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THE EFFECT OF SOME ADDITIVES ON THE THERMAL RESPONSE OF PLURONIC® L61 POLY(ETHYLENE GLYCOL)-POLY(PROPYLENE GLYCOL)-POLY(ETHYLENE GLYCOL) TRIBLOCK COPOLYMER IN AQUEOUS SOLUTION

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The influence of some inorganic and organic additives upon the thermal response of the Pluronic L61 poly(ethylene glycol)-poly(propylene glycol)-poly(ethylene glycol) triblock copolymer in aqueous solution was investigated by means of the cloud point CP) method. The experiments showed that the addition of salts influenced CP by both their anion and cation, their effect displaying an additive character. In addition to electrolytes, some nonelectrolyte additives, like alcohols, amines and carboxylic acids, were shown to affect the CP by means of the alkyl chain length and architecture (linear or branched) and polarity of the hydrophilic organic functional group. The effects on CP of the additives tested here proved to be similar for both Pluronic L61 and PNIPAM (co)polymers, except for the C_1-C_3 n-alkyl alcohols, in which case the different chemical structure of the main chain of these polymers led to a different behavior.

Keywords: poly(ethylene glycol), poly(propylene glycol), Pluronic L61, cloud point, thermosensitive block copolymers, additives

1. Introduction

Thermosensitive polymers displaying a lower critical solution temperature (LCST)-behavior in aqueous solution have been around for several decades already. Their reversible soluble - insoluble transition at the phase transition temperature (T_{ph}) includes them into the "smart materials" category and proved to

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be useful for applications from many fields, like for example flow modifiers, smart clothing, membranes and windows, controlled drug delivery, tissue engineering, media for cell culture, valves, sensors, catalysts, emulsifiers [1-10]. The most well-known examples of such water soluble LCST-displaying polymers are probably poly(N-isopropylacrylamide) [11], poly(N-vinylcaprolactam) [12] and poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) triblock copolymers, also known as Pluronics or Poloxamers [13].

A large variety of PEO-PPO-PEO triblock copolymers are commercially available, differing each other by the overall molecular weight and EO/PO unit ratio. They are biocompatible, being employed in many food and biomedical applications as a consequence of their approval by the United States Food and Drug Administration for use as food additives, pharmaceutical ingredients and components in drug delivery systems, tissue engineering and agricultural products [13,14]. Both Pluronic blocks display thermosensitive behavior in water, but their LCSTs appreciably differ each other, leading to the surfactant character of Pluronics. The LCST of PEO is around 100 °C [15], while in the case of the more hydrophobic PPO only lower molecular weight (MW) samples are water-soluble and at temperatures below room temperature [16], unlike higher MW samples whose solubility in water is very low even near 0°C [17]. Thus, the PEO-PPO-PEO triblock copolymer is completely hydrated and dissolved in water as unimers at low temperature, but as temperature increases the PPO block becomes water-insoluble at the critical micellar temperature (CMT), leading to the formation of micelles with a PPO-made hydrophobic core and hydrated PEO chains as the corona [18]. As temperature further increases, the PEO block keeps dehydrating and its solubility decreases, so that the micelles aggregate, and the solution turn cloudy at a certain temperature called the cloud point (CP) [19]. The cloudiness of the solution is determined by the separation of the micelles-made aggregates as a disperse second phase which still contains some water [17]. For Pluronic copolymers applications, both CMT and CP are important. They depend on the PO/EO unit ratio and MW of the triblock copolymer [13], and also on the presence of various additives, like salts, surfactants, alcohols, etc., in the polymer solution [18-27]. It is important to know the influence of these additives in order to be able for example to adjust CMT and CP to the requirements of a certain application or to predict how they will modify when the copolymer is dissolved in a solution of a certain composition.

Pluronic L61 is one of the few PEO-PPO-PEO triblock copolymers with a CP around room temperature (CP = 24°C in 1% aqueous solution [13]) because of its relatively hydrophobic structure, displaying many important applications in the pharmaceutical field [14,28,29]. The influence of the additives upon its CP was little investigated, to the best of our knowledge only one paper being published on this subject so far [27]. However, the range of additives investigated in that work was limited to individual inorganic salts. In the present paper, we expanded the range of additives investigated to organic salts and short alkyl-chain organic nonelectrolytes, as well as mixtures of inorganic salts. We studied the influence of both anion and cation, alkyl chain length and architecture (linear or branched) and polarity of the organic functional group (alcohol, amine, carboxyl) upon the CP of a 1 wt.% Pluronic L61 aqueous solution, and the results were compared with the behavior of PNIPAM (co)polymers.

2. Experimental

Materials

Pluronic® L61 triblock copolymer (PL61, Aldrich) with $M_n \approx 2000$ Da and the approximate chemical composition 2.27/31.03/2.27 EO/PO/EO mole ratio, as indicated by the manufacturer, was used as received. All additives, of more than 98% purity, were employed without further purification, except for LiCl and n-butylamine ($BuNH_2$), which were dried at 150°C for 3 h or fractionally distilled under nitrogen at normal pressure, respectively, before use. Doubly distilled water (DDW) was used in all experiments.

Sample preparation

Polymer solutions of 1 wt.% concentration were prepared by loading 20 - 30 mg of the liquid PL61 copolymer into 7-mL screw-cap glass vials, followed by the addition of the calculated amount of additive aqueous solution. The mixture was stirred in an ice-water bath for 2 h until homogeneous, stored in a refrigerator overnight and analyzed next day.

Characterization

The cloud point temperatures (CP) of the triblock copolymer solutions were determined at a wavelength of 600 nm on an USB-4000 Ocean Optics UV-VIS spectrometer working in transmission mode and connected to a qpod 2e temperature-controlled cuvette holder with magnetic stirring (Quantum Northwest, U.S.A.). About 2 mL of PL61 solution were placed in a quartz cuvette with 1 cm optical path and the temperature was raised by 0.2 °C/min after an initial equilibration time of 20 min. The corresponding additive solution was used as reference. The temperature scan was started about 10 °C before the estimated CP and stopped around 10 °C after CP. In the case of temperatures below 10 °C, the measurements were carried out under a nitrogen blanket in order to avoid that atmospheric moisture to condense inside the cuvette holder. The temperature corresponding to 50% transmittance was taken as the CP.

3. Results and discussion

Influence of salts on CP

The T_{ph} of the thermosensitive polymers, which in many paper was estimated by means of CP because of the connection of this one with the formation of the second phase [30,31], is strongly affected by the presence of salts. Salts exert their influence on T_{ph} by means of both anion and cation they contain, but the effect of the anion is usually stronger [32]. In the case of anions, their effect is suggested by the position within the Hofmeister series [19,33]:

$$CO_3^{2-}>SO_4^{2-}>S_2O_3^{2-}>H_2PO_4^{-}>F^{-}>Cl^{-}>Br^{-}\sim NO_3^{-}>I^{-}>SCN^{-}$$

The anions located on the left side of the series, called kosmotropes, are well hydrated and display a "salting out" influence, leading to T_{ph} reduction, while the anions on the right, called chaotropes, are poorly hydrated and demonstrate a "salting in" effect and T_{ph} increase at low concentrations [19]. The effect of the well hydrated anions is due to both diminishing the interaction among the water molecules and the hydrophilic polymer parts through a polarization effect and the increase of the interfacial tension at the polymer/water interface which reduces the hydrophobic hydration of the hydrophobic polymer segments, while the T_{ph} increase by the poorly hydrated anions was ascribed to their binding to the hydrophobic moieties of the polymer [19,32].

The influence of various monovalent anions of sodium salts and monovalent cations as chlorides upon the CP of the 1 wt.% PL61 aqueous solutions was investigated on the 0.1 - 0.4 M concentration range (Fig. 1), where the concentration dependency is expected to be linear [19,32,33]. The effect of anions was in agreement with the Hofmeister series, NaI inducing a slight increase of CP, while the other three anions tested displayed a CP depressing effect, whose magnitude increased in the order $Br^- < Cl^- < H_2PO_4^-$ (Fig. 1a), similarly with the poly(N-isopropylacrylamide)-poly(ethylene glycol)-poly(N-isopropylacrylamide) (PNIPAM-PEG-PNIPAM) triblock copolymers [34]. However, unlike the PNIPAM-PEG-PNIPAM copolymers, the width of the phase transition interval was not affected by the salt addition (Fig. 1b,c).

The effect of some cations, both inorganic (Li^+, Na^+, K^+) and organic (tetraethylammonium, TEA, triethylbenzylammonium, TEBA) as chloride salts was also studied (Fig. 1d). Similarly, with the case of anions, the expected linear dependency of CP on salt concentration [19,32,33] was confirmed in this case as well. A "salting out"-type influence was noticed in all cases, except for the more hydrophobic TEBA cation, which did not affect CP irrespective of its concentration. The CP decrease effect was more pronounced for the inorganic cations and followed the order $Na^+ \approx K^+ > Li^+$, similarly with previous reports on

PNIPAM (co)polymers [34,35]. The larger CPs noticed in the case of the organic cations in comparison with the inorganic ones may be explained through the hydrophobic interaction between the alkyl/aryl groups of the ammonium cation and the hydrophobic PPO chain, which leads to the absorption of the salt on the polymer chain, thus increasing its hydrophilicity [36]. However, when evaluating the effect of a salt, it should be kept in mind that this is a combination of the effects of both its anion and cation. For example, in the case of tetraethylammonium chloride (TEAC), its overall "salting out" effect" is probably a combination of the slight "salting in" effect of the TEA cation and the strong "salting out" effect of the chloride anion.

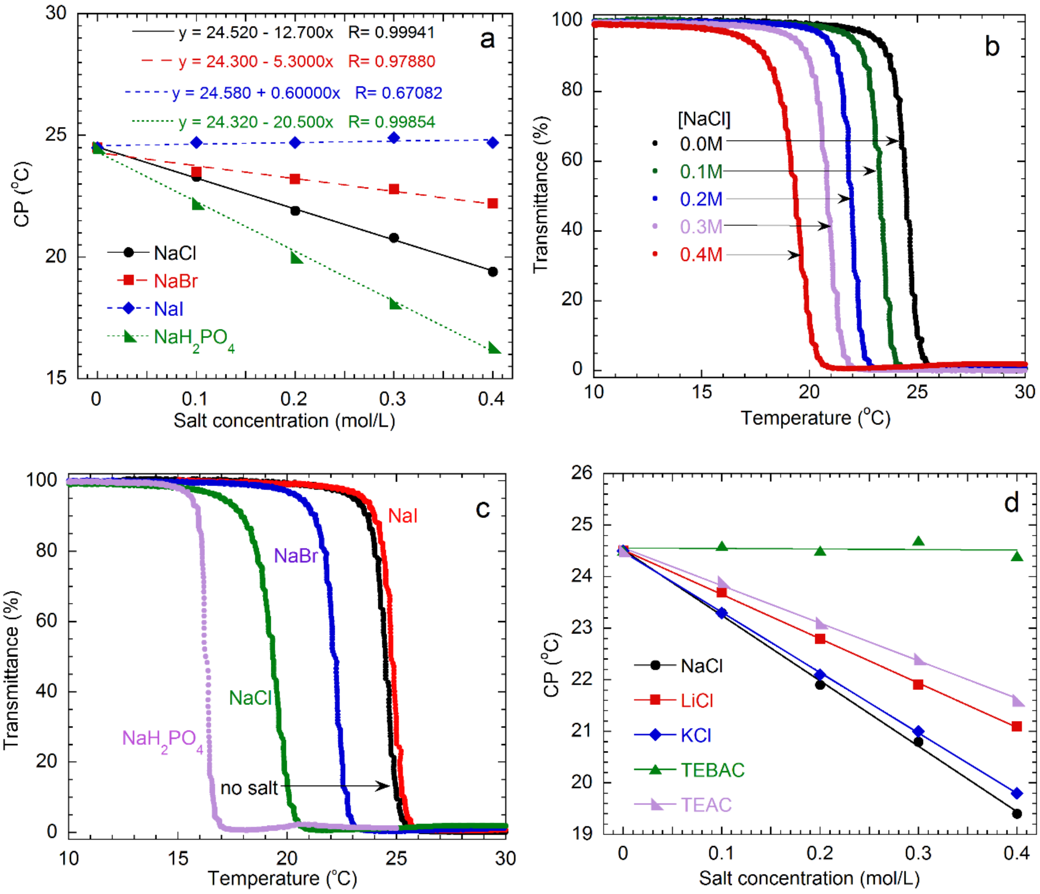

Fig. 1. Influence of some anions and cations on the CP and transmittance of the 1 wt.% PL61 aqueous solution. a) CP - salt concentration plots for various anions; b) Transmittance - temperature plots in the presence of various concentrations of NaCl; c) Transmittance - temperature plots in the presence of various salts at 0.4M salt concentration; d) CP - salt concentration plots for various cations.

In most cases, the thermosensitive polymer has to be dissolved in aqueous solutions containing more than one salt, like for example phosphate buffer saline (PBS), which is largely used in biomedical tests. Therefore, its thermal phase transition would be a result of the influence of all salts contained by the solution [35]. To see how a mixture of salts would influence T_{ph} of the 1 wt.% PL61 aqueous solution, a salt with a more pronounced "salting in" behavior than NaCl, i.e. NaI, and a more "salting out" salt, i.e. NaH_2PO_4, respectively, both in 0.1M concentration, were added to 0.1-0.4M NaCl solutions (Fig. 2). The results showed that the addition of the "salting in" NaI determined an increase of CP, while the "salting out" NaH_2PO_4 produced a decrease of CP, as expected.

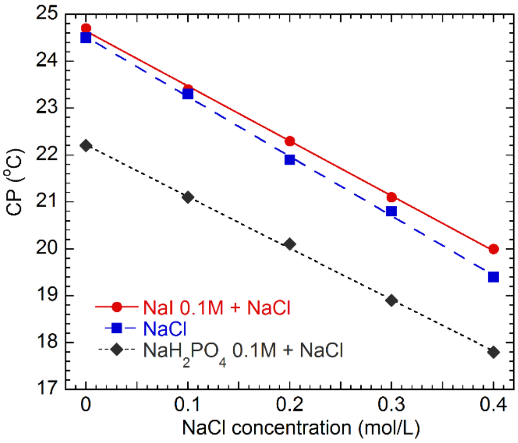

Fig. 2. Influence of salt mixtures on the CP of 1 wt.% PL61 aqueous solutions

To check for the additivity of the salt effect, the CPs of the 1 wt.% PL61 aqueous solution in the presence of NaI - NaCl mixtures with various compositions but constant mole concentration/ionic strength were measured (Table 1).

Table 1

Influence of the composition of the NaCl - NaI mixture on the CP of the 1 wt.% Pluronic L61 aqueous solution at constant ionic strength

Exp.	Salt concentration (mol/L)		CP in monosalt solution[a] (°C)		CP in NaCl+NaI solution (°C)	
	NaI	NaCl	NaI	NaCl	Experimental[b]	Calculated[c]
1	0.4	0	24.7	24.5	24.7	24.74
2	0.3	0.1	24.9	23.3	23.7	23.41
3	0.2	0.2	24.7	21.9	22.5	22.76
4	0.1	0.3	24.7	20.8	21.1	20.75
5	0	0.4	24.5	19.4	19.4	19.42

[a] Experimentally determined CPs of the 1 wt.% PL61 solutions containing only one salt;

[b] Experimentally determined CPs of the 1 wt.% PL61 solutions containing both salts. Total salt concentration = 0.4 mol/L;

[c] Calculated CPs of the Pluronic L61 solutions containing both salts by using eq. 1:

$$CP_{calc} = 24.5 + S_{NaI}\times[NaI] + S_{NaCl}\times[NaCl] \qquad (1)$$

where: - 24.5 is the CP value of the 1 wt.% Pluronic L61 solution in DDW;

- S_{NaI} and S_{NaCl} are the slopes of the linear dependency of CP on the concentration of NaI and NaCl, respectively (Fig. 1a)

The experimentally determined CPs were compare with the CP values calculated based on the contribution of each salt, as determined from the linear CP - salt concentration plots obtained in the case of the monosalt solutions (Fig. 1a). The results showed a very good agreement between the experimental and calculated values, the error being less than 0.35°C in all cases (Table 1). Similar additivity of the salt effect on CP was previously reported in the case of PNIPAM oligomers in aqueous solution [35].

Influence of organic nonelectrolytes on CP

Water soluble organic nonelectrolytes, like alcohols [23,26,34,37], amines [38], urea derivatives [37], nonionic surfactants [26,37], have been reported as affecting the T_{ph} of thermosensitive polymers. In this paper we studied the effect of alcohol addition on the CP of the 1 wt.% PL61 aqueous solution as far as the influence of both n-alkyl chain length (Fig. 3a) and alkyl chain branching degree (Fig. 3b) is concerned.

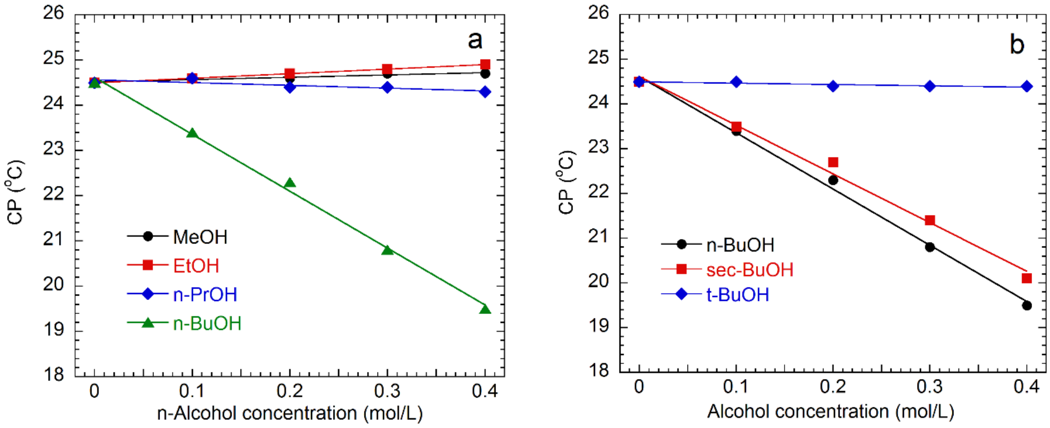

Fig. 3. Influence of alcohol structure on the CP of the 1 wt.% PL61 aqueous solution:
a) n-alkyl chain length; b) alkyl chain branching degree

The results showed that methanol (MeOH), ethanol (EtOH) and n-propanol (n-PrOH) displayed a small influence on CP, i.e. less than ±0.5 °C at 0.4M alcohol concentration, unlike n-butanol (n-BuOH) which exerted a strong kosmotropic effect, i.e. about 5 °C decrease of CP at 0.4M concentration (Fig. 3a). MeOH and EtOH behaved as chaotropic additives, while n-PrOH as a weak kosmotropic one. This behavior of PL61 in the presence of C_1-C_4 alcohols was similar to that of Pluronic L64 ($EO_{13}PO_{30}EO_{13}$, $M_n = 2900$), except for the fact that C_1-C_3 alcohols were all chaotropic additives for Pluronic L64 [23], but different in comparison with PNIPAM (co)polymers in which case MeOH had a neutral effect, while the C_2-C_4 alcohols showed a progressively depressing effect upon CP increasing in the order EtOH < n-PrOH < n-BuOH [34,37,39]. The CP depressing effect of n-alkyl alcohols in the case of PNIPAM (co)polymers was ascribed to the entropy decrease of the system because of the added alcohol hydrophobic hydration, having as a consequence an easier dehydration of the polymer [34,39,40]. For alcohols with longer alkyl chains, the hydrophobic hydration cage formed around the alkyl moiety is made up of a bigger number of water molecules. Therefore, the entropy decrease is more pronounced, as well as the CP depression [40]. One should also keep in mind that PNIPAM dissolution in water involves hydrogen bonding between the polar amide groups and water molecules, as well as hydrophobic hydration of both the hydrocarbon main chain and isopropyl groups. The different effect of C_1 - C_3 alcohols in the case of Pluronic L61 and L64 triblock copolymers as compared with PNIPAM (co)polymers may be explained by a similar entropy of the Pluronic - water system in the absence as well as in the presence of low concentrations of C_1 - C_3 alcohols, because of the similar structure of the Pluronic hydrophobic moieties, i.e. ethylene and propylene groups, and alcohol alkyl groups. This would lead to only small modifications of the system entropy after the addition of either MeOH, EtOH or n-PrOH, leaving CP practically unaffected.

The alkyl chain branching degree of the alcohol additive also affected the CP of the PL61 aqueous solution, as shown in the case of butyl alcohols: n-BuOH, sec-BuOH and t-BuOH (Fig. 3b). Similarly, with the case of PNIPAM (co)polymers [34,40], the more branched the alcohol, the less pronounced its depressing effect on the CP of the PL61 solution was. The phenomenon was explained by Costa and Freitas [40] by the influence of the shape of the alcohol molecule resulting in hydration structures whose stability increases with the branching degree. Therefore, the less stable hydration shell of the more linear n-BuOH molecule needs a larger number of water molecules than the one of the more spherical t-BuOH molecule, and as a consequence an easier dehydration of the PL61 chain occurs in the presence of n-BuOH, leading to a lower CP.

The CP of the PL61 aqueous solution can be also influenced by the polar functional group of the organic nonelectrolyte additive, as demonstrated by means of a series of three organic additives possessing a linear four-carbon-atoms hydrocarbon chain and different functional groups, namely n-BuOH, n-butylamine ($n\text{-}BuNH_2$) and n-butyric acid (n-BuCOOH) (Fig. 4).

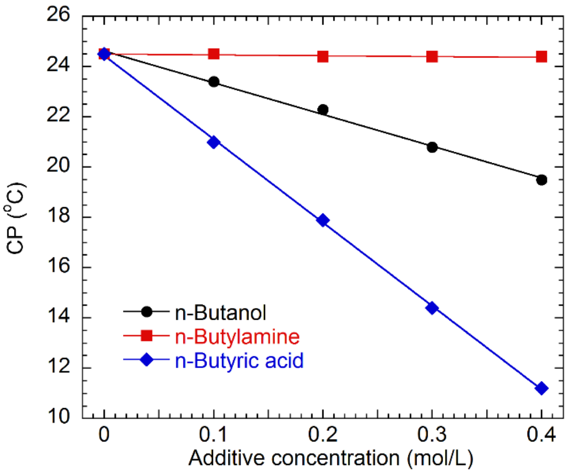

Fig. 4. Influence of the organic additive functional group on the CP of the 1 wt.% PL61 aqueous solution

Similarly, with the alcohol additive case, CP depended linearly on additive concentration. n-BuNH$_2$ did not affect CP which remained practically constant irrespective the amine concentration was on the interval investigated, while the addition of n-BuOH and n-BuCOOH had a depressing effect on CP, whose amplitude was larger for n-BuCOOH. The ability of these additives to decrease CP was in agreement with the polarity of the functional groups involved, which increased in the order NH$_2$ < OH <COOH [41]. A similar behavior was reported in the case of PNIPAM-PEG triblock copolymers [34]. There may be two possible explanations for this polar group effect: a) more polar groups determine a stronger water structuration than the less polar ones, having as a result a more advanced dehydration of the polymer; b) additives with more polar groups form a larger number of physical bonds with the ethereal oxygen atoms of PL61 chain, leading to a more hydrophobic polymer with a lower CP [34].

6. Conclusions

The effect of some inorganic and organic additives upon the thermal response of the Pluronic L61 poly(ethylene glycol)-poly(propylene glycol)-poly(ethylene glycol) triblock copolymer in aqueous solution was investigated by means of the cloud point method. It was shown that the addition of salts influenced CP by both their anion and cation, the concentration dependency being a linear one up to at least 0.4M. The monovalent anions studied, as sodium salts, displayed an effect in agreement with their position within the Hofmeister series. The influence of monovalent cations, both inorganic (Li^+, Na^+, K^+) and organic (tetraethylammonium, triethylbenzylammonium) was also investigated, and a "salting out" effect was recorded for all inorganic salts and TEAC, whose magnitude increased in the order TEAC < Li^+ < K^+ ≈ Na^+, while the addition of TEBAC showed no CP change. The effect of the salts was demonstrated to be additive, so that CP in the presence of a mixture of salts can be predicted from the individual effect of these ones.

In addition to electrolytes, nonelectrolyte additives, like alcohols, amines and carboxylic acids, affected the CP value of the PL61 aqueous solution by means of the alkyl chain length and architecture (linear or branched) and polarity of the hydrophilic organic functional group. We showed that for C_1-C_4 n-alkyl monoalcohols CP was only slightly affected by MeOH, EtOH and n-PrOH, while n-BuOH displayed a strong "salting out" behavior. Alkyl chain branching was also proved to exert an influence upon CP, as shown for the butyl alcohols series, where the CP depressing effect increased as the chain branching degree decreased, i.e. t-BuOH < sec-BuOH < n-BuOH. For various hydrophilic functional group, the more polar the functional group, the stronger the depressing effect of the additive on CP was, as demonstrated by the CP reduction becoming more significant in the order n-$BuNH_2$ < n-BuOH < n-BuCOOH. The effects on CP of the additives tested within this paper proved to be similar for both Pluronic L61 and PNIPAM (co)polymers, except for the C_1-C_3 n-alkyl alcohols, in which case the different chemical structure of the main chain of these polymers led to a different behavior.

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