A supramolecular switch with molecular memory

Judith M. Lavin and Ken D. Shimizu*

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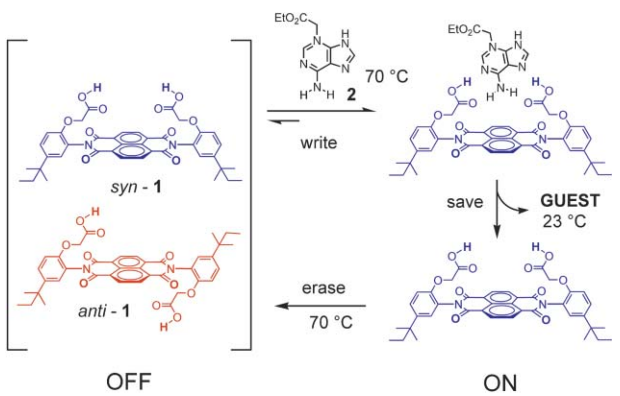
A supramolecular switch is demonstrated that maintains a stable ON state even in the absence of guest at room temperature.

Molecular switches that turn ON and OFF in response to a guest molecule are key components in data storage,[1] molecular electronics,[2] and chemical signaling systems.[3] However, one limitation of supramolecular switches is their stability. The ON states of supramolecular switches are typically fragile host·guest complexes, and thus, they require the constant presence of the guest molecule and also mild conditions that favor complex formation. The instability of supramolecular switches is advantageous in sensing applications[1] but it also limits their use in memory and information storage applications. Most supramolecular switches involve either a spectroscopic or a conformational change on complexation. In most cases, these complexation induced changes require the constant presence of the guest species and removal of the guest returns the supramolecular switches to the OFF state. For example, rotaxane based supramolecular switches have been developed that can shuttle back and forth between two stations.[2b] Fluorescent switches have also been developed that can be turned ON or OFF by complexation of a guest molecule *via* quenching or PET mechanisms.[2a] However, in both cases, the removal of the guest species usually returns these systems to their OFF states. In this communication, we demonstrate the abilities of atropisomeric diacid **1** as a stable supramolecular switch. Thus, diacid **1** can be switched ON and OFF with a guest at elevated temperatures (Scheme 1). However, on cooling to room temperature, diacid **1** can maintain the ON and OFF states in the absence of guest or even when redissolved in a wide range of competitive environments. This ability to retain a memory of the guest molecule is in contrast to most supramolecular switches. This is possible because the ON and OFF states of diacid **1** are metastable atropisomers. Thus, the memory of the ON and OFF states is maintained even when the external stimuli (guest or absence of guest) are removed due to restricted rotation. The conformational stability of the molecular switch allows it to retain its molecular memory for longer periods of time with high fidelity. This stability allows the ON and OFF states to be read-out with greater accuracy.



Scheme 1 OFF–ON switching of diacid **1** with ability to stay ON in the absence of guest due to restricted rotation.

Department of Chemistry and Biochemistry, University of South Carolina, Columbia, SC 29208, USA.
E-mail: shimizu@mail.chem.sc.edu; Fax: (803) 777-9521;
Tel: (803) 777-6523

Diacid **1** is a member of a class of molecular receptors with restricted rotation that have unique dynamic recognition properties.[4–6] In diacid **1**, steric hindrance about the two C_{aryl}–N_{imide} bonds twists the terminal aryl rings out of plane with the central diimide spacer, yielding diastereomeric *syn*- and *anti*-conformers. The steric hindrance about the C_{aryl}–N_{imide} bonds[4,7] is sufficient for the *syn*- and *anti*-isomers to be stable and isolable at room temperature. We have recently described the synthesis and binding characteristics of the atropisomeric diacid **1**, which was notable for its enhanced organic solubility due to the pendent *tert*-amyl groups.[8] The *syn*- and *anti*-configurations were confirmed by X-ray crystallography. More importantly, the *syn*-/*anti*- ratio of diacid **1** was responsive when heated with hydrogen bonding guests. In particular, guests containing the adenine recognition moiety were identified as forming a strong hydrogen bonded complex to the *syn*-isomer of diacid **1** and thus showed a strong ability to shift the equilibrium toward the *syn*-isomer.

The ability of **1** to act as a molecular switch was evaluated by heating diacid **1** first in the presence and then in the absence of adenine **2**. To turn the switch ON, diacid **1** was heated at 70 °C for 12 h with 1.0 equivalents of adenine **2** in 1,1,2,2-tetrachloroethane (TCE). The solution was cooled to room temperature and adenine **2** was removed by washing the organic solution with aqueous 1 M HCl. A 93 : 7 *syn*/*anti* ratio was measured for diacid **1**, which was assigned as the ON state.† This *syn*-enriched sample was then heated under identical conditions (TCE, 70 °C, 12 h) in the absence of guest. A 52 : 48 *syn*/*anti* ratio was measured, which was assigned as the OFF state.

A key feature of the switching behavior of diacid **1** was the stability of the *syn*/*anti* ratio at room temperature, regardless of the environment or presence of the guest molecule. For example, the 97 : 3 *syn*/*anti* ratio of the ON state remained constant whether measured directly in the TCE solution containing the adenine guest, from the TCE solution after removal of the guest, or from a sample in which TCE was removed *in vacuo* and diacid **1** was redissolved in another solvent such as acetonitrile or chloroform. The stability of the *syn*/*anti* ratio allowed for more

accurate read-out of the ON and OFF states. For example, the above *syn*/*anti* ratios were measured by HPLC, which normally would be incompatible with supramolecular switches as the chromatographic process disrupts the fragile host·guest complexes. For comparison, the *syn*/*anti* ratios were also monitored *in situ* by integration of the ^{1}H NMR spectra. However, this method was less accurate due to the presence of overlapping peaks from the guest and was easily disrupted by small amounts of polar impurities that shifted the peaks corresponding to the *syn*- and *anti*-isomers.

Next, the fidelity of molecular switch **1** was tested by repeatedly heating (70 °C, 12 h) the same sample of diacid **1** in TCE in the presence and absence of guest (Fig. 1). After each cycle the adenine guest was removed by extraction of the TCE solution with 1 M HCl. Diacid **1** was recovered by removal of the TCE solvent under reduced pressure, and this same sample was used in the next OFF–ON cycle. After seven OFF–ON cycles, no significant loss in material or efficiency in switching ability was observed. The fidelity of the molecular switch **1** can be attributed to the simple mechanism of the switching process which involves a simple bond rotation and therefore, there are no significant side reactions.

The ability of the guest to shift the *syn*/*anti* ratio at elevated temperatures arises from the differential binding affinities of the *syn*- and *anti*-conformers for the adenine guest. This was confirmed by ^{1}H NMR titrations of the individual *syn*- and *anti*-conformers of **1** with adenine **2** in CD_3CN (Fig. 2). Association constants of 1820 M^{-1} and < 10 M^{-1} were measured for *syn*-**1** and *anti*-**1**, respectively. The high binding constant and the guest induced chemical shifts in *syn*-**1** were consistent with the complexation of the adenine guest with both carboxylic acids as shown in Fig. 2. Conversely, the low binding affinity of the *anti*-conformer suggested that the adenine guest can only interact *via* a single carboxylic acid. The 1 : 1 stoichiometry of the *syn*-**1**·**2** complex was confirmed by a Job plot analysis. The binding constant for the *anti*-**1**·**2** was too low and only the 1 : 1 complex was observed. The difference in binding affinity between the *syn* and *anti* conformers theoretically equates to a $\Delta\Delta G \approx 3.0$ kcal mol^{-1}, which corresponds to a *syn*/*anti* ratio of 170 : 1. The measured *syn*/*anti* ratio of 32 : 1 ($\Delta\Delta G = 2.0$ kcal mol^{-1}) was lower but this is consistent with the weakening of the hydrogen bonded complexes at the higher temperature that is required for switching.

Next the kinetic stability of diacid **1** was measured. The isomerization barriers of $\Delta G_{syn\rightarrow anti}^{\ddagger}$ and $\Delta G_{anti\rightarrow syn}^{\ddagger}$ were calculated from the experimentally measured isomerization rate constant (k_{isom}) and the isomeric ratio at equilibrium ([*anti*-**1**]$_\infty$/[*syn*-**1**]$_\infty$) using eqns. 1 through 5. A *syn*-enriched sample of **1** was heated at 65 °C in TCE and the rate of isomerization monitored by NMR (eqn. 1). The isomerization rate of 2.06×10^{-4} s^{-1} and the near 1 : 1 [*anti*-**1**]$_\infty$/[*syn*-**1**]$_\infty$ equated to $\Delta G_{syn\rightarrow anti}^{\ddagger}$ and $\Delta G_{anti\rightarrow syn}^{\ddagger}$ of 26.0 kcal mol^{-1} (Fig. 3). This corresponds to a half-life of 31 min at 70 °C and 11 days at 23 °C in TCE (eqns. 5 and 6). While the isomerization of diacid **1** was slow at room temperature, it was faster than expected as samples had maintained a stable isomeric ratio for months at room temperature. Further, studies showed that the rate of isomerization is much faster in solution than in the solid state. Thus removal of the solvent is a simple method for maintaining the fidelity of the ON and OFF states for longer periods of time. For example, a sample of isomerically pure *syn*-**1** in TCE showed considerable isomerization at room temperature after seven days (*syn*/*anti* = 80 : 20). A neat sample of the same isomerically pure *syn*-**1**, in contrast, showed no measurable isomerization after seven days. Isomerization of **1** will occur in the solid-state at elevated temperatures but at a much slower rate than in solution.

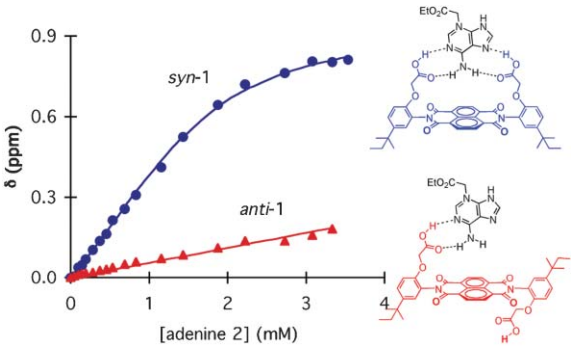


Fig. 2 ^{1}H NMR titration studies of adenine **2** with *syn*-**1** (K_a = 1820 M^{-1}) and *anti*-**1** ($K_a < 10$ M^{-1}) in CD_3CN and proposed hydrogen bonded complexes between adenine **2** and *syn*- and *anti*-**1**.

$$\text{enriched } syn-\mathbf{1} \xrightarrow{k_{isom}} syn-\mathbf{1} + anti-\mathbf{1} \quad (1)$$

$$syn-\mathbf{1} \underset{k_{anti}}{\overset{k_{syn}}{\rightleftharpoons}} anti-\mathbf{1} \quad (2)$$

$$k_{isom} = (k_{syn} + k_{anti}) \quad (3)$$

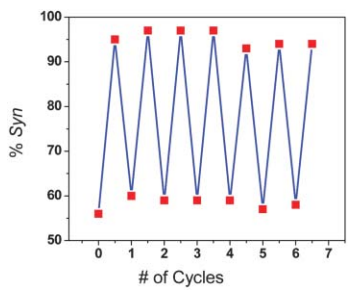


Fig. 1 Seven OFF–ON cycles of molecular switch **1** in which **1** is heated (TCE, 70 °C) in the absence and presence of adenine guest **2**.

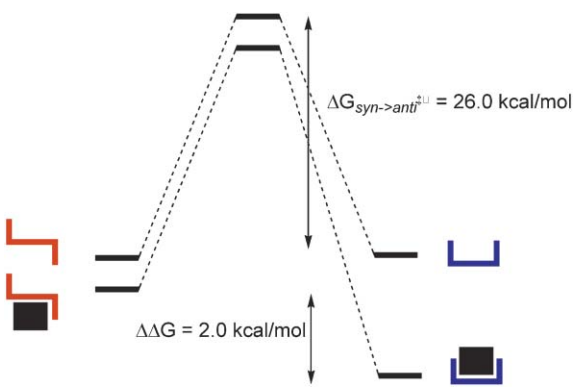


Fig. 3 Reaction coordinate diagram for the conformational switching at 70 °C in the absence and presence of guest.

$$\frac{k_{syn}}{k_{anti}} = \frac{[anti-\mathbf{1}]_{\infty}}{[syn-\mathbf{1}]_{\infty}} \quad (4)$$

$$k_{syn\,\text{or}\,anti} = \frac{k_B T}{h} e^{\left(-\Delta G^{\neq}/RT\right)} \quad (5)$$

$$t_{1/2} = \ln 2/(k_{\text{isom}}) \quad (6)$$

Next we investigated the influence of the guest **2** on the kinetic stability of diacid **1**. From the titration and switching experiments, it was clear that guest **2** preferentially stabilizes the ground state of *syn*-diacid **1**. At the elevated temperatures required for isomerization (70 °C), a 2.0 kcal mol^{-1} preference for the *syn*-isomer was observed in the presence of adenine **2**. However, we were interested in whether the guest or other additives also stabilize the transition state and change the kinetic barrier. A d_2-TCE solution of *anti*-**1** (5 mM) was heated in the presence of varying amounts of adenine **2** (0.5, 1, 2, 5 equivalents) at 65 °C and monitored by ^{1}H NMR. It was found that the barriers ($\Delta G_{anti \rightarrow syn}^{\ddagger}$) were identical in all cases when corrected for the different final equilibrium ratios. Thus, the guest only changes the thermodynamic equilibrium ratio of the molecular switch and not the kinetic stability. The rate of isomerization was also measured by heating a sample of *anti*-**1** in d_2-TCE at 65 °C in the presence of 200 equivalents of DMSO, pyridine or THF. Again, no significant change in the rate of isomerization was observed.

Finally, the influence of the cooling rate on the final *syn*/*anti* ratios was examined in order to identify conditions that yielded the the highest *syn*/*anti* ratio. Mixtures of diacid **1** and adenine **2** (1 : 1) were heated in TCE at 100 °C for 12 hours. The hot solutions were then cooled either by rapid quenching in an ice bath or by gradually cooling over 2 h in an oil bath. *syn*/*anti* ratios of 8 : 1 and 16 : 1, respectively, were measured for the two cooling methods. Thus, the more slowly cooled solution showed the higher *syn*/*anti* ratio. This suggests that the *syn*/*anti* ratio is determined not by the highest temperature to which a sample is heated but by the temperature at which rotation stops. In the case of the rapid quenching, the *syn*/*anti* ratio corresponding to the equilibrium at 100 °C was preserved. When the sample cools more slowly, the *syn*/*anti* equilibrium will continually change with the decreasing temperature until it reaches a point at which rotation effectively stops somewhere below 70 °C. Thus, the higher *syn*/*anti* ratio of the more slowly cooled sample corresponds to the equilibrium ratio at this lower temperature. These heating and cooling studies suggest that much faster switching times are possible by heating to higher temperatures and slowly cooling.

In conclusion, we have demonstrated that diacid **1** is a supramolecular switch that can be turned ON and OFF with high fidelity by heating with a hydrogen bonding guest molecule. More interestingly, the ON and OFF states are kinetically stable at room temperature even in the absence of guest. This stability allows the ON and OFF states to be read out with great accuracy using HPLC. This new platform offers a synthetically accessible and soluble molecular switch with room temperature stability and potential in interim memory storage.

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Notes and references

† The *syn*/*anti* ratio of diacid **1** was measured by HPLC (normal phase silica, 12.5% CH_3CO_2H–$CHCl_3$).

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