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# Conformationally Imprinted Receptors: Atropisomers with "Write", "Save", and "Erase" Recognition Properties

**Charles F. Degenhardt, III, Judith M. Lavin, Mark D. Smith, and Ken D. Shimizu***

*Department of Chemistry and Biochemistry, University of South Carolina, Columbia, South Carolina 29208*

*shimizu@mail.chem.sc.edu*

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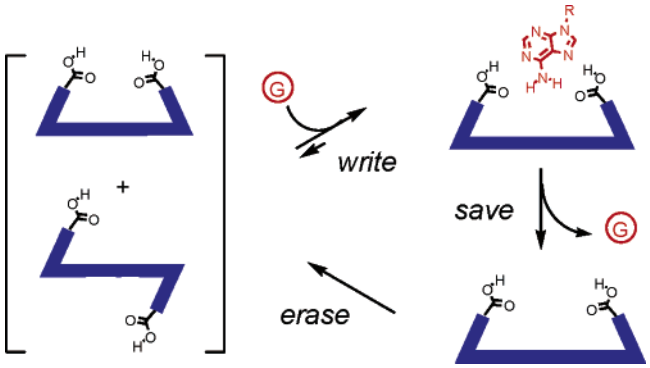
## ABSTRACT




**An atropisomeric receptor with "write", "save", and "erase" recognition properties is presented. The receptor adopts a complementary conformation when heating in the presence of an ethyl adenine-9-acetate guest molecule. This complementary hydrogen bonding conformation is "saved" upon cooling to room temperature due to the reestablishment of restricted rotation and is stable even upon removal of the guest. Finally, the atropisomeric receptor can be "erased" by heating in the absence of the guest.**

Synthetic molecular receptors are important for applications in sensing, separations and biomimetics.[1] However, the development of new synthetic receptors is challenging due to the difficulties in accurately predicting the stability of host−guest complexes and the difficulties in synthesizing highly functionalized and rigid molecular frameworks. We present an alternative strategy for the preparation of molecular receptors termed "conformational imprinting"[2] in which the guest molecule selects a complementary host conformation and amplifies its concentration. The approach is efficient, combining the design, synthesis, and selection in a single step. The key was to use an atropisomeric host that is conformationally flexible at elevated temperatures and conformationally rigid at room temperature due to restricted rotation.[3] These dynamic properties allow the atropisomeric host to adopt a complementary shape simply by heating in the presence of the guest molecule. While many conforma-

(1) Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vogtle, F. *Comprehensive Supramolecular Chemistry*; Pergamon: Oxford, 1996.

(2) Conformational imprinting is a type of dynamic combinatorial library in which a host selects a conformer from an equilibrating libary of conformers. For references on dynamic combinatorial libraries, see: (a) Huc, I.; Nguyen, R. *Comb. Chem. High Throughput Screening* **2001**, *4*, 53−74. (b) Lehn, J.-M.; Eliseev, A. V. *Science* **2001**, *291*, 2331−2332. (c) Eliseev, A. V.; Lehn, J.-M. *Curr. Top. Microbiol. Immunol.* **1999**, *243*, 159−172. (d) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *641*, 898−952.

(3) (a) Hayashi, T.; Asai, T.; Borgmeier, F. M.; Hokazono, H.; Ogoshi, H. *Chem. Eur. J.* **1998**, *4*, 1266−1274. (b) Hayashi, T.; Asai, T.; M.; Hokazono, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1993**, *115*, 12210−12211. (c) Kuroda, Y.; Kawashima, A.; Urai, T.; Ogoshi, H. *Tetrahedron Lett.* **1995**, *36*, 8449−8452. (d) Bampos, N.; Marvaud, V.; Sanders, J. K. M. *Chem. Eur. J.* **1998**, *4*, 335−343. (e) Eliseev, A. V.; Nelen, M. I. *J. Am. Chem. Soc.* **1997**, *119*, 1147−1148. (f) Berl, V.; Huc, I.; Lehn, J.-M.; DeCian, A.; Fischer, J. *Eur. J. Org. Chem.* **1946**, *11*, 3089−3094. (g) Sugasaki, A.; Ikeda, M.; Takeuchi, M.; Robertson, A.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, *22*, 3259−3264. (h) Gawronski, J.; Kacprzak, K. *Chirality* **2002**, *14*, 689−702.

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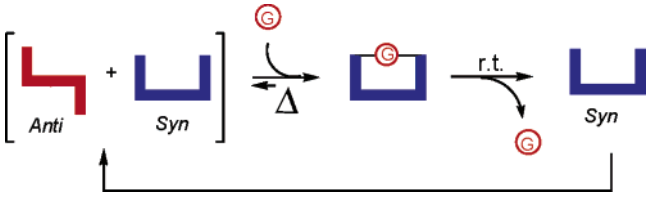
tionally flexible recognition systems can respond to the presence of a guest molecule, these induced fit recognition systems are not stable and "forget" the conformationally imprinted conformation on removal of the guest molecule. Atropisomeric hosts, in contrast, can "remember" and maintain the imprinted conformation due to the reesestablishment of restricted rotation at lower temperatures (Scheme 1). The entire sequence of steps is reversible as no covalent

**Scheme 1.** Schematic Representation of the Conformational Imprinting of an Atropisomeric Host with a Guest Molecule




bonds are formed or broken in the conformational imprinting process. Thus, heating in the absence of guest returns the system back to its original state. In this manner, recognition properties can be repeatably "written", "saved", and "erased". We have previously demonstrated the viability of the conformational imprinting strategy using strong metal ligand interations to a $PdCl_2$ guest.[4] We now present an example using much weaker hydrogen-bonding interactions to an ethyl adenine-9-acetate (EA9A) guest.

Atropisomeric diacid **1** was designed to have restricted rotation about its two $C_{aryl}-N_{imide}$ bonds. This leads to the formation of distinct *syn*- and *anti*-conformers, in which the two carboxylic acids are either on the same face or opposite face of the 1,4,5,8-naphthalene diimide surface (Figure 1). Diacid **1** was prepared in a single step by the condensation of 2-amino-3-methylbenzoic acid with 1,2,4,5-benzenetetracarboxylic acid anhydride.[5] The *syn*- and *anti*-isomers were demonstrated to be stable at room temperature ($\Delta G^{\ddagger} = 29.4$ kcal/mol), which correlates to a half-life of 10.9 days at 23 °C. The *syn*- and *anti*-isomers were isolated and separated by silica gel column chromatography.

The recognition abilities of *syn*- and *anti*-**1** for EA9A were measured by $^1$H NMR titration (Figure 1). As predicted, *syn*-**1** showed strong binding ($K_a = 1098$ $M^{-1}$), whereas *anti*-**1** showed weak binding ($K_a < 5$ $M^{-1}$). The low solubility of *anti*-**1** prevented a more precise estimation of the binding constant with EA9A. The structure of the *syn*-**1**·EA9A complex was further verified by examination of its X-ray crystal structure (Figure 2**)**. The stoichiometry of the complex was 1:1 with both carboxylic acids of *syn*-**1** hydrogen bonded to the same adenine guest molecule,

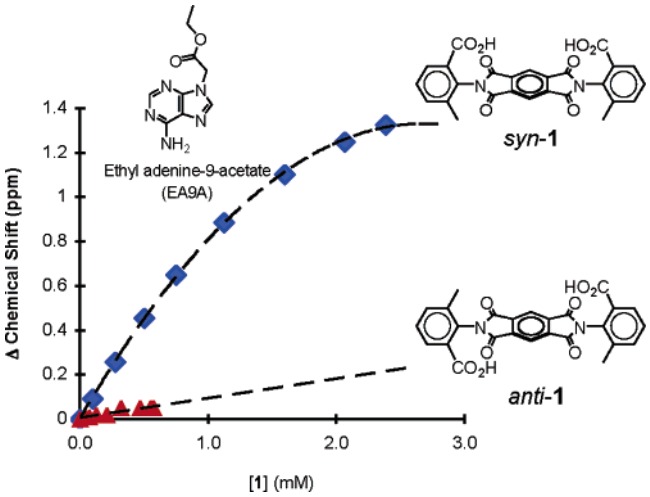



**Figure 1.** Plot of $^1$H NMR titration curves of EA9A with *syn*-**1** and *anti*-**1** in $CD_3CN$.

forming four hydrogen bonds. The 1,2,4,5-benzene diimide surface was bent to accommodate the guest.[6]

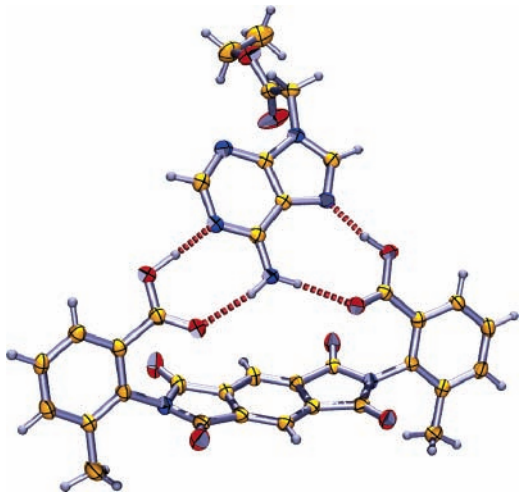


**Figure 2.** X-ray crystal structure of the 1:1 *syn*-**1**·EA9A complex. Hydrogen bonds are denoted by broken lines.

The next set of experiments tested whether the differences in recognition properties between the *syn*- and *anti*-atropisomers were sufficient to favor one isomer on heating with EA9A. Benzonitrile was selected as the solvent as it had a high boiling point and was able dissolve the diacids and EA9A. Benzonitrile also did not contain strong hydrogen-bonding donor or acceptor groups that might disrupt the hydrogen-bonded complex.

(4) Chong, Y. S.; Smith, M. D.; Shimizu, K. D. *J. Am Chem. Soc.* **2001**, *123*, 7463−7464.
(5) Degenhardt, C. F.; Shortell, D. B.; Adams, R. D.; Shimizu, K. D. *Chem. Commun.* **2000**, 929−930.
(6) The energetic penalty to pyramidalize the imide nitrogen is relatively low and has been observed in other diimide structures. (a) Shimizu, K. D.; Dewey, T. M.; Rebek, J. *J. Am. Chem. Soc.* **1994**, *116*, 5145−5149. (b) Degenhardt, C. F.; Smith, M. D.; Shimizu, K. D. *Org. Lett.* **2002**, *4*, 723−726.

Diacid **1** (5 mM) was heated with EA9A (20 mM) at 90 °C for 6 half-lives (21 h). The solution was cooled to room temperature where the *syn*/*anti* ratio was stable even in the absence of guest, and thus, a *syn*/*anti* ratio of 90:10 was measured by HPLC (Table 1). Heating diacid **1** under similar conditions in the absence of EA9A yielded a 1:1 *syn*/*anti* ratio (47:53). The importance of hydrogen-bonding interactions between diacid **1** and EA9A were probed by carrying out the same experiments in DMSO. In DMSO, both *syn*- and *anti*-**1** showed no measurable association for EA9A, as DMSO disrupts the formation of the hydrogen-bonded complex. Again, a near unity *syn*/*anti* ratio was measured (50:50).

**Table 1.** Ability of Different Guests To Control the Syn/Anti Ratio of Diacid **1**[a]

| guest (mM) | solvent | % syn/anti | |
|---|---|---|---|
| none | benzonitrile | 47 | 53 |
| EA9A | benzonitrile | 90 | 10 |
| EA9A | DMSO | 50 | 50 |
| DABCO | benzonitrile | 51 | 49 |
| *N*-acyl-2-aminopyridine | benzonitrile | 48 | 52 |

[a] Concentration of diacid **1** was held constant at 5 mM and the guest concentration at 20 mM. All tests were heated at 90 °C for 6 half-lives in benzonitrile and measured by HPLC.

Control experiments were also carried out using other basic guests including 1,4-diazo[2.2.2]bicyclooctane (DABCO) that has two basic nitrogens and *N*-acyl-2-aminopyridine that can complex one carboxylic acid using a similar hydrogen-bonding pattern as EA9A (Table 1). Each of these also gave 1:1 *syn*/*anti* ratios, suggesting that only guest molecules that show strong affinity for one atropisomeric form of diacid **1** over the other will be able to act as a conformational imprinting template.

The effect of guest concentration on the efficiency of the conformational imprinting process was studied. Diacid **1** (5 mM) was heated with varying amounts of EA9A (0−50 mM) at 90 °C for 21 h. The mixtures were cooled, and the *syn*/*anti* ratio was measured by HPLC (Figure 3). The presence of increasing amounts of EA9A steadily shifted the conformational preference in favor of the *syn*-isomer up to 2 equiv. Subsequent additions of EA9A did not shift the equilibrium further. This saturation behavior gave further evidence for the formation of a well-defined complex between *syn*-**1** and EA9A that favors the formation of the *syn*-conformer under equilibrating conditions.

The effect of temperature on the efficiency of the conformational imprinting process was studied under two parallel conditions (Figure 3, inset). Diacid **1** and either 0.5 or 2.0 equiv of EA9A were equilibrated for 6 half-lives over a range of temperatures from 70 to 110 °C. A clear trend was observed where lower *syn*/*anti* ratios were observed at higher temperatures. The trend suggests that the samples have been cooled sufficiently rapidly and that they have trapped the isomeric ratio of the equilibrium temperature.

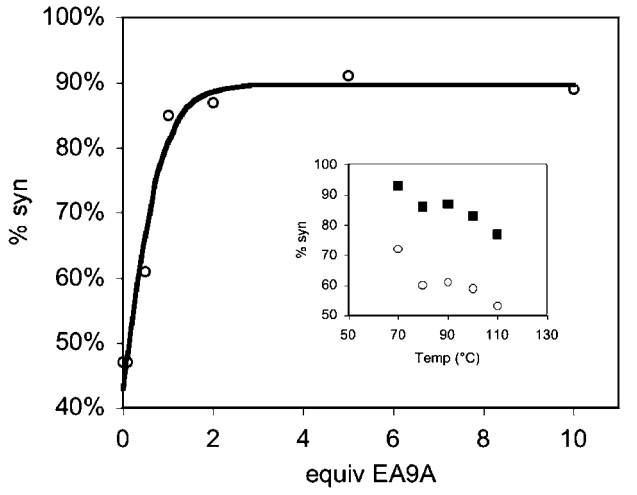



**Figure 3.** Plot of the concentration dependence of the percent *syn*-**1** on heating with EA9A. The inset shows the temperature dependence of the percent *syn*-**1** on heating with 2.5 mM (circles) and 10 mM (squares) of EA9A. All tests were conducted with 5.0 mM diacid **1** at 90 °C for 21 h in benzonitrile.

In summary, we have shown when atropisomeric diacid **1** is heated in the presence of a guest molecule it will rotate and coordinate with the guest molecule via hydrogen bonding. This results in an isomeric shift to the guest accommodating *syn* conformer. This complementary conformation is stable even upon removal of guest and lowering of temperature. The imprinted host can be returned back to its original state by heating in the absence of a guest. The hope is that these conformationally imprintable atropisomer systems will lead to more complex dynamic recognition systems in which recognition properties can be turned on and off and also modified without any additional covalent synthesis.

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**Supporting Information Available:** Conditions for the conformational imprinting process and the CIF files for the X-ray structure of the *syn*-**1**·EA9A complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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