

Thermo-, pH-, and Light-Responsive Supramolecular Complexes Based on a Thermoresponsive Hyperbranched Polymer

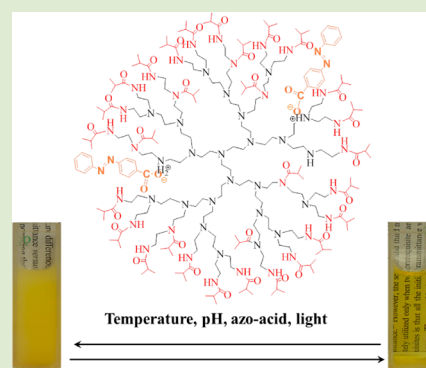
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S Supporting Information

ABSTRACT: Hyperbranched polyethylenimine terminated with isobutyramide groups (HPEI-IBAm) was mixed with 4-(phenylazo)benzoic acid (PABA) to form supramolecular complexes through the neutralization reaction between the amino groups of HPEI-IBAm and the carboxylic acid group of PABA, which was verified by ¹H and 2D NOESY ¹H NMR spectroscopy. The obtained supramolecular complexes with a molar ratio of PABA to HPEI-IBAm of ≤ 8 were soluble in water and exhibited thermoresponsive properties. Their cloud point temperature (T_{cp}) was sensitive to PABA content, and PABA molecules were exchanged between HPEI-IBAm hosts. The topology of the polymer affected the change in T_{cp} of the complexes. At pH ~ 7 , increasing the PABA content decreased T_{cp} , whereas it caused T_{cp} to increase at pH ~ 9 . Reversible *trans*-to-*cis* photoisomerization of azobenzene units in the complexes occurred following irradiation with UV or visible light. At pH ~ 7 , *trans*-to-*cis* isomerization of azobenzene units increased T_{cp} , whereas the opposite occurred at pH ~ 9 .



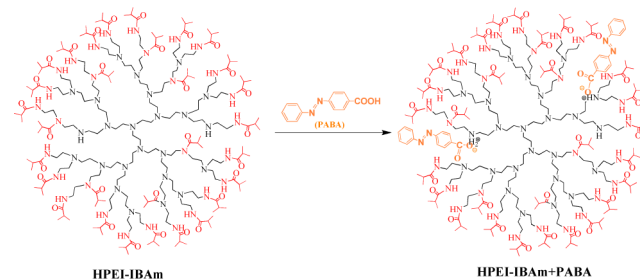
During the past decade, polymers with stimuli-responsive properties, such as fast and reversible conformational or phase changes in response to variations in temperature and/or pH, have attracted much interest.¹ An appealing stimuli-responsive species is thermoresponsive polymers with a lower critical solution temperature (LCST) in aqueous solution, which show a large decrease in solubility in water above a specific temperature.² To date, research concerning a single thermo-stimulus has been extended to dual^{3–16} and even triple stimuli.^{17–24} Besides temperature, other typical stimuli include pH,^{5–7,16–23} light,^{10–13,18–20,25} redox potential,²² and ionic strength.^{8,9,21}

Thermoresponsive polymers are common, but supramolecular complexes with thermoresponsive properties are not.^{26–29} Compared with polymers containing only covalent bonds, supramolecular complexes with noncovalent bonds possess advantages including: (1) convenient preparation, (2) facile variation of composition, and (3) varied properties because of the dynamic noncovalent bonds. Thermoresponsive supramolecular complexes that respond to more than two stimuli have seldom been prepared.³⁰ Herein, we report a triply responsive supramolecular complex that is sensitive to temperature, pH, and light.

We have studied hyperbranched polyethylenimine (HPEI) terminated with isobutyramide (IBAm) groups (HPEI-IBAm),^{7–9} which is thermoresponsive and shows LCST in water when it contains a certain number of IBAm units. Mixing HPEI-IBAm with 4-(phenylazo)benzoic acid (PABA) should

form supramolecular complexes through acid–base neutralization (Scheme 1).

Scheme 1. Preparation of the Supramolecular Complex of HPEI-IBAm and PABA



PABA is soluble in dimethylformamide (DMF) but not in pure water, so the supramolecular complex was prepared in a mixture of H₂O and DMF (v/v = 9:1). After heating above a certain temperature, a great deal of precipitate formed, which was collected and characterized by ¹H NMR spectroscopy (Figure 1A). Formation of a supramolecular complex between HPEI-IBAm and PABA was evidenced by: (1) Both HPEI-IBAm and PABA units appear in ¹H NMR spectra (Figure 1A). (2) The signals from PABA units are much broader than those

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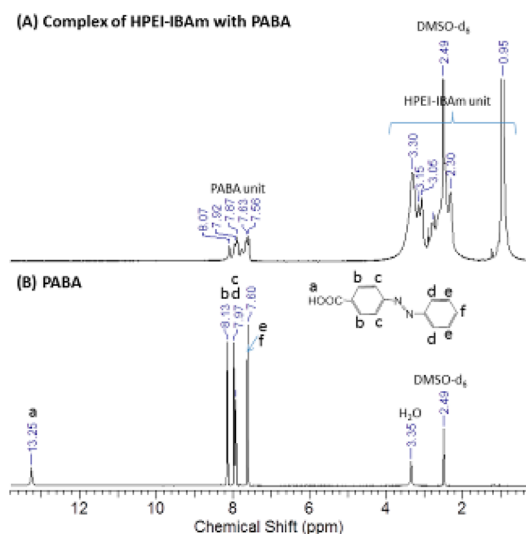


Figure 1. Typical ^1H NMR spectra of (A) a complex of HPEI-IBAm with PABA and (B) PABA.

in the ^1H NMR spectrum of PABA alone (Figure 1B), which can be attributed to the rotational and diffusional mobility of PABA molecules being confined by complex formation. (3) The carboxylic acid (COOH) signal of PABA at ca. 13.25 ppm is not observed in Figure 1A, implying acid–base neutralization has occurred between the amino groups of HPEI-IBAm and the COOH groups of PABA. (4) The chemical shift of the protons on the aromatic ring adjacent to the carbonyl group (signal b) of PABA (Figure 1B) shifts upfield from 8.13 to 8.07 ppm in Figure 1A. This implies the formation of carboxylate anions (COO^-) because COO^- is a weaker electron-withdrawing group than COOH.

2D NOESY ^1H NMR spectroscopy is a powerful technique to investigate the interaction between two different components in close proximity (<0.5 nm). A 2D NOESY ^1H NMR spectrum of the supramolecular complex (Figure S1 in the Supporting Information) showed strong positive cross-peaks between the aromatic rings of PABA and the methyl groups of HPEI-IBAm, revealing the formation of a complex of HPEI-IBAm and PABA.

All the obtained supramolecular complexes with a molar ratio of PABA to HPEI-IBAm ≤ 8 were soluble in water. Aqueous solutions of these complexes became turbid after being heated above certain temperatures and went transparent again when they were cooled down (Figure S2 in the Supporting Information). This indicated that the obtained supramolecular complexes were thermoresponsive. Figure 2A depicts the typical temperature dependence of the light transmittance of aqueous solutions of the complexes. All of the supramolecular complexes show lower cloud point temperatures (T_{cp}) than their polymeric precursor HPEI-IBAm. Figure 2B shows that increasing the PABA content in the complex leads to an almost linear decrease of T_{cp} when the PABA content is sufficiently high, indicating that the thermoresponsive properties of these supramolecular complexes are sensitive to PABA content.

Two complexes with different PABA content (molar ratios of PABA to HPEI-IBAm of 1:1 and 8:1) were mixed together. The light transmittance of this solution at different temperatures after different mixing time was plotted (Figure S3 in the Supporting Information). If dynamic exchange of PABA molecules did not occur between HPEI-IBAm hosts, two

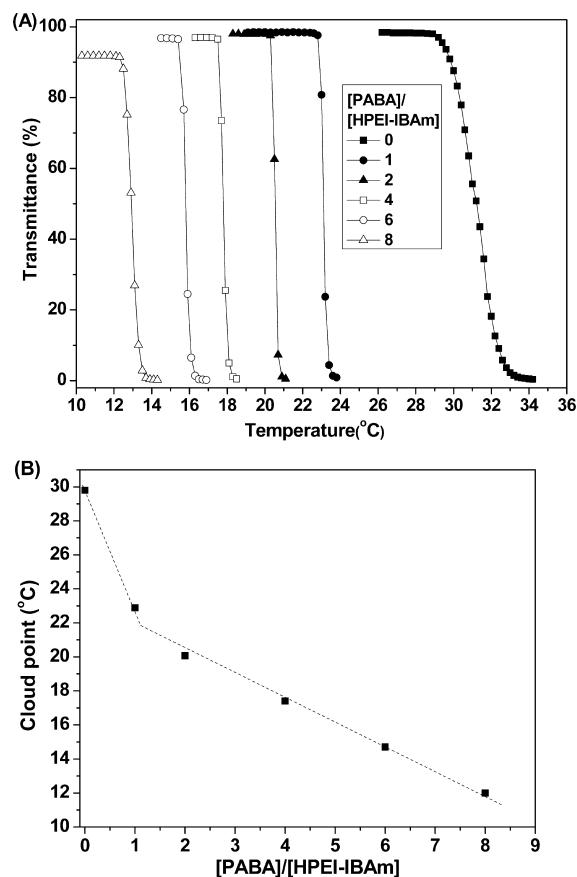


Figure 2. Influence of (A) temperature on the light transmittance of HPEI-IBAm + PABA complexes in deionized water and (B) the ratio of PABA to HPEI-IBAm on T_{cp} (concentration of complex is 10 mg/mL).

phase transitions would be expected. However, only one phase transition was observed, although it took some time for the mixed complexes to reach a constant T_{cp} . Thus, dynamic exchange of PABA molecules between the HPEI-IBAm hosts occurs in these complexes.

Increasing the hydrophobicity of thermoresponsive polymers decreases the phase transition temperature, whereas increasing the hydrophilicity increases it.³¹ PABA consists of a polar COOH group and an apolar azobenzene unit. After complexation of PABA with HPEI-IBAm, the apolar azobenzene unit will decrease T_{cp} , but the polar COOH group will increase it, especially following neutralization between the COOH of PABA and the amino groups of HPEI-IBAm to generate more polar COO^- and ammonium (N^+) groups. Figure 2 indicates that it is the apolar azobenzene unit in the dendritic complex that determines the change in T_{cp} . We attempted to verify if this behavior also held for a thermoresponsive linear polymer system, poly(*N,N*-dimethylamino ethyl methacrylate) (PDMAEMA). PDMAEMA was mixed with PABA under the same conditions as HPEI-IBAm. Unlike the HPEI-IBAm system, introduction of PABA increased the T_{cp} of PDMAEMA (Figure S4 in the Supporting Information), indicating that the polar COOH group of PABA dominates the change of T_{cp} in the PDMAEMA system. Overall, these experiments show the topology of the polymer in the complex affects the change in T_{cp} . The varying influence of PABA in these supramolecular systems is tentatively explained as follows: NMR characterization verified that PABA can effectively react with the amino

groups of HPEI-IBAm or PDMAEMA to form ionic groups (N^+ and COO^-). In the PDMAEMA system, the COO^- groups have enough space to move in the loosely coiled PDMAEMA chains, so N^+ and COO^- ions are in the free state or form loose ion pairs that can affect T_{cp} more than the hydrophobic azobenzene. Compared with PDMAEMA, HPEI-IBAm is very compact. Once the $COOH$ group of PABA reacts with the inner amino groups of HPEI-IBAm, the free space for the formed COO^- is less than in the PDMAEMA system. Moreover, a large number of amide groups are close by, which can hydrogen bond with the carbonyl groups and further restrict the movement of COO^- . Thus, in the complexes of HPEI-IBAm with PABA, besides free ions and loose ion pairs, the less polar compact ion pairs of N^+ and COO^- must be present, which lowers the T_{cp} of the dendritic complex. It is known that CO_3^{2-} effectively forms compact ion pairs with N^+ groups of HPEI-IBAm, decreasing T_{cp} .⁹

The thermoresponsive properties of the supramolecular complexes of HPEI-IBAm and PABA are pH-sensitive (Figure 3A). However, the pH response of the complexes differs from that of their polymeric precursor, HPEI-IBAm. The pH of the formed complexes and HPEI-IBAm precursor in water is close to 7. For HPEI-IBAm, increasing the acidity of the solution significantly increases T_{cp} . Conversely, adjusting the pH to around 9 lowers the T_{cp} to a constant value. For solution of the

supramolecular complexes, increasing the acidity causes PABA molecules to precipitate out of the solution, and T_{cp} increases as the pH is raised until it levels off when the pH approaches 9 (Figure 3A). Comparing T_{cp} of the complexes and their polymeric precursor at pH ~ 9 (Figure 3B) reveals that increasing the PABA content leads to an almost linear increase of T_{cp} , which differs from the change in T_{cp} observed at pH ~ 7 . The different pH responses of the complexes and their polymeric precursor are interpreted as follows: As the acidity of an aqueous solution of HPEI-IBAm increases, more amino groups of HPEI-IBAm are protonated to form more polar N^+ groups. The significant increase in polarity increases T_{cp} . In contrast, increasing basicity gradually turns the more polar protonated N^+ groups into less polar amines, decreasing T_{cp} . For the supramolecular complexes, at pH ~ 7 , the polar COO^- group of PABA has a strong ionic attraction to the inner protonated N^+ groups of dendritic HPEI-IBAm, so PABA molecules are embedded inside the HPEI-IBAm macromolecule (Scheme 1). When the acidity of the solution is increased, the COO^- group of PABA transforms back to $COOH$, destroying the strong ionic attraction. Increasing the acidity also increases the interior polarity of HPEI-IBAm because of further protonation of residual amino groups. Therefore, the less polar PABA molecules are expelled out of the polar interior of HPEI-IBAm. Because PABA is insoluble in water, a yellow precipitate forms. Increasing the basicity of the solution transforms the protonated N^+ groups into neutral amines, which also destroys the strong ionic attraction so the COO^- group of PABA is in the free-ion state. Because the interior of HPEI-IBAm is transformed into less polar neutral amines, the interaction between PABA and HPEI-IBAm might change. Anionic surfactants with polar COO^- , SO_3^- , or OSO_3^- head groups and long hydrophobic hydrocarbon chains can increase the phase transition temperature of the traditional linear thermoresponsive polymer poly(*N*-isopropylacrylamide) (PNIPAM), and these surfactants interact with PNIPAM directly through the entropy-driven hydrophobic interaction between the long hydrocarbon chain of the surfactant and the hydrophobic moieties of PNIPAM.^{32,33} At pH ~ 9 , PABA can also increase T_{cp} of HPEI-IBAm, and T_{cp} of the supramolecular complexes increases with increasing PABA content. This implies that PABA molecules with free COO^- ions in the dendritic system act just like the anionic surfactants and loosely pack on the hydrophobic surface of HPEI-IBAm through hydrophobic interactions (Figure S5 in the Supporting Information).

Azobenzene is a well-known light-responsive molecule that undergoes reversible isomerization between *trans* and *cis* configurations under irradiation.³⁴ We investigated if the light-induced configuration change of PABA units affected the thermoresponsive properties of the supramolecular complexes. Solutions of the supramolecular complexes were irradiated by UV light (365 nm) to induce *trans*-to-*cis* photoisomerization of azobenzene units. This isomerization was monitored by UV-vis spectroscopy (Figure S6 in the Supporting Information), where the absorbance intensity of *trans*-PABA at 327 nm decreased under irradiation. The change of the intensity of *trans*-PABA at 327 nm suggested that about 70% of *trans*-PABA could be converted to *cis*-PABA under the irradiation conditions used, and more PABA units in the supramolecular complexes led to lower conversion (Figure S7 in the Supporting Information). Furthermore, the rate of *trans*-to-*cis* photoisomerization was higher at pH ~ 9 than ~ 7 . This was

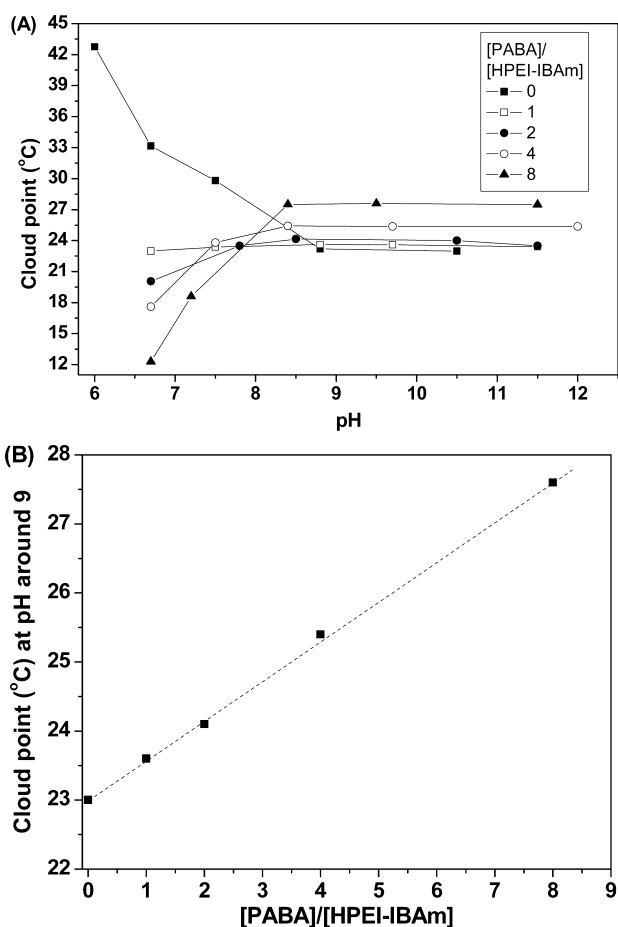


Figure 3. (A) Influence of pH on T_{cp} of HPEI-IBAm and supramolecular complexes of HPEI-IBAm and PABA. (B) Effect of the ratio of PABA to HPEI-IBAm on T_{cp} at pH ~ 9 (concentration of complex or polymer is 10 mg/mL).

because the PABA units at pH ~ 9 were not restricted by the HPEI-IBAm host as much as at pH ~ 7 (compare Scheme 1 with Figure S5 in the Supporting Information). The reversibility of photoisomerization was also measured. After irradiation for 1 h, the solutions of the supramolecular complexes were irradiated by visible light for 1 h to induce *cis*-to-*trans* photoisomerization. This procedure was repeated for four cycles, revealing that photoisomerization between *trans* and *cis* configurations using light irradiation was fully reversible (Figure S8 in the Supporting Information).

The thermoresponsive properties of the supramolecular complexes following irradiation by UV light were measured. Figure 4 (and Figure S9 in the Supporting Information) shows

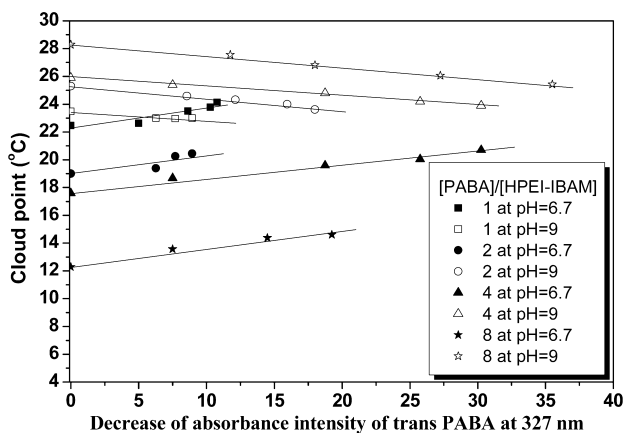


Figure 4. Influence of the change of the absorbance of *trans*-PABA at 327 nm on T_{cp} of thermoresponsive supramolecular complexes with different PABA content in water at pH = 6.7 and 9 (concentration of complex is 10 mg/mL).

that the thermoresponsive properties of the obtained supramolecular complexes are also light-responsive. However, the change in T_{cp} is also pH dependent. At pH ~ 7 , T_{cp} increases following UV light irradiation, and the increase of T_{cp} is almost directly proportional to the decrease of the absorbance intensity of *trans*-PABA at 327 nm. However, at pH ~ 9 , the opposite behavior is observed. We interpreted these findings by considering two factors. One is the change in polarity, and the other is the volume change during *trans*-*cis* isomerization. The polarity of different isomers of PABA (embodied as the dipole moment) was calculated using MOPAC2009 software (Figure S10 in the Supporting Information). The *cis* configuration of PABA or the compact ion pair between PABA and ammonium ions possesses higher dipole moments than the corresponding *trans* configuration; this situation is reversed when the PABA anion is in the free state. At pH ~ 7 , a strong ionic interaction exists between PABA units and HEI-IBAm, and *trans*-to-*cis* isomerization has almost no influence on this strong ionic interaction. Because the PABA molecules are deeply embedded in the HPEI-IBAm host, two factors might contribute to the increase of T_{cp} during *trans*-to-*cis* isomerization: one might be the volume expansion of the complex because the *cis* isomer is bulkier than the *trans*, which lowers the density of the periphery of the dendritic host and increases T_{cp} .⁶ The other factor is the increased polarity of the *cis* configuration of PABA anions in the compact ion-pair state compared to the *trans* one. *Trans*-to-*cis* isomerization increases the local polarity of the supramolecular complexes, increasing T_{cp} . At pH ~ 9 , the COO⁻ ion of PABA is in the free state. In

this case, the *trans* configuration of PABA possesses a higher dipole moment than the *cis*. Therefore, *trans*-to-*cis* isomerization reduces the polarity of PABA units, lowering the overall polarity of the complexes. Thus, at pH ~ 9 , T_{cp} decreases following exposure to UV light.

In summary, supramolecular complexes that responded to temperature, pH, and light were prepared simply by mixing thermoresponsive HPEI-IBAm with PABA. Their T_{cp} was sensitive to PABA content, and dynamic exchange of PABA molecules occurred between HPEI-IBAm hosts. The topology of the polymer determined the change in T_{cp} of the resulting complex. The interaction mode of HPEI-IBAm with PABA depended on pH. At pH ~ 7 , the main interaction was ionic attraction, while at around 9, it was entropy-driven hydrophobic interactions. This meant the phase transition temperature of the supramolecular complexes varied in the opposite manner at pH ~ 7 and ~ 9 when the content of PABA units in the complexes and the extent of *trans*-to-*cis* photoisomerization of PABA units changed.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental details and additional figures including 2D NOESY ¹H NMR spectrum, turbidity, light transmittance of a mixed solution, influence of PABA on T_{cp} of PDMAEMA, etc. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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