molar quantity of DEGMA.[20,27−30] While numerous studies have been carried out involving the copolymerization of these two monomers, no consensus has been reached regarding the mechanisms underlying the capability to tune the LCST through copolymerization. Compared with their homopolymers, copolymers of the same degree of polymerization (DP) containing two or more thermoresponsive monomers can have different MW, hydrophobicity, surface area, radius of gyration, and so on. It is unclear if a single factor dominates the LCST or a combination of multiple factors. Moreover, parameters that contribute to determining the LCST in one system may not be general for others.

To isolate influence of copolymer hydrophobicity upon T_{CP}, we prepared a series of copolymers of OEGMA and various alkyl methacrylates (RMA), varying the composition within each series by changing the hydrophobic molar composition in order to observe the effect of both alkyl chain length (hydrophobicity) and initial feed ratio. Alkyl methacrylates (e.g., MMA, *n*BMA, LMA) were selected as comonomers due to their commercial availability, compatibility with polymerization conditions, and simple hydrocarbon side chain structure. Overall copolymer MW and composition range (i.e., targeted hydrophobic mol %) were maintained as consistently as possible across each series.

The copolymers were prepared via reversible addition−fragmentation chain transfer (RAFT) polymerization in 1,4-dioxane for 6−8 h until targeted DPs were reached (Figure 2A). The final molar and mass composition of the purified copolymers were determined using ^{1}H NMR spectroscopy by relative integration of resonances corresponding to each monomer (Figures 2B and S16−S19). Kinetic analysis was conducted to confirm the statistical nature of the copolymerizations. As shown in Figure 2C (and Figures S12−S15), both OEGMA and RMA monomers were consumed at an approximately equal rate. Molecular weight distributions (MWDs) for the P(OEGMA-*co*-RMA) copolymers were determined using size-exclusion chromatography (SEC). As shown in Figure 2D (and Figures S12−S15), copolymers were obtained with narrow and symmetrical MWDs. Variations in number-average MW (M_n) and dispersity ($Đ_M$) values were determined by calculating coefficients of variance. Using this measure, M_n varied by only 17% across the entire data set, while $Đ_M$ varied by 5% with all values <1.40.

Turbidity measurements were conducted using UV−vis spectroscopy in order to measure the T_{CP} of the copolymers. Changes in the percentage transmittance were recorded at λ = 550 nm within the temperature range of 20 to 93 °C. Temperature points that corresponded to 50% transmittance values were taken as the T_{CP} of polymers (see Supporting Information for the detailed method). In general, T_{CP} decreased for P(OEGMA-*co*-RMA) copolymers with increasing RMA content (Figure 2E). This inverse relationship was further corroborated by microcalorimetry (μDSC), which measures changes in heat flow as a function of temperature for dilute liquid samples. For these data, the maximum point of the first derivative of the heating traces were chosen as the T_{CP} values. Figure 2F shows a similar decrease in T_{CP} as the hydrophobic content of the copolymers increased. Good agreement between the T_{CP} values obtained from both measurements confirmed their consistency. A similar analysis was performed for the other copolymer series (see Supporting Information).

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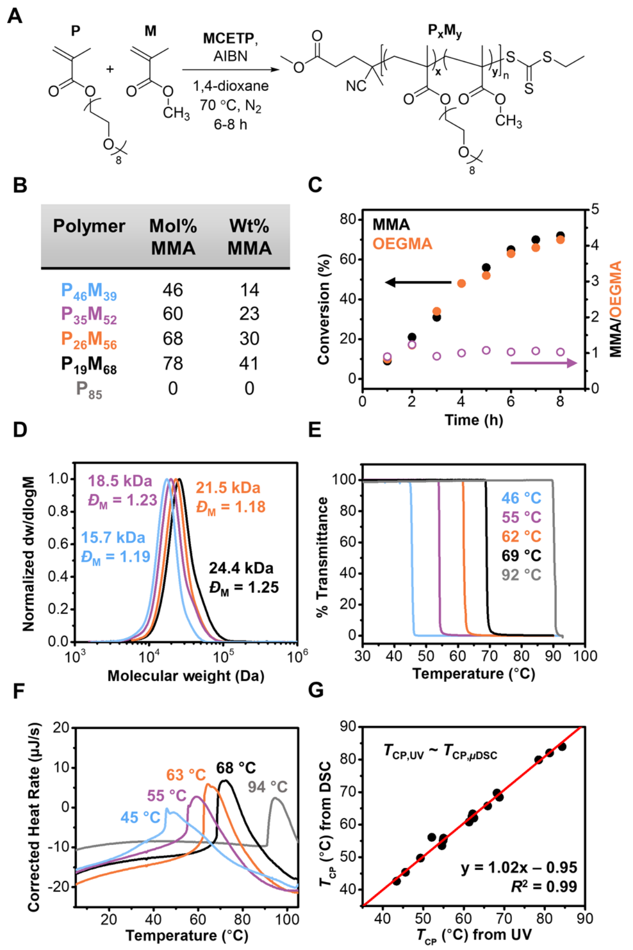

Figure 2. (A) Representative synthetic scheme for the preparation of P(OEGMA-*co*-RMA) statistical copolymers. MMA is used as the comonomer in this example. (B) Composition of P(OEGMA-*co*-MMA) copolymers, as determined by ^{1}H NMR spectroscopy. (C) Kinetics of monomer conversion during the synthesis of P(OEGMA-*co*-MMA) with an initial monomer molar feed ratio of 1:1 OEGMA/MMA. (D) Normalized SEC molecular weight distributions for the P(OEGMA-*co*-MMA) series (eluent: $CHCl_3$ + 0.5 v/v% NEt_3, PS standards). (E) Percent transmittance as a function of temperature for the P(OEGMA-*co*-MMA) copolymers dissolved in H_2O at 5 mg/mL as measured by UV−vis spectroscopy (λ = 550 nm, 20−93 °C, 1 °C min^{-1}). (F) μDSC thermograms for the P(OEGMA-*co*-MMA) copolymers (3 atm, 0−115 °C, 0.5 °C min^{-1}). (G) Comparison of T_{CP} values measured by UV−vis spectroscopy and μDSC. The solid red line represents a linear fit of the data. The colors in (D), (E), and (F) correspond to those assigned to the various copolymers in (B).

We next sought to understand the relationship between measured T_{CP} values and copolymer hydrophobicity.

Log P_{oct}, which describes the partitioning of a substance between octanol and water and reflects transfer free energy, was used as the means of quantifying and comparing hydrophobicity.[31−33] Toward this end, we calculated log P_{oct} values for short oligomers as proxies for the synthesized copolymers and normalized them with surface areas of optimized conformations using Molecular Dynamics (MD) simulations (see Supporting Information for the detailed model). We then attempted to relate these calculated log P_{oct}/SA values to measured T_{CP} values.

As shown in Figure 3A, log P_{oct}/SA increased with increasing RMA content, consistent with the established relationship

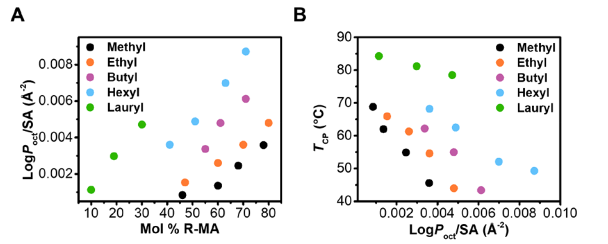

Figure 3. (A) Calculated log P_{oct}/SA values for various copolymer oligomers as a function of the mol % of hydrophobic comonomer. (B) Plot of T_{CP} as measured by UV−vis spectroscopy vs log P_{oct}/SA for the same copolymer series.

between hydrophobicity and log *P*. Comonomers with longer alkyl chains had a more dramatic impact on log P_{oct}/SA than those with shorter ones and thus produced relationships with relatively steeper slopes. Figure 3B shows the relationship between T_{CP} and log P_{oct}/SA. Here, inverse linear relationships were observed for each series, confirming our hypothesis that increased copolymer hydrophobicity, resulting from increasing the molar ratio of hydrophobic comonomer in the P(OEGMA-*co*-RMA) copolymers, acted to decrease T_{CP}. We also hypothesize log P_{oct}/SA values reflect localized degrees of hydrophobicity and the size of the oligomeric models represents a length scale that may not extend to longer range topological influences. As such, each series possessed a unique slope that was related to the alkyl chain length of the comonomer and thus no general correlation could be drawn between copolymer log P_{oct}/SA and T_{CP}.

The complexity of the LCST process was further reinforced by investigating the influence of hydrophobicity on the heat of phase separation (ΔH) calculated from the μDSC data.[34] As shown in Figure S22, weak correlations and lack of a general linear relationship were noted between log P_{oct}/SA or polymer composition and ΔH. These data indicate that hydrophobicity contributes to the LCST for statistical copolymers. However, they also imply that a picture of hydrophobicity based on transfer free energy (log *P*) and conformational insight (SA) only partially captures the LCST process for brush-like copolymers and that other factors must be considered.

The mixing of polymer molecules with H_2O, described by ΔG_{mix}, represents a balance of the enthalpically favorable binding of H_2O molecules (ΔH_{mix} > 0) and their increased ordering upon binding (ΔS_{mix} > 0). The LCST phenomenon is thus understood as a disruption in the balance of these contributors at higher temperatures, where the entropic term dominates.[10,35] Based on this argument and the fact that log *P* represents a transfer free energy term,[36] it was somewhat surprising that a general relationship could not be drawn between copolymer hydrophobicity and T_{CP}, as we anticipated ΔH_{mix} to be directly relatable to hydrophobicity. To better understand determinants of T_{CP}, we searched for relationships involving other polymer descriptors such as molar (mol % RMA) and mass (wt % RMA) composition, M_n, $Đ_M$, and DP. Figure S1 shows a scatterplot matrix highlighting the intercorrelations between descriptors or correlations with the response variable T_{CP}. It should be noted that data from all of the copolymer series were combined prior to analysis. From these data, relationships were apparent between T_{CP} and each of the descriptors, with the molar and mass compositions exhibiting the strongest correlations. Intriguingly, this initial visualization seemed to imply that the identity (chemistry) of

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the comonomer was less important in determining T_{CP} than was its quantity in the copolymers. Single and stepwise multivariable linear regression analyses were then applied to the collected data set to develop a quantitative structure–activity relationship (QSAR) model (see SI for full discussion). The model was trained on experimental data using stratified k-fold data sets. An initial optimized model based on two descriptors, the mol % and wt % RMA comonomer, was obtained using either R^2 or RMSE as the selection parameter. However, this model was deemed inappropriate due to concerns regarding the influence of collinearity between these parameters on model predictive power for future data sets. Instead, a simplified model using only the mol % of comonomer was adopted, allowing for a simple prediction of T_{CP} based on copolymer composition.

We then sought to validate this simple model against T_{CP} data for OEGMA copolymers in the literature. A total of 94 T_{CP} values for OEGMA copolymers with two different side chain lengths were extracted from about 20 reports.[37] These data were selected based on the following criteria: (1) they pertained to $OEGMA_{500/300}$ statistical copolymers; (2) they included T_{CP} measurements obtained via UV–vis spectroscopy on dilute polymer solutions (i.e., ≤5 mg mL^{-1}) in H_2O; (3) the comonomers were ideally simple in structure and/or commercially available; and (4) the comonomers did not possess ionizable groups that would introduce additional stimuli-responsiveness. Comonomers included diethylene glycol methyl ether methacrylate (DEGMA), methyl methacrylate (MMA), *N*-isopropylacrylamide, pentafluorostyrene (PFS), and others (Figure 4A). Again, the data was visualized

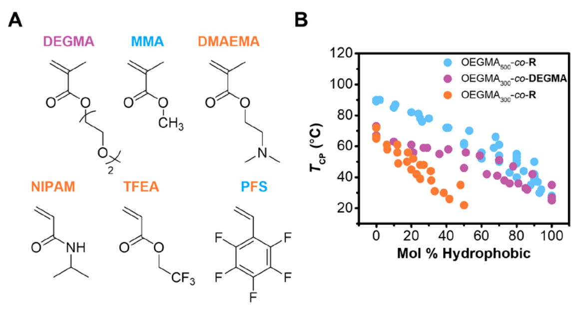

Figure 4. (A) Example comonomers present in P(OEGMA-*co*-R) copolymers for which T_{CP} values have been measured. (B) Plot of T_{CP} as a function of the molar quantity of comonomer constructed using data collected from literature sources.

using a scatterplot matrix (Figure S4), revealing a similarly strong correlation between T_{CP} and comonomer molar composition. As shown in Figure 4B, linear relationships could generally be drawn between T_{CP} and mol %, with two clusters similar in slope that corresponded to OEGMA copolymers with different OEG side chain lengths. $OEGMA_{300}$-*co*-DEGMA copolymers exhibited exceptional behavior, sharing slopes with both clusters depending on composition. Interestingly, the data collected from the literature for $OEGMA_{500}$ copolymers agreed strongly with our experimental observations (Figure 5A). The same model describing the relationship between T_{CP} and mol % was used to evaluate these literature data. As shown in Figure 5B, this model was reasonably successful in predicting the literature T_{CP} values. This further supported the hypothesis that comonomer chemistry plays a limited role in determining

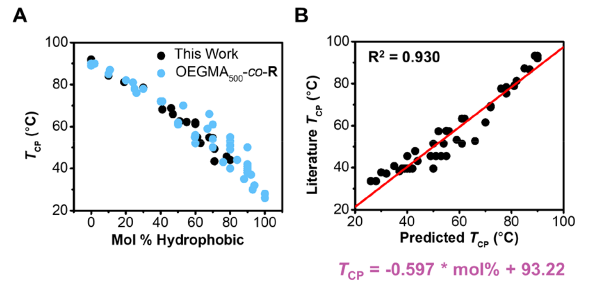

Figure 5. (A) Plot of T_{CP} vs the molar quantity of comonomer. Data from $P(OEGMA_{500}$-*co*-R) copolymers obtained from literature sources is overlaid with experimental data from this report. (B) Comparison between literature T_{CP} values and those predicted from molar compositions. The solid red line represents a linear fit of these data.

T_{CP} for OEGMA copolymers. Given the "brushy" nature of poly(OEGMA), an increase in comonomer molar quantity can be viewed as a decrease in grafting density. A simple model relating T_{CP} to grafting density may be generally appropriate for other brush copolymers.

To conclude, we report the synthesis of a series of P(OEGMA-*co*-RMA) copolymers via copolymerization of OEGMA and different alkyl methacrylate monomers. LCST behavior of the brush-like copolymers was investigated by using complementary methods. We then attempted to relate T_{CP} to hydrophobicity based on a thermodynamic perspective (log *P*) and a structural parameter (SA); however, the multifaceted nature of T_{CP} complicated a predictive model. Instead, linear and stepwise regression analysis using a variety of predictors revealed that T_{CP} appeared to depend most significantly on the mol % of comonomer, suggesting that grafting density is the most important determinant of the LCST for OEGMA brush copolymers. Our analysis of both experimental and literature data implies that a wide variety of functional copolymers can be prepared using this guiding principle, as the identity of the comonomer in P(OEGMA-*co*-R) copolymers does not appear to influence T_{CP}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmacrolett.0c00461.

Materials, characterization techniques, experimental procedures, and additional data (statistical analysis, SEC, ^{1}H NMR, μDSC, and UV–vis spectra) (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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