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Redox-responsive Inclusion Complexation between β-Cyclodextrin and Ferrocene-functionalized Poly(*N*-isopropylacrylamide) and its Effect on the Solution Properties of this Polymer

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Ferrocene-functionalized polymers (poly(NIPAM/FCN)) and their β-CD (β-Cyclodextrin) complex have been prepared. The inclusion complexation between them was investigated by several techniques, including ^{1}H NMR spectra, cyclic voltammetry, UV–vis spectra and dynamic light scattering measurements. The results showed that β-CD could interact with the reduced ferrocene side groups and hardly affect the oxidized form. Thus a redox-responsive inclusion complexation system based on β-CD and poly(NIPAM/FCN) was obtained. In addition, the effect of this inclusion complexation on the solution properties of this polymer was also investigated. LCST (lower critical solution temperature) increased and the viscosity decreased upon addition of β-CD into the reduced polymer solution due to the disruption of the hydrophobic interaction between the ferrocene side groups by the inclusion complexation. Yet LCST and viscosity of the oxidized polymer solution changed slightly, which resulted from the weak interaction exerted by β-CD.

Keywords: Supramolecular structures; Stimuli-sensitive polymers; Redox polymers; Molecular recognition

INTRODUCTION

Cyclodextrins (CDs) are well known in supramolecular chemistry as molecular hosts. Host-guest interactions through the hydrophobic cavities of CDs lead to the formation of inclusion complexes within the cavities with guest molecules smaller than the cavity size [1,2]. Recently the design and preparation of novel supramolecular systems based on the recognition between CDs and side groups of polymers have attracted much attention [3–7]. In these systems, the hydrophobic associations between the side groups are inhibited due to the inclusion by CDs, which can significantly modify the properties of the polymers, such as solution viscosity [3,4], LCST [5,6]. And this type of site selective inclusion complexation may play an important role in the construction of artificial supramolecular structures in polymeric systems.

It is well known that changes in the properties of the guest molecules could lead to modification of the inclusion complexation. For example, the *trans* azobenzene can form stable inclusion complex with α-CD, while the *cis* azobenzene cannot [3,7]. It is not surprising that a responsive inclusion complexation could be realized through the application of external stimuli. Photochemical [3,7], pH [8] and electrical [9,10] stimuli are all reasonable possibilities to exert control on the inclusion complexation.

Molecules containing ferrocene moieties have proved perfect guests for β-CD [9–13]. The complexation between β-CD and the ferrocene groups will be strongly diminished upon oxidation of the ferrocene groups as the positively charged ferrocenium species is not bound effectively inside the nonpolar cavity of β-CD [12,13]. Although redox-responsive inclusion complexation between β-CD and derivatives of ferrocene has been described in numerous papers [4,9,10], to the best of our knowledge, there is no paper on redox-responsive systems utilizing molecular recognition of ferrocene side groups of polymers by β-CD.

On the basis of these studies, we designed a kind of ferrocene-functionalized polymer (poly(NIPAM/FCN)) and investigated the redox-responsive

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inclusion complexation between β-CD and ferrocene side groups of the polymer through a series of techniques. In addition, the effect of the inclusion complexation on the solution properties of this polymer was also investigated.

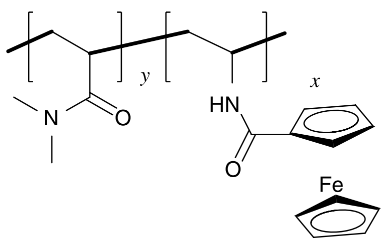
RESULTS AND DISCUSSION

Synthesis of Copolymer

Scheme 1 shows the structure of the ferrocene-functionalized polymer (poly(NIPAM/FCN)), which was prepared through radical copolymerization of FCN (N-allylferrocenecarboxamide) and NIPAM (N-isopropylacrylamide). FCN monomer contains a ferrocenyl ion which can act as a radical scavenger in the radical polymerization system [14]. In addition, the ferrocenyl group of FCN seems to be exerting a steric effect. All the above led the yield and FCN content to decrease with increasing FCN content in the feed, and in high monomer FCN content, the polymerization could not take place, as shown in Table I.

Inclusion Complexation Between β-CD and FCN Side Groups of the Copolymer

Cyclic voltammetry (CV) is the best technique of choice for studies on ferrocene-CD interactions due to the electroactive nature of ferrocene [9–13]. As shown in Fig. 1, the presence of the host β-CD shifts the apparent half-wave potential ($E_{1/2}$, determined from the mean of the anodic and cathodic peak potentials) to more positive values, which reveals that the reduced ferrocene side groups is more stabilized by complexation than the oxidized form. And a considerable increase in the anodic peak current is also detected. Since the peak current in CV under condition of constant scan rate is proportional to the square root of the diffusion coefficient of reactant species [15]. In the presence of β-CD, hydrophobic associations of ferrocene side groups are disrupted, which results in the decrease in the specific viscosity (as shown in the following part of this paper) of the polymer solution. In addition, the copolymer aggregates size decreases from 44.2 nm to 13.6 nm (as shown in the following part of this paper) due to the same reason. The two effects result in the increase in the diffusion coefficient, thus increase the anodic peak current, which also confirms the formation of the inclusion complex between β-CD and the reduced ferrocene side groups.



SCHEME 1 Structure of poly(NIPAM/FCN)

TABLE I Copolymerization of NIPAM with FCN

Copolymer (mol ratio)	Yield (%)	FCN Content (mol %)	Molecular Weight $\bar{M}n$	Molecular Weight $\bar{M}w/\bar{M}n$
(NIPAM: FCN)				
100:0	90.6	0.0	2299	1.272
40:1	81.8	1.79	2948	1.288
20:1	64.2	2.29	2347	1.229
10:1	53.0	4.71	2809	1.263
5:1	31.2	8.93	2445	1.218
5:2		No polymerization		
1:1		No polymerization		

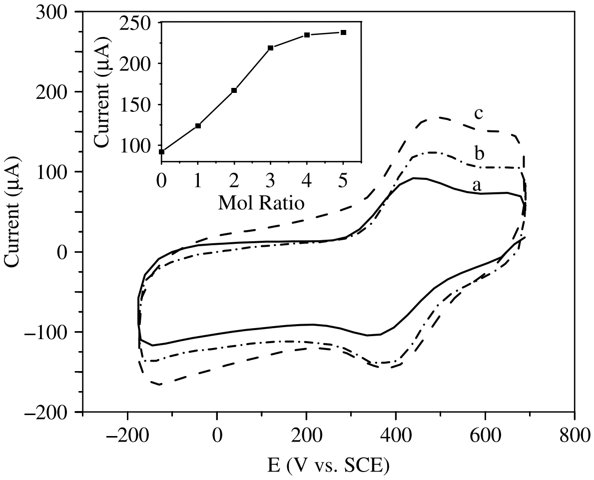


FIGURE 1 Cyclic voltammograms (scan rate: 0.1 V/s) of 0.5 wt% poly(NIPAM/FCN) in 0.2 M KCl aqueous solution under different mol ratio of β-CD and FCN side groups: (a) 0; (b) 1; (c) 2. The inset shows plot of anodic peak currents versus the mol ratio of β-CD and FCN side groups.

As shown in the insetting plot in Fig. 1, the peak current increases fast with increasing the mol ratio, and then changes slightly. The increase is caused by incorporation of more and more of ferrocene into the cavity of β-CD. At the mole ratio near three, all the ferrocene side groups have been included in the cavities of β-CD.

The inclusion complexation between β-CD and the reduced ferrocene side groups is also confirmed by ^{1}H NMR spectra. Figure 2 shows ^{1}H NMR partial spectra of poly(NIPAM/FCN) (a), poly(NIPAM/FCN)/β-CD inclusion complex (b) and β-CD (c), respectively. First, variations of the chemical shifts of β-CD protons are observed. Because H1 peak is insensitive to guest inclusion due to its remote location on the outer cavity surface, the chemical shift of other protons could be monitored relative to the anomeric H1 proton signal [16–18]. Upshield shifts of H3, H5, H6 are observed, and the peak of

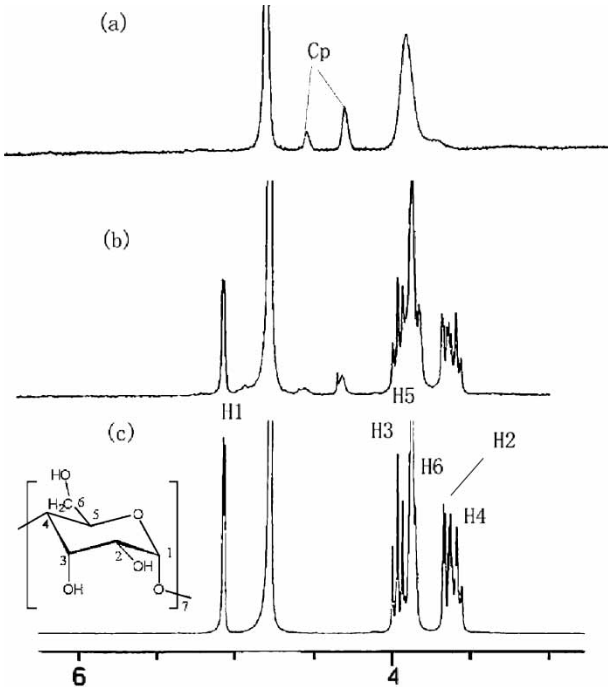


FIGURE 2 ^{1}H NMR partial spectra (300 MHz, D_2O) of poly(NIPAM/FCN) (0.5 wt%) (a), poly(NIPAM/FCN)/β-CD inclusion complex (0.5 wt%, mol ratio of β-CD/ferrocenyl group = 3) (b), and β-CD (0.88 mM) (c).

H2, H4 removes to the downfield. Since H3 and H5 protons of constituent glucose residues in β-CD point into β-CD cavity where guest molecules are located, the chemical shifts of these protons are the most sensitive to the complexation induced changes [16–18]. Large variations of the chemical shifts of H3 ($\Delta\delta = -0.037$), H5 ($\Delta\delta = -0.058$) protons indicate the formation of an inclusion complex. Second, the strongest interaction between ferrocene side groups and β-CD is demonstrated by the peak corresponding to the unsubstituted cyclopentadienyl ring (4.29 ppm) which splits into two peaks. Furthermore, the two peaks (4.29 ppm, 4.54 ppm) are substantially shifted to the downfield. All the observations indicate that the reduced ferrocene side groups have been encapsulated within β-CD cavities.

The redox-responsive inclusion complexation between β-CD and the ferrocene-functionalized poly(NIPAM/FCN) are also proven by the results of UV-vis spectra and dynamic light scattering measurements.

Figure 3 shows the UV–vis spectra of the reduced and oxidized polymer in the absence and presence of β-CD (0.5 wt%, mole ratio of β-CD/ferrocenyl group = 3, 10°C). Upon addition of β-CD into the polymer water solution, the absorption peak assignable to the reduced ferrocene group is blue shifted from 430 nm to 425.5 nm and the absorbance increases. On the other hand, the absorption peak assignable to the oxidized ferrocenyl group (ferrocenium cation) at 636 nm is affected slightly. This indicates that β-CD could form inclusion complexes with the reduced polymer, while the hydrophilic ferrocenium cations could hardly enter into the hydrophobic cavity of β-CD. The result indicates that the inclusion complexation between β-CD and poly(NIPAM/FCN) is redox-responsive.

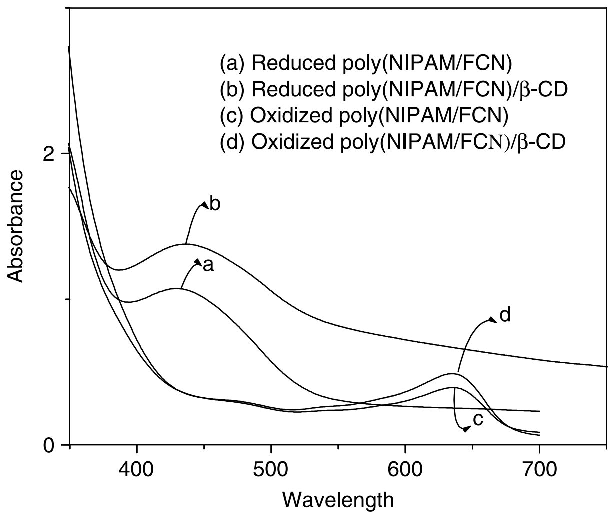


FIGURE 3 UV-vis absorption spectra of the reduced and oxidized poly(NIPAM/FCN) (0.5 wt%) aqueous solution in the absence and presence of β-CD (mol ratio of β-CD/ferrocenyl group = 3).

Figure 4 shows the size distributions of the reduced and oxidized poly(NIPAM/FCN) in the absence and presence of β-CD (0.5 wt%, mole ratio of β-CD/ferrocenyl group = 3, 10°C). After addition of β-CD into the aqueous solution of the reduced polymer, the average diameter decreases. This is assigned to the disruption of the interaction between the hydrophobic ferrocene side groups by the inclusion complexation with β-CD. On the other hand, the average diameter of the oxidized polymer is affected slightly. The result also indicates that a redox-responsive inclusion complexation between β-CD and poly(NIPAM/FCN) is obtained.

Effect of Inclusion Complexation on Poly(NIPAM/FCN) Aqueous Solution Properties

Addition of β-CD into the a aqueous solution of poly(NIPAM/FCN) leads to significant reduction in the solution viscosity and dynamic moduli as the free cyclodextrin sequesters hydrophobic association sites [19,20]. Figure 5 shows the effect of adding different amounts β-CD to 0.5 wt% the reduced and oxidized poly(NIPAM/FCN) aqueous solution on the specific viscosity obtained at 10°C. The viscosity reduction of the reduced polymer is due to the removal of the hydrophobic aggregation as the hydrophobic ferrocene side groups form inclusion compounds with β-CD. However, the viscosity of the oxidized polymer changes slightly. This also indicates the formation of the responsive inclusion complex. As shown in

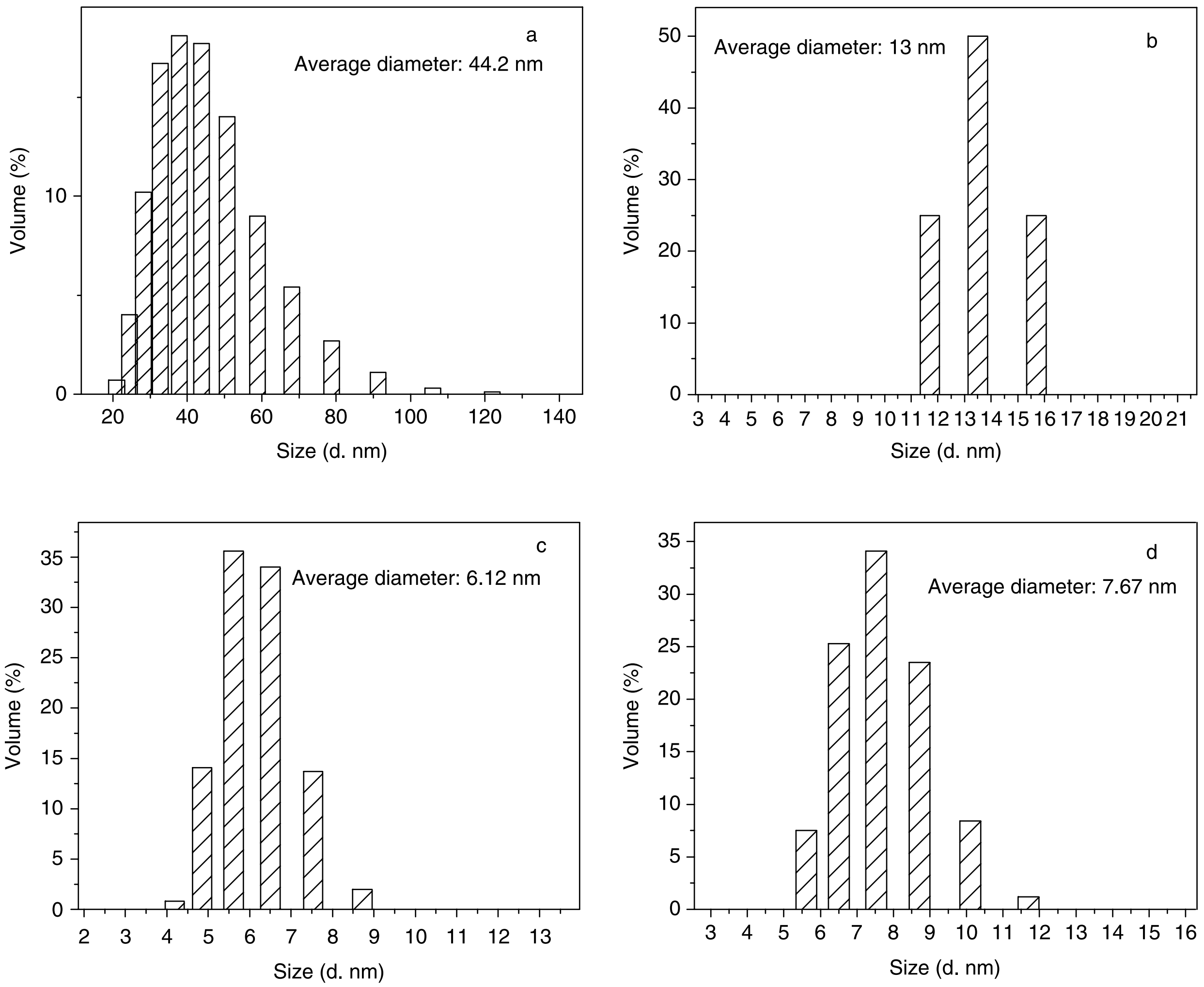


FIGURE 4 Particle size distribution of the reduced and oxidized poly(NIPAM/FCN) (0.5 wt%) in aqueous solution in the absence and presence of β-CD (mol ratio of β-CD/ferrocenyl group = 3) determined by DLS measurement: (a) Reduced poly(NIPAM/FCN); (b) Reduced poly(NIPAM/FCN)/β-CD; (c) Oxidized poly(NIPAM/FCN); (d) Oxidized poly(NIPAM/FCN)/β-CD.

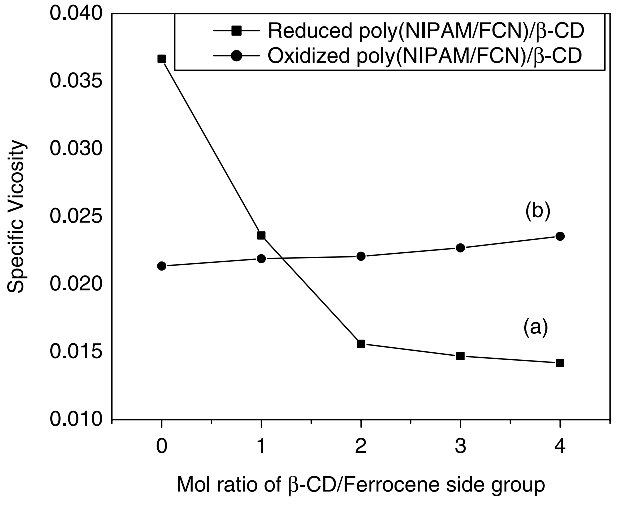


FIGURE 5 Effect of β-CD/ferrocene side group mol ratio on the specific viscosity of 0.5 wt% reduced poly(NIPAM/FCN) (a), and 0.5 wt% oxidized poly(NIPAM/FCN) (b) aqueous solution.

Fig. 5(a), with the addition of β-CD, the specific viscosity of the reduced viscosity sharply decreases and levels off at a β-CD/ferrocenene side group mole ratio of about three, which indicates that under these conditions, the hydrophobic associations of the reduced polymer can be completely eliminated, and the ferrocene side groups are almost totally included in the cavities of β-CD. This result is in accordance with that obtained in CV characterization. As reported by other authors, β-CD forms 1:1 inclusion complexes with the ferrocene group [9–13]. However, in this complexation system, a larger concentration of β-CD is needed in order to completely include the ferrocene side groups of the reduced polymer and eliminate hydrophobic association between the hydrophobic side groups. It is possible that the apparently weaker binding of the ferrocenne side groups by β-CD than that of the small molecules ferrocene end groups is due to steric interference by the polymer backbone.

LCST of the poly(NIPAM/FCN) polymer in the absence and presence of β-CD is shown in Fig. 6

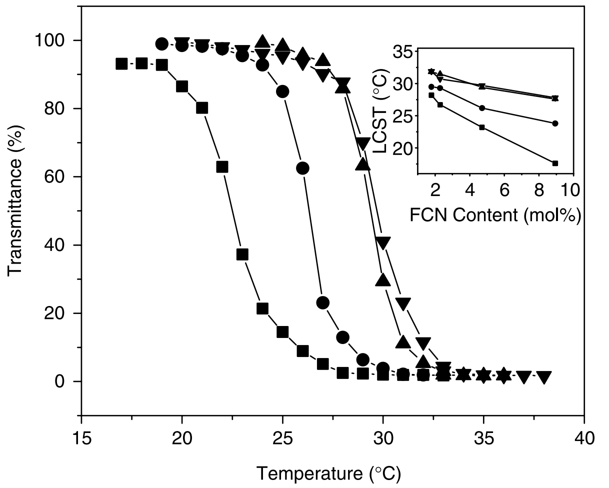


FIGURE 6 Transmission variations of 0.3 wt% aqueous solutions of the reduced /oxidized copolymers in the absence and presence of β-CD (mol ratio of β-CD/ferrocenyl group = 3) as a function of temperature; ■ Reduced polymer without β-CD; ● Reduced polymer with β-CD; ▲ Oxidized polymer without β-CD; ▼ Oxidized polymer with β-CD.

(0.3 wt%, mole ratio of β-CD/ferrocenyl group = 3). The disruption of the hydrophobic associations between the ferrocene side groups and the increased hydrophilicity of the complex of poly(NIPAM/FCN) and β-CD lead to the increase in LCST of the reduced polymer. As expected, LCST of the oxidized copolymer is influenced slightly. As shown in the inset-plot in Fig. 6, increasing ferrocene content brings about a decrease in LCST, which is resulted from the higher hydrophobicity of the inclusion complex compared with NIPAM. The more ferrocene side groups that the polymer possesses, the lower the LCST is.

CONCLUSION

β-CD could interact with the reduced ferrocene side groups of the ferrocene-functionalized poly(*N*-isopropylacrylamide) to form a stable inclusion complex, but hardly affect the oxidized polymer. Thus a redox-responsive inclusion complexation was realized. This inclusion complexation makes the LCST increase and the solution viscosity decrease in the reduced polymer, but hardly influences the two properties of the oxidized polymer. This method will provide a new route to prepare smart supramolecules or smart hydrogel, which are expected to have applications in sensor or controlled release system.

EXPERIMENTAL

Materials

N-isopropylacrylamide (NIPAM, Aldrich Chemical Co., Inc., USA) was purified by recrystallization in a mixture of benzene and n-hexane. Ferrocenecarboxylic acid (Yixing Weite Petrochemical Additives Plant) was recrystallized from toluene. AIBN was purified by recrystallization from ethanol. β-Cyclodextrin (β-CD) (Junsei Chemical Co.) was recrystallized twice from water. Oxalyl chloride (Sinopharm Chemical Reagent Co., Ltd), Ammonium persulfate, Sodium bissulfite, Allylamine, Triethylamine, N,N-dimethylformamide (DMF), Tetrahydrofuran (THF), Dichloromethane (CH_2Cl_2), HCl, n-hexane were used as received.

Monomer (FCN) Preparation

THF solution (25.0 mL) of ferrocenecarbonyl chloride [6] (2.92 g, 12.56 mmol) was added to THF solution (20.0 mL) of allylamine (1.9 mL, 25.12 mmol) and triethylamine (1.8 mL, 25.8 mmol) at 0°C. After stirring at room temperature for 6 h, the reaction mixture was filtered and the solvent was removed. The resulting yellow-orange solid was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$, 0.1 M HCl, and saturated NaCl, respectively, and dried over $MgSO_4$. The crude product was recrystallized from THF/n-hexane mixture and dried in vacuum. Yield: 2.16 g (64%); mp 138–140°C. ^1H NMR ($CDCl_3$): δ 5.98 (s, 1H, vinyl H), 5.81 (t, 1H, NH), 5.17–5.27 (t, 2H, vinyl H), 4.69 (s, 2H, $NHCH_2$), 4.36 (s, 2H, η-C_5H_5-CO), 4.22 (s, 5H, η-C_5H_5), 4.07 (s, 2H, η-C_5H_5-CO). IR (KBr, cm^{-1}): 3281, 3081, 2981, 2916, 1675 ($\nu_{C=C}$), 1623 ($\nu_{C=O}$), 1536 ($\delta_{N\text{-}H}$), 1447, 1409, 1339, 1290, 1218, 1180, 1118, 1014, 996, 916, 821. Anal. Calcd for $C_{14}H_{15}FeNO$: C, 62.45; H, 5.58; N, 5.20. Found: C, 63.01; H, 5.62; N, 5.15.

Copolymer Preparation

Copolymer poly(NIPAM/FCN) was prepared by a conventional radical polymerisation in THF with AIBN as an initiator at 65°C for 24 h. The polymer was isolated by precipitation in n-hexane, purified by three times precipitation from THF into n-hexane, and dried overnight in vacuum at approximately 50°C to give the copolymer as yellow powder. A series of copolymers were prepared under different mol ratio of NIPAM and FCN. Follows are IR and ^1H NMR results of the copolymer obtained as the monomer mol ratio is 10. IR (KBr, cm^{-1}): ν3430 (m), 3304 (m), 3073 (w), 2969 (m), 1643 (vs), 1541 (s), 1456 (m), 1384 (m), 1364 (m), 1257 (w) 1173 (m), 1128 (m), 1106 (w). ^1H NMR (D_2O): 8.05 (s, N*H*R), 4.54 (s, η-C_5H_5-CO), 4.29 (br, η-C_5H_5), 3.89 (br, C*H*Me2, η-C_5H_5-CO), 2.6–1.6 (br, CH_2CH).

Characterization

Infrared spectra were obtained from KBr pellets with a Perkin–Elmer FT-2000 Fourier-transform infrared spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM EX270 NMR spectrometer (300 MHz). The copolymer compositions were determined from the maximum absorbance at 436 nm, assignable to the ferrocene group of FCN. *N*-propylferrocenecarboxamide was used as a standard substance for the composition determination. GPC measurements were performed at 40°C with a JASCO GPC-900 system. Cloud points of the copolymer aqueous solutions (3 g/L) were determined by the 50% transparency level at 750 nm at the heating rate of 0.5°C/min, using a 10 mm length quartz cell. UV spectra were recorded on UV spectrophotometer (VARIAN cary 100 Con, USA). A BIS-100A electrochemical analyzer was used for cyclic voltammetry. A standard three-electrode cell configuration was adopted with a saturated calomel electrode (SCE), a Pt counter electrode, and a 3 mm diameter glassy carbon as the working electrode. Voltammograms were recorded from − 0.2 V to 0.7 V (vs SCE) at a scan rate of 0.1 V/s. The solution viscosities of the copolymer in the absence and presence of β-CD were tested with an Ubbelholde viscometer under LCST. The aggregates size of the copolymer was measured by dynamic light scattering (a Zetasizer Nano ZS90).

Acknowledgements

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