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The relationship of thermosensitive properties with structure of organophosphazenes

Youn Soo Sohn*, Jin Kyu Kim, Rita Song, Byeongmoon Jeong

Division of Nano Science, Ewha Womans University, Seodaemun-Ku, Daehyun-Dong, 11-1, Seoul 120-750, South Korea

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Abstract

The lower critical solution temperature (LCST) of cyclotriphosphazenes and polyphosphazenes grafted with a hydrophilic poly(ethylene glycol) (PEG) and a hydrophobic amino acid ester (AAE) as side groups could be quantitatively correlated with the overall hydrophobicity given by linear combination of the logarithmic partition coefficients of the corresponding free PEG and AAE measured in the 1-octanol/water system. Thus the LCSTs of phosphazenes were found to be well described as a linear function of a new parameter P_t defined as linear combination of the logarithmic partition coefficients of the free side groups, K_{peg} and K_{aae} : $P_t = x \log K_{peg} + (2 - x)\log K_{aae}$ where x is the mole fraction of PEG. The LCST of cyclotriphosphazenes has shown to be more sensitive to change in hydrophobicity than polyphosphazenes, indicating that the nature of the molecular structure plays an important role in determining their LCST. The additivity of the logarithms of the two partition coefficients for the parameter may indicate that the contribution of each constituent is independent, providing a facile method for prediction of the LCST of thermosensitive polymers.

Keywords: Polyphosphazene; LCST; Thermosensitive polymer

1. Introduction

It is generally known that polymers bearing both hydrophilic and hydrophobic parts in their molecular structure exhibit thermosensitive properties and usually have a lower critical solution temperature (LCST) in aqueous solution. The LCST of such thermosensitive polymers in water results from a delicate balance between the hydrophilicity and hydrophobicity within the polymer molecules [1–4]. For example, poly(*N*-isopropylacrylamide) shows a LCST at 32 °C [5]. Below the LCST, the polymer favorably interacts with water to form a hydrated conformation. However, above the LCST, the polymer-water interaction becomes unfavorable and phase separation occurs. Such a phase separation was thermodynamically explained by an entropy-driven process [6]. Poly(vinyl methyl ether), poly(propylene glycol), poly(vinyl methyl oxazoline), poly(silamine), methyl cellulose, hydroxy propyl cellulose, poly(ethylene glycol)/poly(propylene glycol) block copolymers, poly(ethylene glycol)/poly(lactic acid-*co*-glycolic acid) copolymers, and poly(*N*-vinyl caprolactam) are typical examples of polymers showing the LCST in water [7–10].

Fine tuning of the LCST of thermosensitive polymers is important when considering their biomedical and biochemical applications. In general, incorporation of more hydrophilic comonomers increases the LCST, whereas, incorporation of more hydrophobic comonomers decreases the LCST of the polymer as reported for *N*-isopropylacrylamide copolymers and polyphosphazene derivatives [11–12]. Especially, cyclotriphosphazenes and polyphosphazenes grafted with a hydrophilic poly(ethylene glycol) and a hydrophobic amino acid ester were reported as a new class of thermosensitive biodegradable polymers [13–15]. In the present study, we have found that the LCST of organophosphazenes can be quantitatively correlated with a parameter defined by a logarithmic function of the product of the two partition coefficients of the corresponding free hydrophilic (PEG) and hydrophobic side groups (AAE) measured in the 1-octanol/water system. The partition coefficient is widely used as a measure of hydrophobicity of a solute [16–17]. We report here the quantitative

* Corresponding author. Tel.: +82-2-3277-2345; fax: +82-2-3277-2384.
E-mail address: yssohn@ewha.ac.kr (Y.S. Sohn).

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relationship between the LCST and the molecular structure of the polymers.

2. Experimental

2.1. Materials

Esters of glycine, alanine and aminomalonic acid, 2-methoxyethanol (ME), 2-(2-methoxyethoxy)ethanol (MEE), methoxy triethylene glycol (TRI), and methoxy tetraethylene glycol (TETRA) purchased from Aldrich were used as received. Methoxy poly(ethylene glycols) with molecular weights of 350 (MPEG350) and 550 Da (MPEG550) purchased from Fluka were used without further purification. Diethyl esters of L-aspartic acid and L-glutamic acid were prepared by the literature method [18]. Free amino acid esters were obtained by treatment with morphorin, followed by recrystallization using a solvent pair of methylene chloride and diethyl ether.

2.2. Determination of partition coefficients

The partition coefficients of amino acid esters (AAE) and poly(ethylene glycols) (PEG) were determined in the 1-octanol/water system. The solute (200–500 mg) was added into a small tube containing a mixture of D_2O (1.0 ml) and 1-octanol (1.0 ml). The tube was shaken by a Vortex mixer for 20 min at room temperature, and then, centrifuged for 20 min at 4000 rpm. An aliquot of the water phase (0.5 ml) was taken up and the concentration of the solute was determined by ^1H NMR spectrometry (Bruker 250 MHz) with acetonitrile as an internal standard. The solute concentration in 1-octanol was calculated from the total amount of the solute used and the amount in water.

3. Results and discussion

3.1. Introduction

In general, thermosensitive polymers exhibit a LCST, at which a reversible phase transition occurs from a soluble to an insoluble state in aqueous solution, and the LCST is also called cloud point. At temperatures below the LCST, strong hydrogen bonding interactions between the polymer and water molecules give rise to a clear solution, but at temperatures above the LCST, hydrophobic interactions among the polymer molecules increase along with weakened hydrogen bonding interactions, resulting in precipitation of the polymer from the solution. Therefore, increased hydrophobicity of the polymer causes a drop in the LCST of the polymer.

3.2. Partition coefficients of PEG and AAE

First of all, in order to study the relationship between the LCST of thermosensitive polymers and their hydrophobicity, quantitative data for hydrophilicity of the hydrophilic moiety as well as hydrophobicity of the hydrophobic moiety of the polymers should be available. The data for hydrophobicity of amino acids in terms of the partition coefficient measured by various methods are available in the literature [19], but to our knowledge, such data for amino acid esters (AAE) and hydrophilic poly(ethylene glycols) (PEG) employed as side groups of our organophosphazenes are not available. Therefore, we have measured in the 1-octanol/water system the partition coefficients of various amino acid esters and poly(ethylene glycols), and the results are listed in Table 1. It is interesting to notice that the partition coefficients of the least hydrophilic poly(ethylene glycol), 2-methoxyethanol ($K_{peg} = 0.486$) and the least hydrophobic glycine methyl ester ($K_{aae} = 0.497$) are almost in the same scale so that the K-values are continuous from the least hydrophobic to the least hydrophilic value.

3.3. Thermosensitive properties of organophosphazenes

We reported previously that both cyclotriphosphazenes and polyphosphazenes bearing the hydrophilic PEG and hydrophobic AAE as side groups exhibited LCSTs in a wide range of temperatures in water [13–15]. The molecular structures of cyclotriphosphazenes and polyphosphazenes are shown in Fig. 1. In cyclotriophosphazenes with equimolar hydrophilic and hydrophobic side groups, the LCST could be controlled from 30 to over 100 °C by changing the graft with different hydrophobicity (Table 2). The hydrophobicity of cyclotriphosphazenes increases with

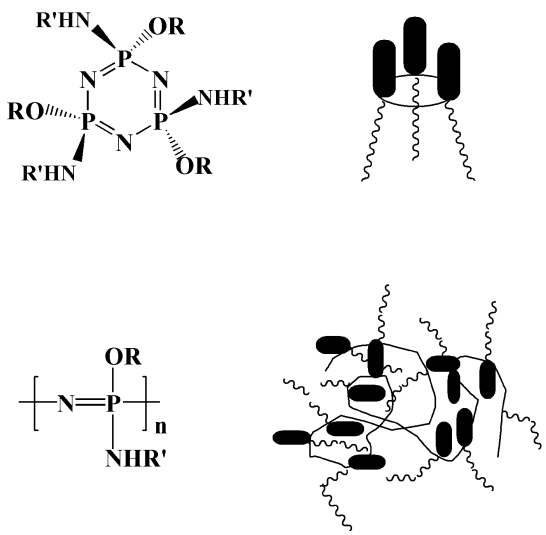

Fig. 1. The molecular structures of cyclotriphosphazenes and polyphosphazenes. Thick cylinder indicates the hydrophobic amino acid ester group (R′NH–) and curled line indicates the hydrophilic poly(ethylene glycol) group (RO–).

Table 1
Partition coefficients of poly(ethylene glycols) (K_{peg}) and amino acid esters (K_{aae}) in the 1-octanol/water system

Poly(ethylene glycols)[a]	ME	MEE	TRI	TETRA	PEG350	PEG550
$CH_3O(CH_2CH_2O)_nOH$	($n = 1$)	($n = 2$)	($n = 3$)	($n = 4$)	($n = 7$)	($n = 12$)
K_{peg}	0.486	0.447	0.410	0.318	0.183	0.134
$\log K_{peg}$	−0.313	−0.350	−0.387	−0.498	−0.738	−0.873
Amino acid esters	Gly(Me)	Gly(Et)	Ala(Et)	$Mal(Et)_2$	$Asp(Et)_2$	$Glu(Et)_2$
K_{aae}	0.497	0.689	1.27	2.23	2.10	3.57
$\log K_{aae}$	−0.304	−0.162	0.104	0.348	0.322	0.553

[a] ME: 2-(methoxy ethanol); MEE: 2-(2-methoxyethoxy)ethanol; TRI: triethylene glycol monomethyl ether; TETRA: tetraethylene glycol monomethyl ether; PEG350 and 550: polyethylene glycols with molecular weights of 350 and 550 Da, respectively.

increasing hydrophobicity of the amino acid ester groups in the order of glycine ethyl ester, aspartate diethyl ester, and glutamate diethyl ester when the hydrophilic moiety is fixed at MEE. A similar trend is shown when the hydrophilic group is fixed to MPEG 350 and hydrophobic moiety is varied from malonic acid diethylester to glutamic acid diethylester. In polyphosphazenes, the molecular hydrophobicity is controlled by changing not only the kinds of the side groups but also the mole ratio of the hydrophilic/hydrophobic side groups for a fixed pair of hydrophilic and hydrophobic side groups (Table 3). When the mole ratio of the hydrophilic/hydrophobic side groups was varied from 0.48/1.52 to 1.42/0.58 for a pair of MPEG350 and glycine ethyl ester, the LCST changed from 58 to 93 °C. When the hydrophobic side group was changed from aspartic acid diethylester to glycine methylester with the hydrophilic moiety fixed at MPEG 350, the LCST changed from 60 to 89 °C.

3.4. Thermosensitivity vs hydrophobicity

In the present study, the LCST of organophosphazenes was presumed to be closely related with the overall hydrophobicity of the polymer molecules, which may be obtained by appropriate combination of the partition coefficients of their hydrophilic (PEG) and hydrophobic (AAE) moieties. The partition coefficient (K) of a solute is defined by the following equation.

$$K = [S]_o/[S]_w$$

Table 2
LCSTs and P_t values for each composition of cyclotriphosphazenes

Trimers[a]	PEG[b]	AAE	LCST(°C)[a]	P_t[c]
1	MEE	GlyEt	>100	−0.512
2	MEE	$AspEt_2$	47.5	−0.029
3	MEE	$GluEt_2$	30.0	0.202
4	PEG350	$MalEt_2$	95.0	−0.389
5	PEG350	$AspEt_2$	83.0	−0.415
6	PEG350	$GluEt_2$	73.0	−0.184

[a] Ref. [14].
[b] MEE: 2-(2-methoxyethoxy ethanol); PEG350: methoxy poly(ethylene glycol) with molecular weight of 350 Da.
[c] $P_t = \log K_{peg} + \log K_{aae}$.

where $[S]_o$ and $[S]_w$ are the concentrations of a solute distributed between 1-octanol and water at room temperature, respectively. The more hydrophobic solute is expected to give rise to the larger partition coefficient. As already mentioned, both cyclotriphosphazenes and polyphosphazenes have two kinds of side groups, that is, hydrophilic PEG, and hydrophobic AAE. We have found from our experimental results previously reported [13,14] that the LCSTs of the organophosphazenes are linearly correlated with the overall hydrophobicity given by a linear combination of the logarithmic partition coefficients of PEG and AAE side groups and may be written as follows:

$$T_{lcst} = a[x \log K_{peg} + (2 - x)K_{aae}] + b$$

where T_{lcst} represents the LCST of a organophosphazene trimer or polymer, K_{peg} and K_{aae} are partition coefficients of its side groups PEG and AAE, respectively, x is the mole fraction of PEG, and a and b are constants.

3.5. Thermosensitivity parameter

Here, we define the linear combination of the two logarithmic partition coefficients, K_{peg} and K_{aae} as a new thermosensitivity parameter, that is, $P_t = x \log K_{peg} + (2 - x) \log K_{aae}$, reflecting the overall hydrophobocity of the

Table 3
LCSTs and P_t values for each composition of polyphosphazenes

Polymers[a]	Composition (mole fraction)				LCST (°C)[a]	P_t[b]
	PEG[c]		AAE			
1	PEG350	0.48	GlyEt	1.52	58.0	−0.600
2	PEG350	0.58	GlyEt	1.42	64.5	−0.657
3	PEG350	0.99	GlyEt	1.01	77.5	−0.892
4	PEG350	1.12	GlyEt	0.88	83.7	−0.967
5	PEG350	1.42	GlyEt	0.58	93.2	−1.14
6	PEG350	1.01	$AspEt_2$	0.99	60.2	−0.426
7	PEG350	1.00	AlaEt	1.00	67.0	−0.633
8	PEG350	1.03	GlyMe	0.97	88.5	−1.05

[a] Ref. [13].
[b] $P_t = \log K_{peg} + \log K_{aae}$.
[c] PEG350: methoxy poly(ethylene glycol) with molecular weight of 350 Da.

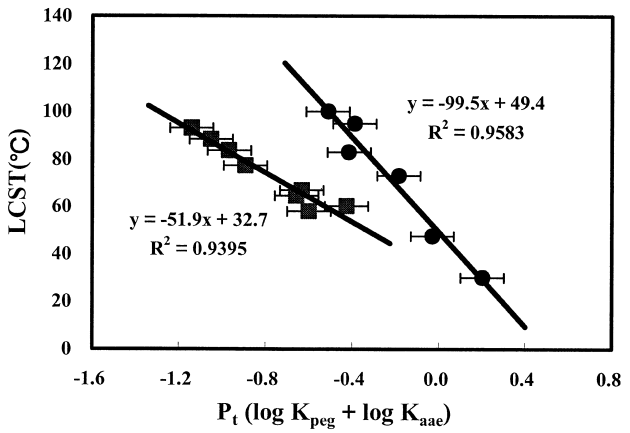

Fig. 2. The linear relationships between the LCSTs vs the thermosensitivity parameter P_t of cyclotriphosphazenes (●) and polyphosphazenes (■).

polymer, and then the equation is written as follows:

$$T_{lcst} = aP_t + b$$

Fig. 2 shows the plots of T_{lcst} vs P_t: the LCSTs of cyclotriphosphazenes and polyphosphazenes increase proportionally as the thermosensitivity parameter P_t increases. Thus the parameter P_t values are linearly correlated with the LCSTs both of cyclotriphosphazenes ($r^2 = 0.96$) and polyphosphazenes ($r^2 = 0.94$), which means that the LCST of a polymer is related with its overall hydrophobicity but not with the hydrophilicity or hydrophobicity of each side group of the polymer molecule. As a matter of fact, hydrophilicity and hydrophobicity are relative terms and as seen in Table 1, so-called hydrophilic PEGs and hydrophobic AAEs are in the reasonable order on the same scale represented by their distribution coefficients K or $\log K$ obtained from the water/octanol system. After all, the new parameter P_t expressed as a linear combination of the logarithmic partition coefficients of the two hydrophilic and hydrophobic side groups seems to represent properly the overall hydrophobicity of the polymer molecule.

3.6. Thermosensitivity vs structure

Another interesting finding is that the slope of the parameter P_t vs T_{lcst} curve for cyclotriphosphazenes ($a = 99.5$) is larger than that of polyphosphazenes ($a = 51.9$). As shown in Fig. 1, the geometry of cyclotriphosphazenes is a peculiar octopus shape with the three hydrophobic side groups conformationally oriented to one side with respect to the phosphazene ring, whereas the hydrophobic and hydrophilic side groups are randomly oriented in polyphosphazenes. Therefore, the hydrophobic groups in cyclotriphosphazenes seem to contribute more efficiently to the LCST and shows higher sensitivity to change in hydrophobicity of the graft as compared with polyphosphazenes. The additivity of the logarithms of the two partition coefficients may indicate that the contribution of each constituent side group is independent. Therefore, the LCSTs of cyclotriphosphazenes and polyphosphazenes comprising any combination of the two side groups may be predicted based on the parameter P_t defined by the above equation. Although we have not attempted yet, we believe that our theory may be applied to other thermosensitive polymers, if the hydrophilic and hydrophobic parts are clearly distinguishable within the polymer molecule.

In conclusion, the LCSTs of organophosphazenes are well correlated with the new thermosensitivity parameter P_t defined by the linear combination of the logarithmic partition coefficients of the constituent hydrophilic and hydrophobic moieties of the polymer measured in the 1-octanol/water system and the molecular conformation of the grafts plays an important role in determining the sensitivity of the LCST to the hydrophobicity of the polymer.

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