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Rapid Screening of a Receptor with Molecular Memory

Judith M. Lavin 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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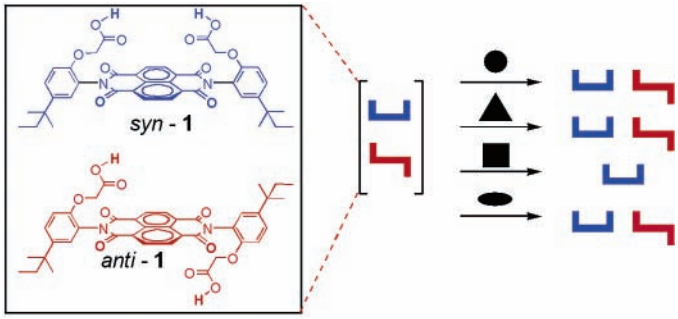
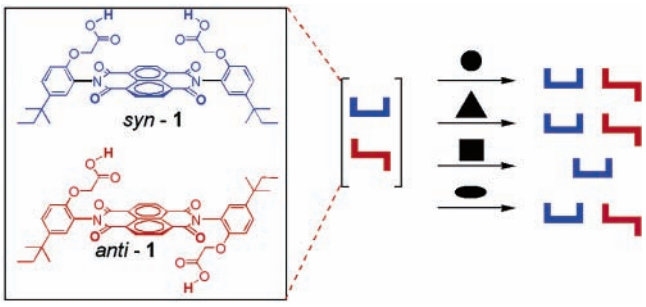
ABSTRACT



Atropisomeric receptor 1 can change conformation and maintain the new conformation when heated and cooled in the presence of a guest molecule. This molecular memory can be used as a rapid method of screening potential guests. Heating atropisomeric diacid 1 with various hydrogen-bonding guests leads to a shift in the *syn*/*anti* ratio that could be easily monitored as it is stable at room temperature even in the absence of the guest molecules.

Synthetic molecular receptors have found utility in a wide range of applications including catalysis, separations, and sensing.[1] The development of new synthetic receptors, however, is a time- and resource-intensive task that typically requires the individual synthesis and screening of multiple generations of receptors. Recently, combinatorial and high-throughput strategies have emerged as an efficient method to prepare large numbers of potential receptors.[2] These high-throughput synthetic strategies also require the concurrent development of methods to rapidly screen the binding affinity of these receptors.[3] Along these lines, we present a rapid and efficient method for identifying complementary receptor•guest pairings by using a receptor with molecular memory arising from restricted rotation.[4] This was demonstrated by screening diacid receptor **1** against a library of guests that contains protected nucleosides, monodiamines, and diamines.[5] The binding affinities were estimated from single-point experiments in which the guest-induced conformational *syn*/*anti* ratios were measured by HPLC (Scheme 1). Diacid **1** was individually heated with the respective guest molecules. On cooling to room temperature, the resulting *syn*/*anti* ratios were "saved" due to the reestablishement of

Scheme 1. Guest-Induced Isomerization Screening Strategy



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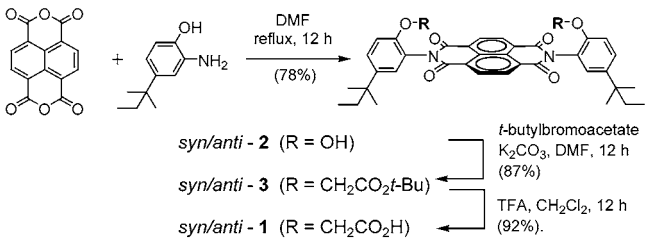
restricted rotation. This allowed the ratio to be easily and accurately measured by HPLC even in the absence of the guest molecule. This screening method has two advantages. First, it avoids the necessity of a multipoint titration experiment for each host·guest pairing. Second, the guest-induced *syn*/*anti* ratios are stable even in the absence of guest and therefore, can be measured with greater accuracy using a wider range of methods and conditions.[6]

Atropisomeric receptor **1** was designed about a rigid 1,4,5,8-naphthalenediimide framework.[7] Restricted rotation about the two $C_{aryl}-N_{imide}$ bonds yields *syn*- and *anti*-atropisomers in which the carboxylic acid groups are on the same and opposite face of the naphthalenediimide surface, respectively. Additional design features include pendant *tert*-amyl groups and flexible OCH_2 spacers for the carboxylic acid to enhance the solubility of the rigid platform in organic solvents.[8]

The synthesis of diacid **1** was carried out in three steps as shown in Scheme 2. Condensation of 2-amino-4-*tert*-amylphenol with 1,4,5,8-naphthalenetetracarboxylic dianhydride gave diol **2** as a slowly equilibrating mixture of isomers.[4d] Alkylation of diol **2** with *tert*-butyl bromoacetate yielded *tert*-butyl ester **3** as a mixture of stable atropisomers.

Scheme 2. Synthesis of Diacid **1**



Finally, deprotection of di-*tert*-butyl ester **3** in trifluoroacetic acid and methylene chloride at ambient temperature overnight yielded the diacid **1**. The atropisomers of diacid **1** were stable at room temperature as evidenced by the ability to isolate and separate the respective isomers by silica gel chromatography (5% CH_3CO_2H/CH_2Cl_2). A rotational barrier of 26.1 kcal/mol was measured by following the equilibration of an *anti*-enriched sample by ^1H NMR at 65 °C in TCE-d_2. Thus, receptor **1** is conformationally stable at 23 °C with a half-life of 12 days and is conformationally flexible on gentle heating with a half-life of 32 min at 70 °C.

The *syn*- and *anti*-isomers were assigned on the basis of the X-ray crystal structure of the more rapidly eluting *anti*-isomer (Figure 1). Crystals were obtained of the more quickly eluting isomer from CH_2Cl_2/MeOH. The X-ray structure also gave confirmation of the expected rigid structure. The phenyl and naphthalenediimide surfaces are twisted out of plane with a dihedral angle of 79.9°. The carboxylic acid moieties of *anti*-**1** are on opposite sides of the naphthalene diimide surface and cannot hydrogen bond to the same guest molecule. Molecular modeling of *syn*-**1**, based on the crystal structure, positions the two carboxylic acids directed toward each other with an O−O distance of 5.4 Å.

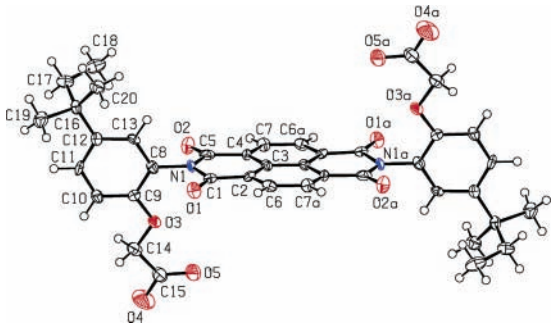


Figure 1. Molecular structure of *anti*-**1** with phenyl and naphthalenediimide surfaces twisted out of plane with a dihedral angle of 79.9°.

To test the ability of the guest-induced isomerization strategy to identify high-affinity guests, a range of different amine guests and control molecules was screened for their ability to bind to receptor **1** (Figure 2). We were particularly interested in whether the atropisomeric receptor **1** would show selectivity for a specific nucleoside (**4**−**9**). Additional monoamine (**10**, **11**) and diamine (**12**−**15**) guests were tested. The screening studies were carried out by heating a 1:1 ratio of receptor **1** and guest (2 mM) in TCE-d_2 for 3 h at 70 °C.

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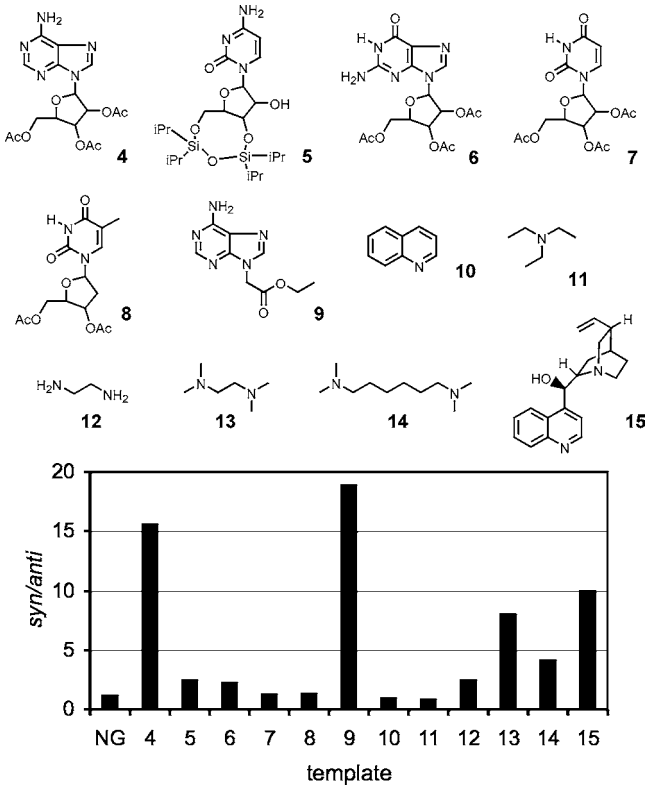

Figure 2. HPLC measured *syn*/*anti* ratios of diacid **1** on heating with no guest (NG) or 1.0 equiv of guest (**1**−**15**) in TCE-d_2 for 3 h at 70 °C.

The solutions were cooled to rt, and the *syn*/*anti* ratios were measured by HPLC (silica, 12.5% $CH_3CO_2H/CHCl_3$).

Of the protected nucleosides tested, adenosine **4** showed the strongest ability to influence the *syn*/*anti* ratio with a final value of 15.7. In contrast, cytosine **5**, guanosine **6**, uridine **7**, and thymidine **8** all showed significantly lower *syn*/*anti* ratios (<3). To verify that the adenosine base was the key recognition element, an adenine derivative **9** lacking the furanose moiety was tested in the isomerization assay. A high *syn*/*anti* ratio of 19 was measured which was comparable to adenosine **4**, confirming the importance of the adenine base in binding to receptor **1**. Molecular modeling of *syn*-**1** suggests an excellent structural and functional complementarity with adenine (Figure 3), with the potential for each carboxylic acid to form bidentate hydrogen-bonding interactions with adenine. Other controls were carried out. Heating receptor **1** without guest (NG) showed only a slight preference for the *syn*-isomer as did monoamines quinoline **10** and triethylamine **11**.

To verify the effectiveness of the *syn*/*anti* ratio in predicting the relative affinities of the guests for receptor **1**, ^{1}H NMR titration studies were carried out on nucleosides **4**−**8** and quinoline **10** in TCE-d_2 (Table 1). In comparison with the isomerization studies that were single-point measurements, the NMR titrations were considerably more difficult experiments. The guest and host needed to soluble over a much wider concentration range for accurate measurement of the binding constants, and thus, the titrations had to be carried out in the more polar acetonitrile. In addition, each titration had different complications arising from overlapping and disappearing peaks. In the end, binding constants for each of the nucleosides was measured. Consistent with the isomerization assay, adenosine **4** had very high affinity, and the other nucleosides had very low affinity for *syn*-**1**. It should be noted that the *syn*/*anti* ratio is a screen for selectivity and not simply affinity. For example, if the both the *syn* and *anti* conformational isomers have a high but equal affinity for the guest molecule then the *syn*/*anti* ratio will still be 1.

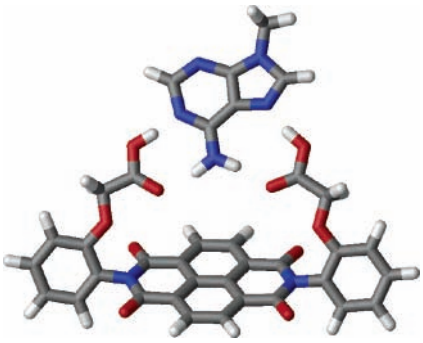

Figure 3. Molecular modeling (PCModel, MMX) calculated structure of the *syn*-**1**·adenine hydrogen-bonded complex. The *tert*-amyl and furanose moieties are not shown for viewing clarity.

Table 1. ^{1}H NMR Titration of Guests against *syn*-**1** and *anti*-**1** in CD_3CN

guest	K_a *syn*-**1** (M^{-1})	K_a *anti*-**1** (M^{-1})
adenosine **4**	3200	284
cytosine **5**	113	31
guanosine **6**	<10	<10
uridine **7**	<10	<10
thymidine **8**	<10	<10
quinoline **10**	<10	<10

The isomerization assay can also evaluate the relative binding of guests that cannot be easily measured by NMR titration. For example, diamines **12**−**15** are all sufficiently basic to deprotonate diacid **1**. Therefore, NMR titration experiments with these guests would be masked by the acid−base chemistry. The isomerization assays suggests that diamines **12**−**15** all have moderate binding to diacid **1** most likely via electrostatic interactions. However, basicity is not the sole predictor of binding affinity as the shorter tetramethyl diamine **13** yields a greater *syn*/*anti* ratio than the longer **14**. The best diamine was the cinchonidine, which induced a 10.1 *syn*/*anti* ratio.

A new more organic soluble atropisomeric diacid receptor was developed. Receptor **1** was found to have high affinity and selectivity for adenine demonstrating the efficacy of the

approach, utilizing a guest-induced isomerization screening strategy. This screening strategy can be easily extended to other atropisomeric receptors that can adopt stable conformations at room temperature and that have conformational isomers with very different recognition properties. For example, diacid **1** is easily derivized to include other recognition moieties, and we are in the course of applying this guest-induced isomerization assay to identify complementary guests for these new receptors.

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Supporting Information Available: Synthetic procedures for the preparation and separation of *syn*- and *anti*-**1**, the CIF file for *anti*-**1**, and procedures for the isomerization assay and titration binding experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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