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Thermo-Responsive Behavior of Borinic Acid Polymers: Experimental and Molecular Dynamics Studies

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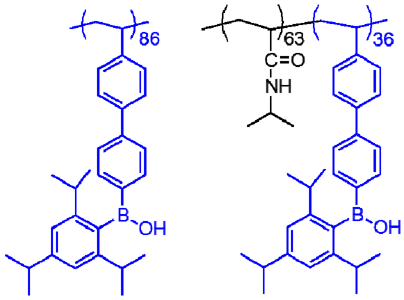
ABSTRACT: The thermo-responsive properties of borinic acid polymers were investigated by experimental and molecular dynamics simulation studies. The homopolymer poly(styrylphenyl(tri-*iso*-propylphenyl)borinic acid (PBA) exhibits an upper critical solution temperature (UCST) in polar organic solvents that is tunable over a wide temperature range by addition of small amounts of H_2O. The UCST of a 1 mg/mL PBA solution in DMSO can be adjusted from 20 to 100 °C by varying the H_2O content from ~0-2.5%, in DMF from 0 to 100 °C (~3-17% H_2O content), and in THF from 0 to 60 °C (~4-19% H_2O). The UCST increases almost linearly from the freezing point of the solvent with higher freezing point to the boiling point of the solvent with the lower boiling point. The mechanistic aspects of this process were investigated by molecular dynamics simulations. The latter indicate rapid and strong hydrogen-bond formation between BOH moieties and H_2O molecules, which serve as crosslinkers to form an insoluble network. Our results suggest that borinic acid-containing polymers are promising as new "smart" materials, which display thermo-responsive properties that are tunable over a wide temperature range.

Introduction

To explore and develop new types of stimuli-responsive or "smart" materials that undergo significant property changes upon exposure to relatively small external signals such as changes in temperature, pH, irradiation with light, etc, has been one of the main goals for material chemists.[1] Thermo-responsive phenomena are among the most effective approaches as they are also commonly observed in nature. The temperature-induced helix-to-coil transition of peptides is an example, in which dramatic conformational changes occur and ultimately new physicochemical properties arise.[2] Taking clues from these natural phenomena, artificial thermo-responsive materials, especially thermo-responsive polymers, have been designed and widely explored. However, even though many thermo-responsive polymers have been developed, polymers with easily tunable critical transition temperatures remain relatively rare and mainly rely on variations in copolymer composition. For example, Schubert and coworkers reported a series of statistical copolymers of poly(N,N-dimethylaminoethyl methacrylate-*stat*-oligoethyleneglycol methacrylate) (PDMAEMA-*stat*-PEGMA) with a lower critical solution temperature (LCST) that is tunable from ~40-70 °C by varying the pH and the PEGMA content from 0 to 100 %.[3] For a related copolymer, poly(methyl methacrylate-*stat*-oligoethyleneglycol methacrylate) (PMMA-*stat*-PEGMA), they achieved a tunable LCST by varying the oligoethylene glycol length, pH and copolymer composition.[4] Other examples include polyacrylamides with proline and hydroxyproline moieties, as well as poly(vinylphosphonate)s.[5] Recently, Roth and coworkers developed hydrophobically modified benzyl acrylamide-sulfobetain copolymers with upper critical solution temperatures (UCST) that are tunable from ~6-82 °C by varying copolymer composition and NaCl concentration.[6] The UCST-driven self-assembly of diblock copolymer micelles has been investigated by Davis, Lowe and coworkers.[7]

Boron-containing polymeric materials have attracted much attention in recent years due to their desirable optical, electronic, and sensory properties.[8] For example, luminescent triarylborane polymers have been exploited in anion sensing applications,[8a, 8d, 9] boron diketonate-functionalized polymers in oxygen sensing and tumor hypoxia imaging,[10] and the high affinity of boronic acid and boroxole-functionalized materials for diols and polyols in disease diagnosis and therapy.[11] Boronic acid block copolymers, in which a boronic acid-functionalized segment is linked to a thermo-responsive acrylamide segment have been shown to display multiple stimuli-responsive behavior,[11c, 11i, 12] where the thermo-responsive properties are based on the LCST behavior of the acrylamide block. However, although the hydrogen bond donor/acceptor properties of boronic ($RB(OH)_2$) and borinic ($R_2B(OH)$) acid[13] functional groups are expected to facilitate interesting polymer-solvent interactions, the thermo-responsive properties of the corresponding boron polymers have not been explored in detail.

Herein, we discuss the thermo-responsive behavior of the borinic acid-containing polymer poly(styrylphenyl(tri-*iso*-propylphenyl)borinic acid[14] (PBA, Chart 1). Sterically demanding tri-*iso*-propylphenyl (Tip) groups are attached to the boron centers in PBA to prevent chemical crosslinking via B-O-B bond formation so that hydrogen bonding is the preferred mode for intermolecular interactions. We demonstrate that the UCST of PBA can be modulated in various polar organic solvents by addition of trace amounts of water. Corresponding studies on the block copolymer PNIPAM-*b*-PBA[15] are also presented. Using molecular dynamics simulations, we offer insights into the mechanistic details underlying the observed linear increase in UCST with added water. Our results provide detailed insights into the scope and origin of the thermo-responsive behavior of borinic acid polymers.



PBA **PNIPAM-*b*-PBA**

Chart 1. Structures of borinic acid (co)polymers.

Experimental Section

Materials. The PBA homopolymer ($M_{n,\,GPC}$ = 38500 g/mol, $Đ$ = 1.26; $DP_{PBA,\,GPC}$ = 94; $DP_{PBA,\,NMR}$ = 86) and PNIPAM-*b*-PBA block copolymer ($M_{n,\,GPC}$ = 27020 g/mol, $Đ$ = 1.26; $DP_{PNIPAM,\,GPC}$ = 82; $DP_{PBA,\,GPC}$ = 42; $DP_{PNIPAM,\,NMR}$ = 63, $DP_{PBA,\,NMR}$ = 36) were prepared as reported previously.[14,15]

Methods. Thermo-responsive data were recorded based on turbidity changes, by measuring the transmittance of the polymer solution (polymer concentration of 1.0 mg/mL) on a Cary-100 spectrophotometer equipped with a Peltier heated multi-cell holder with a Cary temperature controller and probe (from 0 to 70 °C with a heating and cooling rate of 1 °C/min [6]). The temperature with a transmittance of 50% in the heating process was used to determine the UCST. Thermo-responsive measurements (from 70 to 100 °C) were performed using an oil bath with a digital thermo-controller, where the temperature with an obvious turbidity change in the heating process was used to determine the UCST. The dynamic light scattering (DLS) measurements were performed at 25.0±1 °C with a Malver Zetasizer Nano-ZS instrument, equipped with a 4 mW, 633 nm He-Ne laser and an Avalanche photodiode detector at an angle of 173°.

Molecular simulations. Explicit solvent MD calculations were performed using the GROMACS 4.5.5 software package.[16] The 10-unit polymer molecule was put in a rectangular simulation box filled with water or DMSO molecules. 3606 water molecules were added in the pure water simulation and 1306 DMSO molecules were added in the pure DMSO simulation. For the DMSO/water mixture simulation, 360 water and 1187 DMSO molecules were added, which results in a ratio of 7%/93% (v/v). Periodic boundary conditions were applied to the simulation boxes. The OPLS all-atom force field and the tip4p water model were used in the simulations.[17] The force field parameters for boron were applied according to Chen's work.[18] For all systems, to relax the initial configurations, the potential energy of the system was minimized by using the steepest-descent method until it converged. The solvent was then relaxed for 500 ps at 300 K, with the positions of the polymer atoms restrained by a harmonic potential. Bond lengths were constrained by the LINCS algorithm.[19] The electrostatic interactions were calculated using the Particle Mesh Ewald algorithm with a cutoff of 1.0 nm.[20] The cutoff radius for the Lennard-Jones interactions was set to 1.0 nm. A relative dielectric constant of 1 and a time step of 1 fs were used. All simulations were performed using the constant NPT ensemble. The temperature of the system was kept constant using the Nosé-Hoover thermostat[21] with a time constant of 0.2 ps. The Parrinello-Rahman method with a coupling time of t_P = 1.0 ps was used to implement the barostat with P_0 = 1 bar.[22]

Results and Discussion

Thermo-Responsive Properties of Borinic Acid Polymers. When studying the solubility characteristics of the borinic acid polymer PBA, we discovered an interesting thermo-responsive behavior in DMSO in the presence of small amounts of water. As shown in Figure 1A, the UCST increases linearly over a wide temperature range from 20 °C (close to the melting point of DMSO) to 100 °C (the boiling point of water) as the amount of water increases from 0 to 2.5% (v/v). The origin of this thermo-responsive behavior of PBA is likely related to competing H-bond formation between BOH moieties on the polymer and H_2O and DMSO solvent molecules (*vide infra*); crosslinking through B-O-B bond formation (dehydration) as observed in other borinic acid species is unfavorable due to the presence of the bulky Tip groups.[23] To investigate the general applicability, additional studies were carried out in other water-miscible solvents, including THF, DMF and tetramethylene sulfone (TMSO, structurally similar to DMSO). The thermo-responsive properties of PBA in THF and DMF with different amounts of water are illustrated in Figures 1B, 1C. Indeed, PBA solutions in THF and DMF show tunable UCSTs. However, in THF, PBA solutions do not show a thermo-responsive behavior when the water content is lower than 13%. A UCST value of ~0 °C (close to the freezing point of water) is observed at ~14% water content and a further increase of water content to ~19% leads to an almost linear increase in the UCST to ~60 °C (close to the boiling point of THF). Similarly, the UCST value of a PBA solution in DMF increases from ~0 °C (close to the freezing point of water) to ~100 °C (close to the boiling point of water) as the water content increases from ~3 to ~17%. It is apparent that the amount of water needed to observe a UCST for PBA increases in the order of DMSO, DMF to THF. This trend seems to correlate with the ability of these solvents to form hydrogen bonds with the borinic acid moieties. Hydrogen bond formation was further verified by ^1H NMR analysis of (iodophenyl(triisopropylphenyl)-borinic acid) as a model compound. In [D_6]-DMSO a peak at 10.3 ppm can be attributed to the BOH moiety, which disappears when 7% of D_2O are added (see Figure S1, ESI).

Based on our observations, the tunable thermo-responsive property of PBA is a general phenomenon (DMSO, THF and DMF), though exceptions are encountered as in the case of TMSO. In TMSO, the PBA solution only showed a single UCST value of

28 °C at 4% of water content (data not shown), but a further increase in the amount of water resulted in permanent phase separation. In comparison to prior studies on the thermo-responsive behavior of polyoxazolines in alcohol/water mixture,[24] it is noteworthy that the UCST of PBA can be achieved in a number of different solvents (DMSO, THF and DMF) and the temperature range over which the UCST can be varied by addition of only very small amounts of water is unprecedented.

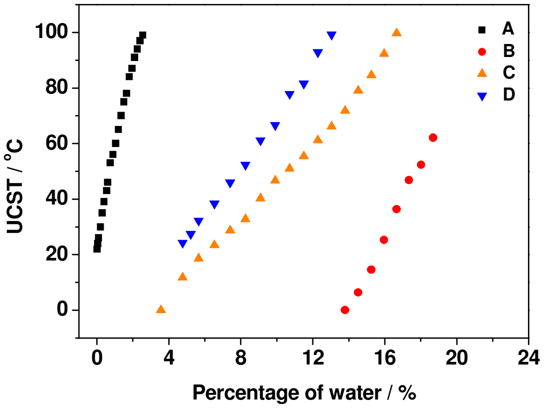


Figure 1. Tunable thermo-responsive behavior of borinic acid (co)polymers in different solvents with different amounts of water. Polymer concentration = 1 mg/mL. (A) PBA in DMSO; (B) PBA in THF; (C) PBA in DMF; (D) PNIPAM-*b*-PBA in DMSO.

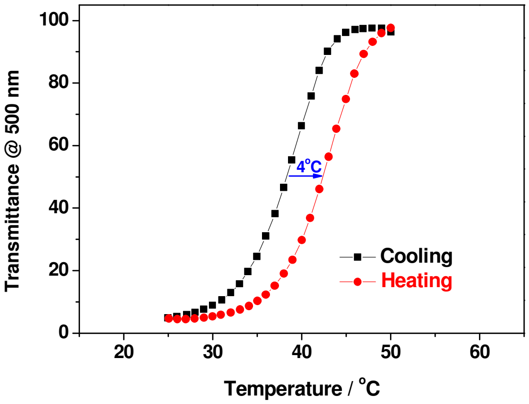


Figure 2. Transmittance vs temperature curve of PNIPAM-*b*-PBA solution in DMSO with 7% of water (v/v); the solution was heated and cooled at a rate of 1 °C/min.

We also investigated the thermo-responsive behavior of the block copolymer PNIPAM-*b*-PBA. The transmittance vs temperature results for a PNIPAM-*b*-PBA solution in DMSO with 7% H_2O (v/v) are displayed in Figure 2. The PNIPAM-*b*-PBA solution shows an obvious UCST-type thermo-responsive behavior. When the temperature is lower than 30 °C, the transmittance of the solution is <10%. The transmittance increases as the temperature rises and reaches >90% above 47 °C. We observed a difference of up to 4 °C between the heating and cooling cycle, which is due the hysteresis between dissolution and setting temperature.[25] The temperature with a transmittance of 50% in the heating process was used to determine the UCST. Again, the UCST was found to depend on the amount of water present in DMSO as seen in Figure 1D. The PNIPAM-*b*-PBA solution remains transparent until the amount of water increases to ~5%. A UCST is observed when the water content is higher than 5% and the UCST value increases from about 20 to 100 °C when further increasing the water content from ~5 to 13%. Compared to the PBA homopolymer, which shows a tunable UCST with 0 to 2.5% of added water, the PNIPAM-*b*-PBA block copolymer requires much more water to reach both the lowest and highest UCST value. Clearly the presence of PNIPAM increases the solubility of the block copolymer in DMSO. We also note that while PNIPAM is known to display an LCST transition in water, in our case the water content is low and an LCST behavior is not observed. Indeed, a solution of PNIPAM in DMSO remains fully transparent even after addition of 13% of water.

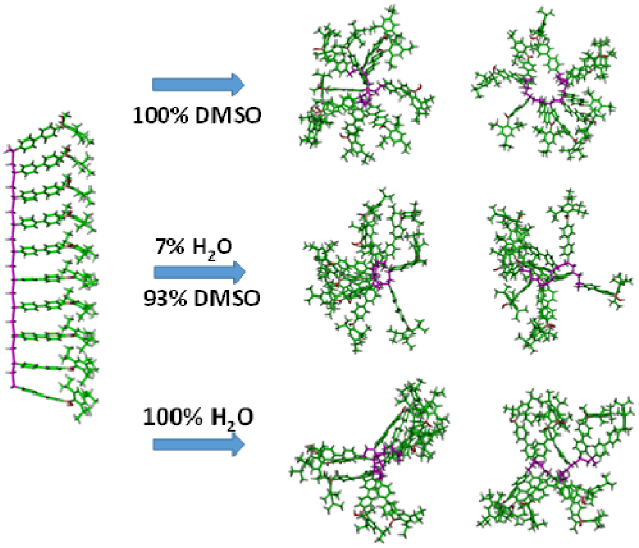


Figure 3. Structural snapshots of the PBA in 100% DMSO, 7% H_2O (93% DMSO) and 100% H_2O at 10 ns in simulations.

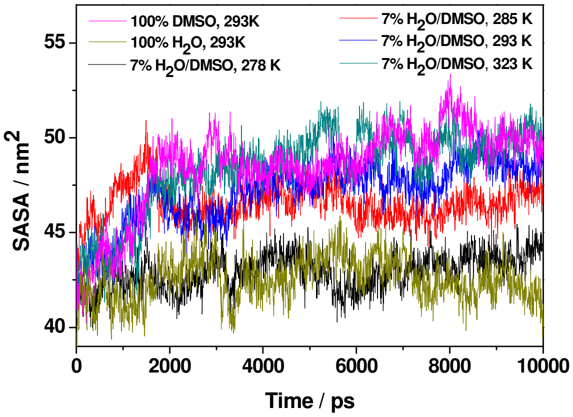


Figure 4. Solvent Accessible Surface Area (SASA) results of PBA in pure H_2O, pure DMSO at 293K, and 7% H_2O/DMSO (v/v) at different temperatures.

Mechanistic Studies on the Thermo-Responsive Properties of PBA in DMSO/H_2O Mixtures. Molecular dynamics simulations were carried out to simulate the PBA polymer (10 repeat units) in pure water and pure DMSO at 293K, as well as in 7% of H_2O in DMSO (v/v) at different temperatures, as shown in Figure 3. The simulations indicate that in pure DMSO, the PBA molecule is well-extended and the sidechains well-solubilized (seperated by DMSO solvent). In contrast, the PBA molecule is compressed in pure H_2O due to hydrophobic effects and the sidechains are bundled together. The PBA molecules behave somewhat in-between in 7% of H_2O in DMSO (v/v) mixture. Some of the sidechains form bundles while others are separated by solvent molecules. These results are consistent with a solvent-accessible surface area (SASA) analysis,[26] which is a well-established method to analyze the solvent exposure of a molecule. SASA of PBA is ~47 nm^2 in pure DMSO, while it is ~38 nm^2 in pure H_2O and in-between for 7% of H_2O/DMSO (v/v) mixture, as shown in Figure 4. These results indicate better solubility of PBA in DMSO and poorer solubility in H_2O, which is consistent with experimental data acquired by dynamic light scattering. A hydrodynamic diameter of 3.4 nm in DMSO indicates that PBA is molecularly dissolved. In contrast, large aggregates with an average diameter of 1990 nm are formed in H_2O and the average size became 1484 nm in 7% H_2O/DMSO (v/v).

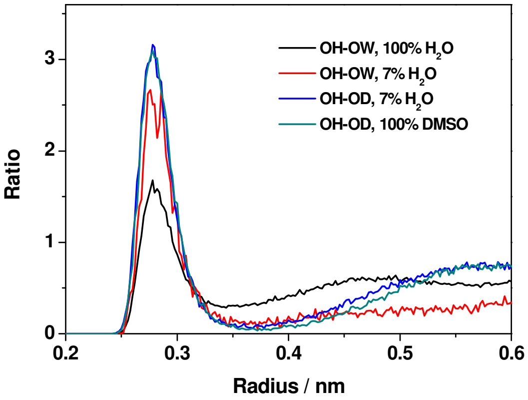


Figure 5. Radial distribution functions (RDF) of the water and DMSO solvent around BOH groups of PBA. "OH" represents the oxygen atom of BOH, "OW" the oxygen atom of water, and "OD" the oxygen atom of DMSO. This analysis is based on a simulation at 293K.

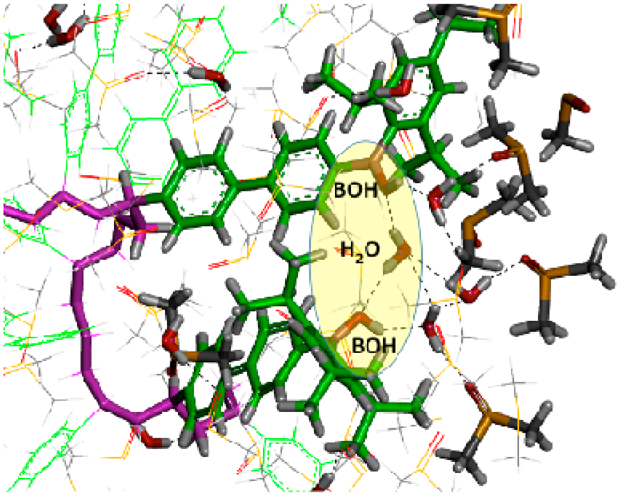


Figure 6. Snapshot of the H-bond network of polymer PBA in 7% H_2O / DMSO (v/v) simulated at 293 K. Yellow zone: H-bond formation between BOH and H_2O.

To investigate the effect of H_2O in PBA/DMSO solutions in more detail, the radial distribution functions (RDF) of H_2O and DMSO solvent around the BOH moieties were calculated as shown in Figure 5. The RDF of BOH-DMSO stays the same (~3.2) in pure DMSO and 7% H_2O/DMSO (v/v) mixture, while the RDF of BOH-H_2O increases significantly (~2.6) in the 7% H_2O/DMSO (v/v) mixture compared with a value of ~1.6 in pure H_2O. These results indicate that DMSO molecules can access the pendent BOH groups in both DMSO and H_2O/DMSO mixture, but H_2O molecules prefer to be close to BOH in the H_2O/DMSO mixture. This explains why trace amounts of H_2O could cause microphase separation of PBA molecules in DMSO. To further investigate the role of H_2O in PBA/DMSO solutions, the structure of PBA molecules in DMSO with 7% H_2O was captured in a molecular simulation, as shown in Figure 6. H-bond formation between BOH and H_2O is obvious where H_2O serves as a crosslinker between BOH groups by forming BOH-H_2O-HOB H-bonds. These crosslinks likely contribute to the microphase separation of PBA chains in DMSO.

To further explore the thermo-responsive behavior of PBA in H_2O/DMSO mixtures, SASA simulations of PBA in 7% H_2O/DMSO (v/v) mixture were carried out at different temperatures, as shown in Figure 4. The SASA of PBA increases as the temperature rises and reaches the same level as for PBA in pure DMSO, where PBA molecules are well dissolved. These results are consistent with microphase separation of PBA molecules in a 7% H_2O/DMSO (v/v) mixture at low temperature and dissolution of the PBA molecules as the accessible surface area of PBA increases. To confirm the strong H-bond formation and the possible role of H_2O as a crosslinker, we investigated the H-bond network in detail by analyzing the number of different types of H-bonds as well as their lifetime (Table 2 and 3). The lifetime of BOH-H_2O H-bonds in DMSO/H_2O mixture is far longer than that in pure H_2O, possibly reflecting the crosslinking effect of H_2O-BOH-H_2O H-bonds in DMSO/H_2O mixture. The number of BOH-H_2O H-bonds decreases from 2.5 to 1.8 as the temperature rises from 278 to 293 K and the number of BOH-DMSO bonds increases from 8.0 to 8.9, which results in improved solubility of PBA in the DMSO/H_2O mixture. A further increase of the temperature results in a decrease of the number of H-bonds between BOH-H_2O, BOH-DMSO, H_2O-DMSO and H_2O-H_2O, which is due to the increased molecular motion as the temperature increases.

Consequently, the lifetime of all H-bond types also decreases dramatically as the temperature rises. Based on these results, the mechanism of the thermo-responsive behavior of PBA in DMSO is entropy-driven as the H-bond networks become unstable at high temperature, which is consistent with the experimental observation that PBA solutions in DMSO/H_2O become transparent when the temperature rises.

Table 2. Distribution of different types of H bonds according to the simulations.

Solvent	T (K)	BOH-H_2O	BOH-DMSO	H_2O-DMSO	H_2O-H_2O
7% H_2O/DMSO	278	2.5	8.0	543.5	80.8
7% H_2O/DMSO	285	2.2	8.7	543.4	78.5
7% H_2O/DMSO	293	1.8	8.9	545.9	73.9
7% H_2O/DMSO	323	1.2	8.0	533.9	71.8
100% DMSO	293	-	9.4	-	-
100% H_2O	293	19.3	-	-	3200

Table 3. Lifetimes (ps) of different types of H-bonds according to the simulations.

Solvent	T (K)	BOH-H_2O	BOH-DMSO	H_2O-DMSO	H_2O-H_2O
7% H_2O/DMSO	278	381	408	213	158
7% H_2O/DMSO	285	281	364	176	138
7% H_2O/DMSO	293	253	316	143	111
7% H_2O/DMSO	323	113	137	58	47
100% DMSO	293	-	298	-	-
100% H_2O	293	22	-	-	5

Conclusions

The thermo-responsive properties of borinic acid polymers, a new class of functional materials, have been investigated in depth. We found that borinic acid-functionalized polymers show a UCST behavior that is tunable over a wide temperature range in various organic solvents containing small amounts of water (from the freezing point of the solvent with higher freezing point to the boiling point of the solvent with the lower boiling point). Molecular dynamics simulations revealed a strong preference for H_2O molecules to be close to the BOH functional groups (and other H_2O molecules), serving as reversible cross-linkers between PBA polymer chains. We expect our results to stimulate new research into borinic acid polymers as "smart" polymers, given the intense current interest in boronic and borinic acid polymers for biological and sensing applications and as building blocks in supramolecular self-assembly.

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Notes

The authors declare no competing financial interest.

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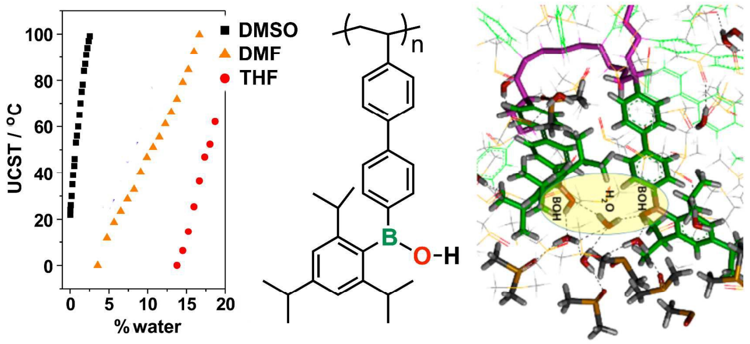
TOC Entry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