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Helical Structures

Molecular Function of Counting the Numbers 1 and 2 Exhibited by a Sulfoneamidohelicene Tetramer

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Abstract: The sulfoneamidohelicene tetramer in solution exhibits different molecular responses to the same cooling stimulus delivered once and twice under thermal hysteresis conditions. Its random-coil state at a high temperature was cooled and maintained at a given temperature for which its molecules remained in a random coil (first cooling); the resulting solution was heated and cooled, after which a helix dimer formed (second cooling). Such a property can be regarded as a molecular function of counting the numbers 1 and 2.

Counting the numbers 1 and 2 is a basic ability of humans. We use fingers to count the numbers 1 and 2 assigning the thumb to 1 and the forefinger to 2 (Figure 1); an abacus is used to count 1 and 2 by moving beads once and twice, respectively; an electronic counter counts 1 and 2 by employing a flip–flop system.[1] The function to count the numbers 1 and 2 contains a memory effect, for which it is remembered that the first input was counted 1 and the second input was counted 2: Assigning the thumb for both the first and second inputs does not entail counting. Note that when inputs 1 and 2 of the same nature exert different outputs 1 and 2 this can be used to count the numbers 1 and 2.

It will be interesting to count the numbers 1 and 2 using a molecule or a molecular system that exhibits different responses (outputs 1 and 2) to the first and second stimuli (inputs 1 and 2). Such a system can be used for counting devices at the molecular level, being applicable to molecular computers.[1–4] A counting phenomenon of the numbers 1 and 2 using a materials system occurs in biology. The Venus flytrap, *Dionaea miscipra*, is a carnivorous plant that catches insects by closing its leaves in response to the mechanical stimulus provided by insects. Among several interesting features of the plant, notable is the closing of its leaves upon two strikes to the hair on the leaf surface: no response (output 1) on the first strike (input 1) and closing (output 2) on the second strike (input 2).[5] To reach the threshold to respond a sufficient amount or strength of stimuli may be involved, and mechanisms involving the accumulation of small charges[6] or biological compounds[7] to reach such a threshold have been proposed.

Recently, we have reported the thermal hysteresis exhibited by the sulfoneamidohelicene tetramer (*M*)-**1** in solution, which exhibits different structural changes during cooling and heating,[8] being a nonequilibrium thermodynamic phenomenon.[9] The molecular hysteresis exhibits a threshold for triggering the formation of a helix dimer and a memory effect for remembering the previous temperature.[8,10] Thus, the function to count the numbers 1 and 2 and thermal hysteresis possess common features of a threshold and a memory effect. This study shows that (*M*)-**1** can be used to count the numbers 1 and 2, for which molecules in a random-coil state do not respond (output 1) to the first cooling stimulus (input 1), but respond to the second cooling stimulus (input 2) by forming a helix dimer (output 2).

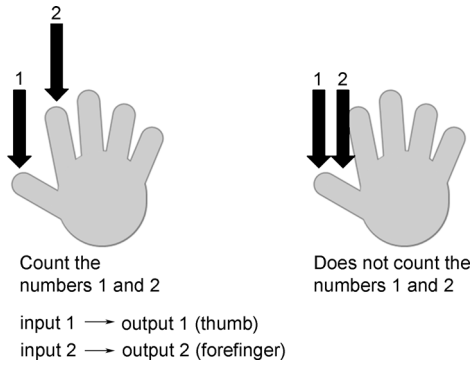

Figure 1. Counting the numbers 1 and 2 using fingers.

A design for counting the numbers 1 and 2 by using (*M*)-**1** under thermal hysteresis conditions is described as follows (Figure 2). A solution of (*M*)-**1** in a random coil state is formed by heating at a high temperature T_1 followed by cooling. Above the threshold temperature T_0, the structure remains as a random coil, even when the cooling is stopped and heating is started. Once the temperature reaches below T_0, a structural change from a random coil to a helix dimer begins. Cooling is stopped at the temperature T_2 (first cooling), and heating is again started, after which (*M*)-**1** does not return to a random-coil, but rather forms a helix dimer. When heated to T_1 and cooled to T_2 (second cooling), a considerable amount of helix

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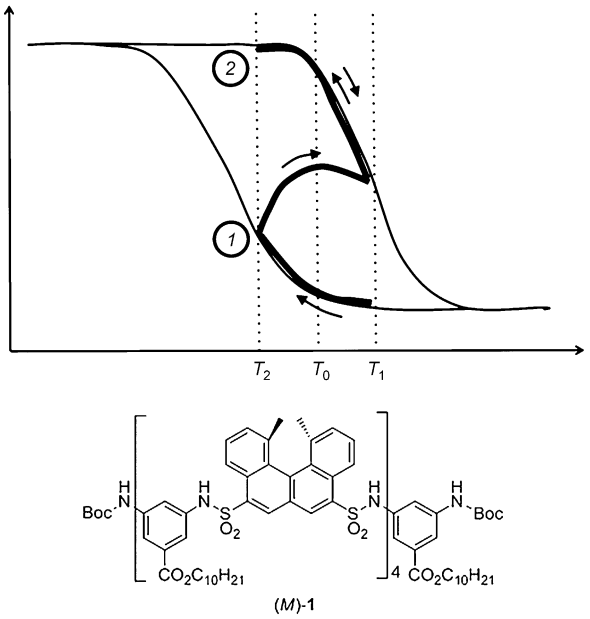

Figure 2. Concept of counting the numbers 1 and 2 using the thermal hysteresis of (*M*)-**1**. Boc = *tert*-butoxycarbonyl.

dimer is formed. The entire process shows that (*M*)-**1** remains in the random-coil state (output 1) during the first cooling to T_2 (input 1), but that it forms a helix dimer (output 2) during the second cooling (input 2). Thus, (*M*)-**1** counted the number 1 as a random coil and the number 2 as a helix dimer by the same cooling stimulus from T_1 to T_2. The counting information was translated to the molecular structures of (*M*)-**1** by using a single reaction of the structural change between a helix dimer and a random coil.

A solution of (*M*)-**1** in 1,3-difluorobenzene (0.6 mM) was heated at 70 °C to form a S-random coil with a $\Delta\varepsilon$ of $-104\,M^{-1}cm^{-1}$ at 320 nm, in which all the molecules are in a random coil.[8a] Then, the solution was cooled to $T_2 = 42$ °C at a rate of 0.25 K min^{-1} (Figure 3a), and the $\Delta\varepsilon$ slightly increased to $-98\,M^{-1}cm^{-1}$, passing a threshold temperature at approximately 45–46 °C (Figure 4). More than 95% of (*M*)-**1** molecules stayed in a random coil in the first cooling stimulus.[8a] Then, heating the solution to $T_1 = 50$ °C at the same rate increased $\Delta\varepsilon$ to $+40\,M^{-1}cm^{-1}$. The second cooling to $T_2 = 42$ °C still increased $\Delta\varepsilon$ to $+80\,M^{-1}cm^{-1}$, which was calculated to correspond to a helix dimer content of 20%.[8a] The third heating and cooling provided a $\Delta\varepsilon$ of $+90\,M^{-1}cm^{-1}$. Thus, the first cooling to 42 °C induced very little structural change of (*M*)-**1** as it remained in the random-coil state, and the second cooling to 42 °C formed a considerable amount of helix dimer. The first and second stimuli (inputs 1 and 2) induced different structural responses (outputs 1 and 2). The heating/cooling curves are arranged against the time of temperature change, and the nature of this process, the ability to count the numbers 1 and 2, is shown (Figure 3b). Thus, the number 1 can be detected as the random-coil state and the number 2 as the helix-dimer state under these cooling conditions.

The responses have certain allowable ranges for the first cooling stimulus, as indicated by the experiments performed

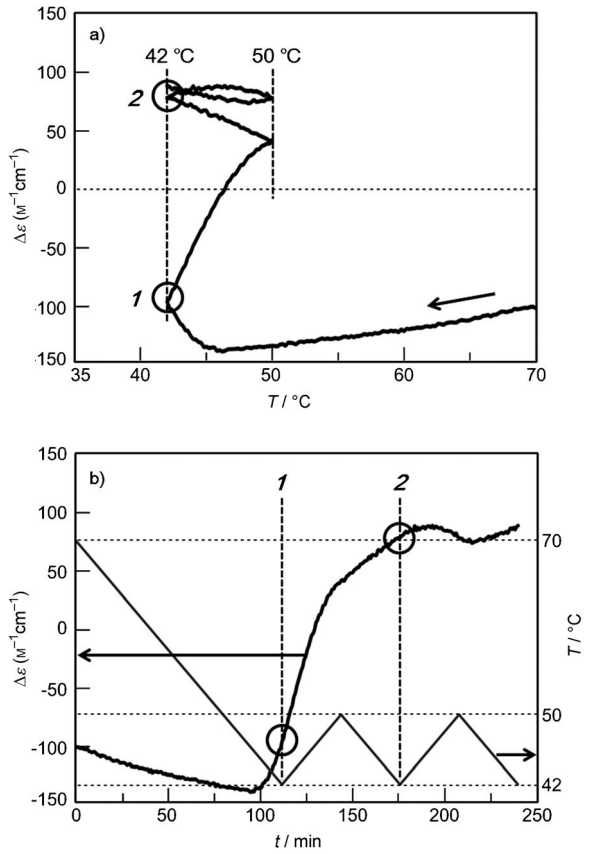

Figure 3. a) $\Delta\varepsilon$ (320 nm)/temperature profiles of a constant-rate (0.25 K min^{-1}) cooling–heating experiment between 42 and 50 °C. A solution of (*M*)-**1** in 1,3-difluorobenzene (0.6 mM) was heated at 70 °C, cooled to 42 °C, heated to 50 °C, cooled to 42 °C, heated to 50 °C, and cooled to 42 °C. b) $\Delta\varepsilon$ (320 nm)/time (——) and temperature (°C)/time (——) profiles.

with different cooling/heating temperature ranges (Figure 4). When the temperature was changed between 40 and 48 °C, the first cooling provided a $\Delta\varepsilon$ of $-56\,M^{-1}cm^{-1}$ and the second cooling a $\Delta\varepsilon$ of $+101\,M^{-1}cm^{-1}$, which were similar to

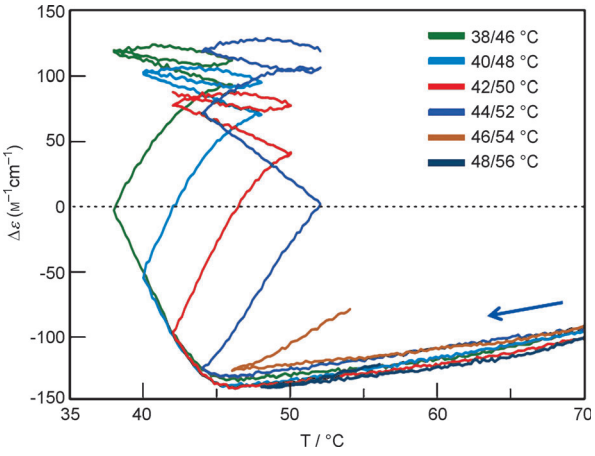

Figure 4. $\Delta\varepsilon$ (320 nm)/temperature profiles of constant-rate (0.25 K min^{-1}) cooling–heating experiment at 38/46, 40/48, 42/50, 44/52, 46/54, and 48/56 °C. A solution of (*M*)-**1** in 1,3-difluorobenzene (0.6 mM) was heated at 70 °C and subjected to a temperature change.

those obtained in the 42/50 °C experiment. In the 46/54 and 48/56 °C experiments, (*M*)-**1** mostly remained in a random-coil state.

The 38/46, 40/48, and 42/50 °C experiments revealed a linear change in the $\Delta\varepsilon$/temperature profiles (Figure 4). However, the 44/52 °C experiment showed a deviation from these trends. The increase in $\Delta\varepsilon$, particularly during the second heating and third cooling, may be explained by a strong force that promotes helix-dimer formation in the temperature range studied. Such deviations were observed in the experiments at 0.5 and 0.7 mM concentrations in the 44/52 and 46/54 °C experiments, respectively (see Figure S1 in the Supporting Information and Figure 5). In the latter, the first heating and second cooling resulted in downward convex curves, which indicated the acceleration of the reaction to form a helix dimer. The results are consistent with self-catalysis at the temperature range close to the threshold by the helix dimer of (*M*)-**1** to convert a random coil to a helix dimer, which was previously proposed.[8a]

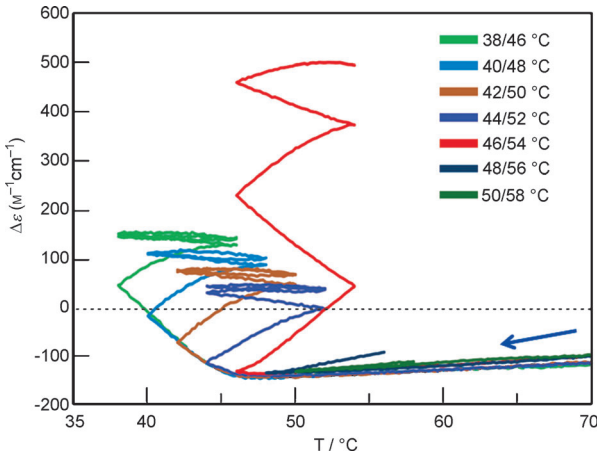

Figure 5. $\Delta\varepsilon$ (320 nm)/temperature profiles of a constant rate (0.25 K min^{-1}) cooling–heating experiment of (*M*)-**1** in 1,3-difluorobenzene at 0.7 mM. A solution of (*M*)-**1** in 1,3-difluorobenzene (0.7 mM) was heated at 70 °C and subjected to a temperature change.

A waiting experiment was conducted in which the first cooling was stopped at 50 °C and a waiting time was inserted (Figure 6). A solution of (*M*)-**1** in 1,3-difluorobenzene (0.6 mM) was cooled from 70 to 50 °C, and remained at that temperature for 20 min, during which time $\Delta\varepsilon$ showed no change. Then, cooling was started at a rate of 0.25 K min^{-1}, and the first and second cooling yielded the random-coil and helix-dimer states, respectively. The results of the 42/50 °C experiment with waiting were similar to those of the 42/50 °C experiment without waiting (Figure 3b). Another waiting 44/52 °C experiment was conducted between the first and second cooling, which gave similar results with regard to the $\Delta\varepsilon$ values at 44 °C (see Figure S2 in the Supporting Information).

A resetting experiment was conducted (Figure 6). A solution of (*M*)-**1** obtained in the 42/50 °C experiment with waiting was heated to 70 °C, and an S-random coil was formed. Cooling to 42 °C and waiting for 20 min at 50 °C followed by a temperature change between 42 and 50 °C resulted in the same profile as that obtained in the first experiment. Thus, the system can be reset by heating at a sufficiently high temperature, and the counting of numbers 1 and 2 was repeated (see also Figures S3, S4, and S5 in the Supporting Information). The reproducibility of the experiment was confirmed (see Figure S6 in the Supporting Information).

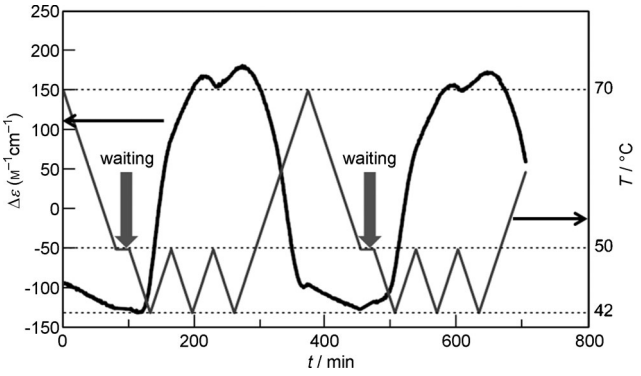

Figure 6. Repeated constant-rate (0.25 K min^{-1}) cooling–heating 42/50 °C experiment of (*M*)-**1** in 1,3-difluorobenzene (0.6 mM) with a waiting period of 20 min at 50 °C.

It will be interesting to discuss the energetic aspect of the above structural changes containing bistability (Figure 7). The process contains a metastable state of a random coil in the first cooling, which is derived from thermal hysteresis.[11] A random-coil is thermodynamically stable at high temperatures but unstable at low temperatures, and its relative thermodynamic stability inverts in the thermal hysteresis of (*M*)-**1**.[8b] All (*M*)-**1** molecules are therefore in the metastable random-coil state at the waiting temperature (Figure 6). Thus, the first cooling (input 1) shows only small changes in the population (output 1), and the second cooling (input 2) induces a considerable structural change to the thermodynamically stable helix dimer (output 2).

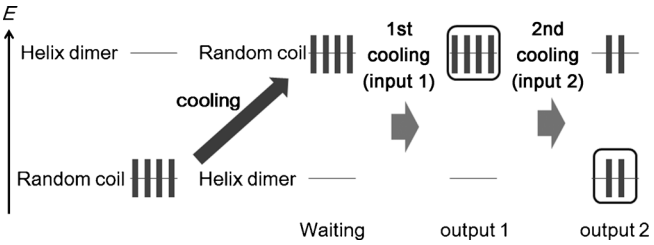

Figure 7. Energy aspect of the counting system using (*M*)-**1**.

Biological systems in some cases employ metastable states, as exemplified by the sodium ion concentration gradient inside and outside cells, which responds to an external stimulus and transports the ion inside the cells.[12] It may be reasonable to wait in a metastable state for a sensitive and quick response to an external stimulus than to activate an equilibrium

state to a reactive state in response to an external stimulus. The leaf closing of the Venus flytrap might involve the counting mechanism, for which the plant molecule or molecular system responsible for counting the numbers 1 and 2 is initially in a metastable state and responds not to the first stimulus but to the second.

To summarize, the sulfoneamidohelicene tetramer (*M*)-**1** exhibits different thermal responses to the first and second cooling in solution. The molecules respond not to the first cooling stimulus but to the second, which changes the structure from a random coil to a helix dimer. This is a molecular function of counting the numbers 1 and 2. If there is a molecule or a molecular system that can interact with the helix dimer of (*M*)-**1**, a mechanical system with a counting function may be constructed.

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