



# Inverse thermoresponse of a water-soluble helicene oligomer in aqueous-organic mixed solvent systems



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## ABSTRACT

A water-soluble ethynylhelicene (*M*)-tetramer with TEG groups exhibited the inverse thermoresponse in water/triethylamine/acetone, in which heating induced the formation of double helix and cooling dissociation. In this study, we examined the solvent effect with regard to water content at temperatures between 5 and 40 °C, and showed that the inverse thermoresponse occurred in different aqueous solution systems. In acetone, the oligomer exhibited the ordinary thermoresponse: Cooling induced the formation of double helix and heating dissociation. The increase in water content to approximately 10% caused the switch to the inverse thermoresponse. Further increase inhibited the association, and did not induce the thermoresponse. When the water content was increased to approximately 50%, the inverse thermoresponse appeared as observed previously study. Two types of inverse thermoresponses, termed type I and II, appeared at high and low water contents, respectively.

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## 1. Introduction

Molecules that form dimeric complexes in solution generally aggregate at low temperatures and dissociate at high temperatures, that is, the ordinary thermoresponse, which generally appears in biological and synthetic molecules in aqueous and organic solvents.<sup>1,2</sup> This response is explained by the competition between the enthalpic gain ( $\Delta H < 0$ ) and the entropic loss ( $\Delta S < 0$ ) of the association reaction.<sup>3</sup>

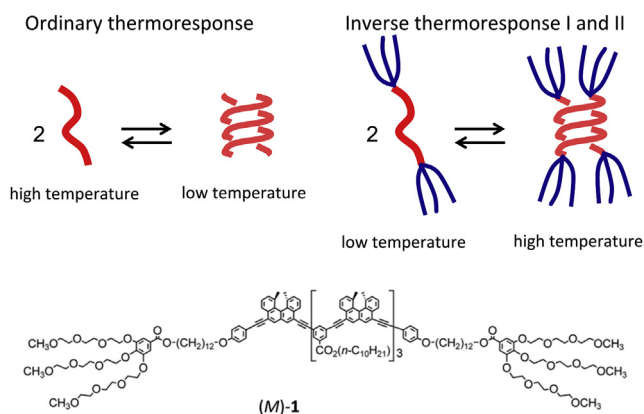
We previously reported the inverse thermoresponse: Molecules formed dimeric complexes upon heating and dissociated upon cooling, which was the inverse of the ordinary association of molecules in solution.<sup>4</sup> The ethynylhelicene (*M*)-tetramer (*M*)-**1** with tri(ethylene glycol) (TEG) groups attached at the terminal positions showed the inverse thermoresponse specifically in an aqueous-organic mixed solvent system composed of water, acetone, and triethylamine. This behavior was explained by the competition between the enthalpic loss ( $\Delta H > 0$ ) and the entropic gain ( $\Delta S > 0$ ) in the association reaction (Fig. 1). This phenomenon was ascribed to the dehydration of the TEG group upon heating, which made the TEG group hydrophobic and promoted the association. Hydrophobic interactions in aqueous solutions generally results in polymeric

aggregates, in which the contact surface area of the hydrophobic molecules with water is reduced.<sup>5</sup> However, an interesting feature observed in the (*M*)-**1** system is the formation of a dimeric complex upon heating, not polymeric aggregates. This feature is explained by considering the lower critical solution temperature (LCST) of the solvent system, in which the solution is homogeneous at low temperatures but separates into two phases at high temperatures.<sup>6</sup> An aqueous-organic mixed solvent system forms cluster domains of water as well as organic solvents upon heating, and the double helix of (*M*)-**1** is incorporated in organic domains, which induces the formation of double helix.

The inverse thermoresponse, especially in the formation of double helix, is interesting, and it is important to determine the scope of this phenomenon. In this study, we showed that the inverse thermoresponse occurs in different aqueous-organic mixed solvent systems for the TEG-modified helicene oligomer (*M*)-**1**. The effect of water content was examined in the water/triethylamine/acetone system, and two types of inverse thermoresponse appeared, referred to as the type I and II inverse thermoresponses. The type I inverse thermoresponse appeared at a high water content of approximately 50% as reported previously,<sup>4</sup> and the type II inverse thermoresponse appeared at a low water content of approximately 10%. In addition, non-LCST systems, namely water/1-butanol/acetone and water/*i*-butanol/acetone also caused the type II inverse thermoresponse at approximately 10% of water content. Along with the ternary solvent systems, binary solvent

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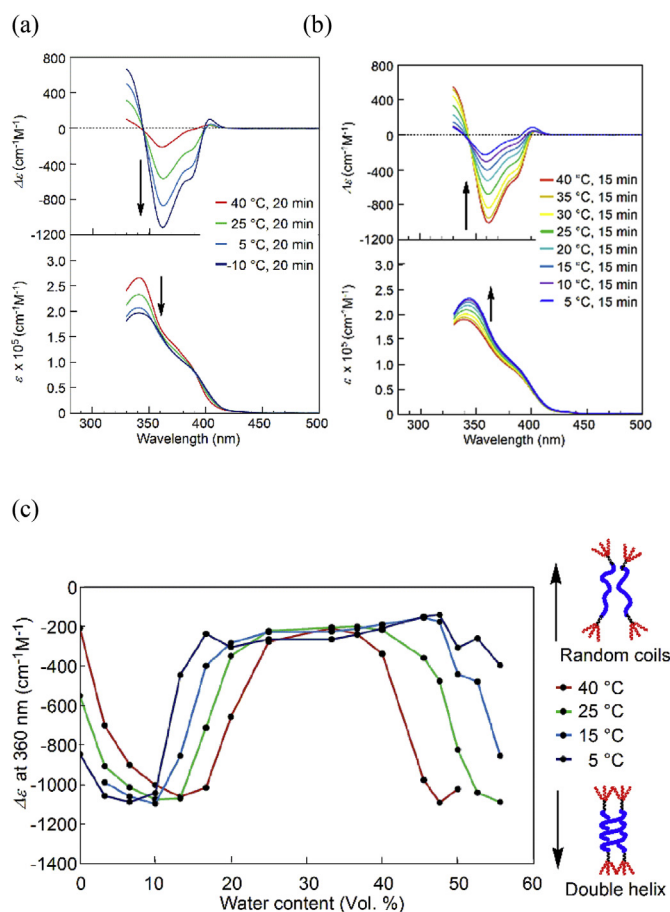
**Fig. 1.** Ordinary thermoresponse and inverse thermoresponse of TEG derivative of ethynylhelicene (*M*)-tetramer (*M*)-1.

systems such as water/acetone and water/THF also showed the type II inverse thermoresponse. These observations indicate that the inverse thermoresponses possess a relatively broad scope.

## 2. Results and discussion

The type I inverse thermoresponse of (*M*)-1 was previously observed in the 2:1:1 mixture of water/triethylamine/acetone (water content, 50%) at a concentration of 10  $\mu\text{M}$ . In this study, the effect of solvent composition was examined by changing the water content between 0% and 60% while keeping the water/triethylamine (2:1) ratio fixed. In acetone, (*M*)-1 showed the ordinary thermoresponse: cooling at 5  $^{\circ}\text{C}$  provided  $\Delta\epsilon -1.1 \times 10^3 \text{ cm}^{-1}\text{M}^{-1}$  at 360 nm as shown in the CD spectrum, a high ratio of double helix to random coil; heating at 40  $^{\circ}\text{C}$  provided  $\Delta\epsilon -2.7 \times 10^2 \text{ cm}^{-1}\text{M}^{-1}$  indicating a high ratio of the random coil to double helix (Fig. 2a and Fig. S1a). UV absorbance decreased upon cooling, which was consistent with the formation of double helix as was observed in our previous studies.<sup>4</sup> DLS analysis showed that the particles were 1–5 nm in diameter (Fig. S1b). At a water content of 3.3%,  $\Delta\epsilon -7.0 \times 10^2 \text{ cm}^{-1}\text{M}^{-1}$  was recorded at 40  $^{\circ}\text{C}$ , indicating a higher double helix concentration in the polar solvent with pure acetone (Fig. S2a). At a water content of 6.6%, the temperature-dependent change in  $\Delta\epsilon$  decreased (Fig. S2b), and no change in  $\Delta\epsilon$  at 10% water content and temperatures between 5 and 40  $^{\circ}\text{C}$  (Fig. S2c) indicated the S-double-helix state, at which the equilibrium completely shifted to the double helix state. It was shown that water had a strong tendency to induce double helix formation.

At a water content of over 13%, the inverse thermoresponse appeared (Fig. S2d). As the water content was increased to 17%,  $\Delta\epsilon -2.4 \times 10^2 \text{ cm}^{-1}\text{M}^{-1}$  was recorded at 5  $^{\circ}\text{C}$ , and  $\Delta\epsilon -1.0 \times 10^3 \text{ cm}^{-1}\text{M}^{-1}$  at 40  $^{\circ}\text{C}$  (Fig. 2b and Fig. S2e). The CD spectra between 5 and 40  $^{\circ}\text{C}$  showed an isosbestic point at 345 nm, which indicated an equilibrium between two species, double helix and random coil. It was observed that the system quickly reached equilibrium within 15 min, and that the same CD spectra were obtained upon cooling the solution from 40 to 35 or 25  $^{\circ}\text{C}$  and by heating to 35 or 25  $^{\circ}\text{C}$  from 5  $^{\circ}\text{C}$ . The temperature-variable experiment provided a thermodynamic parameters for the association reaction:  $\Delta H = +1.7 \times 10^2 \text{ kJ mol}^{-1}$  and  $\Delta S = +0.67 \text{ kJ mol}^{-1} \text{ K}^{-1}$  (Fig. S5). The large absolute values are consistent with the sharp thermoresponse,<sup>4</sup> for which only a difference of 35 K between 5 and 40  $^{\circ}\text{C}$  induced large changes in the relative amounts of double helix and random coil in solution. The increase in UV–Vis intensity upon cooling was consistent with the dissociation of double helix to random coil (Figs. S1 and S2). Thus, the inverse thermoresponse



**Fig. 2.** Effects of solvent composition and temperature in the water/triethylamine/acetone system of (*M*)-1 (10  $\mu\text{M}$ ) as shown by CD and UV–Vis spectra in (a) acetone and (b) 2:1:9 mixture (water content, 17%). The black arrows indicate the change upon cooling. (c)  $\Delta\epsilon$  (360 nm)/water content profiles at various temperatures.

observed at 17% water content was called the type II inverse thermoresponse, to differentiate it from the type I inverse thermoresponse occurring at higher water contents.<sup>4</sup>

DLS analysis at 17% water content showed the formation of particles approximately 10 nm in diameter with a small temperature effect between 5 and 40  $^{\circ}\text{C}$ , and indicated the absence of a highly aggregated state (Fig. S3a). The results indicated that the type II inverse thermoresponse was a molecular event, not resulting from polymeric aggregation. Larger hydrodynamic diameters were obtained in the type II inverse thermoresponse than previously observed in the type I inverse thermoresponse,<sup>4</sup> which were typical for the DLS analyses in this study in the solvent systems containing water and acetone at the low water contents. The formation of small clusters of double helix cannot rigorously be excluded at present but must be negligible in amount, considering the presence of the isosbestic point in the CD spectra.

When the water content was increased to 20% in the water/triethylamine/acetone system, the CD intensity at 40  $^{\circ}\text{C}$  decreased (Fig. S2f), which indicated a decrease in the ratio of double helix to random coil (Fig. S2g). At water contents of 27, 33, and 40, and 50%, similar CD spectra were obtained (Fig. S2g–j), which showed no temperature dependence between 5 and 40  $^{\circ}\text{C}$ .

At water contents of 46, 48, 50, 53, and 56%, the type I inverse thermoresponse appeared (Fig. S2k–o), as previously reported.<sup>4</sup> DLS analysis showed that the type I inverse thermoresponse I was also a molecular event and did not involve polymeric

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