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# A Small Molecule Diacid with Long-Term Chiral Memory

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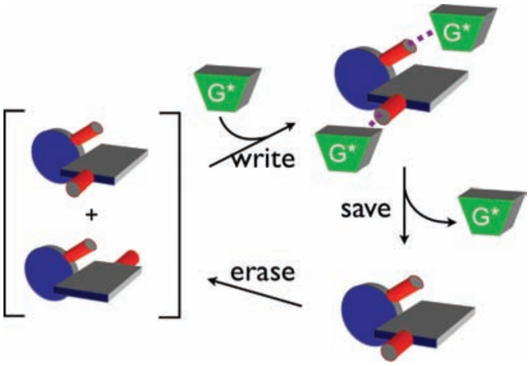
## ABSTRACT



**A small, axially chiral diacid was designed with chiral memory based on restricted rotation. Heating a racemic sample with a chiral alkaloid led to an enantiomeric excess of up to 40% ee. The guest-induced chirality was preserved on cooling to rt, which was maintained even in the absence of guest ($t_{1/2}$ = 14*y*). The chiral enrichment process was also reversible, allowing the diacid to be used as a chiral switch.**

The efficient transfer of chiral information from one molecule to another is an important process for many applications including asymmetric transformations and enantiomeric sensing.[1] For example, flexible receptors have been developed with the ability to adopt chiral conformations in the presence of chiral guests. This induced-fit mechanism has been used to measure ee and to assign absolute stereochemistry.[2] The utility of this approach, however, has been limited by the inability of the flexible hosts to maintain their chiral conformations in the absence of guest. Recently, a number of receptors and supramolecular systems with chiral memory have been developed.[3] In this paper, we present a small molecule diacid receptor **1** with excellent long-term chiral memory (Scheme 1). Heating **1** with a chiral alkaloid guest leads to enantiomeric enrichment, which is preserved on cooling to rt due to restricted rotation about the central $C_{aryl}-N_{imide}$ single bond.

Chiral memory systems represent a direct and potentially efficient route to optically active molecules and chiral molecular switches.[1d,4] The chiral templation process does not involve any bond-forming steps. In addition, the chiral guest is not consumed in the process and can be recovered and reused. The practical utility of chiral memory systems, however, has been limited by their poor stability at rt and by their large size. For example, most chiral memory systems will racemize within minutes or days at rt.[3a−o] The receptors are also usually large polymeric or self-assembled structures.[3d−r] Chiral memory system **1** addresses both of these limitations. The rotational barrier of diacid **1** is

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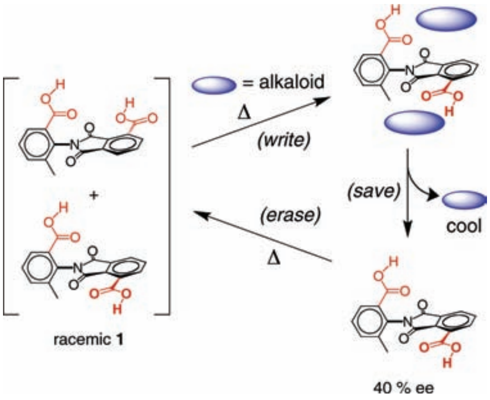
**Scheme 1.** Three-Step Chiral Memory Cycle for Diacid **1** Using the Alkaloids Quinine or Quinidine (Blue Ovals)

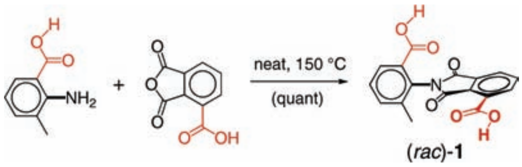


sufficiently high (29.6 kcal/mol) that it can maintain its optical activity for months at rt without measurable isomerization. Diacid **1** is also a small organic molecule, which opens up applications as a chiral building block, auxiliary, or catalyst.[5]

The chiral memory properties of diacid **1** are a consequence of restricted rotation about its central $C_{aryl}-N_{imide}$ single bond,[6] which generates enantiomeric rotamers (atropisomers) that are stable at room temperature. Thus, at elevated temperatures, the axially chiral rotamers of **1** are in equilibrium, and the equilibrium can be biased by complexation with a chiral guest. On cooling to rt, restricted rotation is reestablished, which "locks in" the guest-induced enantiomeric enrichment and allows the guest to be removed. The entire process is also reversible, and heating diacid **1** in the absence of guest "erases" the enantiomeric excess. Alternatively, heating **1** with an alkaloid guest of opposite chirality can directly yield the opposite enantiomer of diacid **1**.

Racemic diacid **1** was prepared in a single step (Scheme 2) by thermal condensation of an aniline (2-amino-3-methylbenzoic acid) with a cyclic anhydride (3-carboxyphthalic anhydride). The reaction proceeds quantitatively in the solid state at 150 °C for 24 h. Structural characterization of *rac*-**1** was established by X-ray crystallographic analysis, which verified the formation of the cyclic imide ring and the twisted axially chiral structure (Supplementary Info).[7] The steric interaction of the aryl methyl and carboxylic groups with the opposing imide carbonyls forces the aryl and phthalimide surfaces out of plane (57°), forming enantiomeric rotamers.

**Scheme 2.** Synthesis of *rac*-Diacid **1**



The chiral memory properties of diacid **1** were initially studied using CD spectroscopy (Figure 1). First, *rac*-**1** was heated neat with quinine or quinidine (2 equiv, 125 °C, 24 h). The mixture was cooled to rt, dissolved in EtOAc, and washed with 0.25 N HCl to remove the basic alkaloid guest. Figure 1 shows the CD spectra of samples of **1** heated neat with quinine (red line) and quinidine (blue line), respectively. The Cotton effects in both spectra were assigned to diacid **1**, as the CD signals cross from positive to negative ellipticity

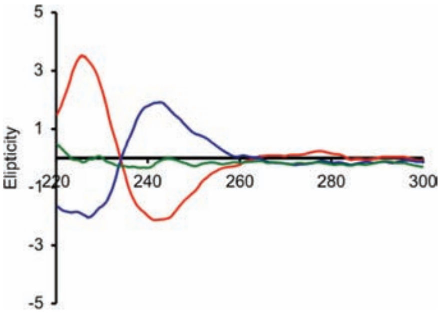


**Figure 1.** CD spectra of *rac*-**1** in $CH_3CN$ after heating (neat, 125 °C, 24 h) with 2 equiv of quinine (red line) or 2 equiv of quinidine (blue line). The CD spectra were taken after removal of the chiral guest by extraction with 0.25 N HCl. The green line is the spectrum of quinine-templated **1** after heating in the absence of guest (neat, 125 °C, 24 h).

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at the adsorption maximum of diacid **1** (234 nm). Quinine and quinidine favor opposing enantiomers of diacid **1**, which is consistent with opposing chirality of the two key chiral centers in these diastereomeric guests. This could be seen by the near mirror image Cotton effects in the CD spectra of the quinine and quinidine heated samples of **1**.[8] The reversibility of the chiral templation process was demonstrated by heating samples of quinine-templated **1** in the absence of guest (neat, 125 °C, 24 h), which led to a complete loss of optical activity (Figure 1, green line).

The excellent kinetic stability of the rotamers of **1** provided the opportunity to more accurately monitor the chiral memory properties using chiral HPLC. This is in contrast to most of the previous chiral memory systems that could only be monitored by in situ methods such as CD and chiral NMR.[3a−c] Diacid **1** was too polar for direct chromatographic analysis. Thus, samples of diacid **1** were esterified with an excess of phenyldiazomethane (1 mM, toluene) prior to analysis by chiral HPLC. The resulting dibenzyl ester **2** displayed clean baseline resolution (Figure 2). In this manner, the chiral templating efficiencies of the quinine and quinidine with diacid were quantitatively assessed. The results corroborated the CD studies as quinine and quinidine templated the formation of opposite enantiomers of **1**. Samples of **1** heated with quinine had a 40% *ee* of the faster eluting (−)-**1**. Samples of **1** heated with quinidine had a 40% ee of the slower eluting (+)-**1**.

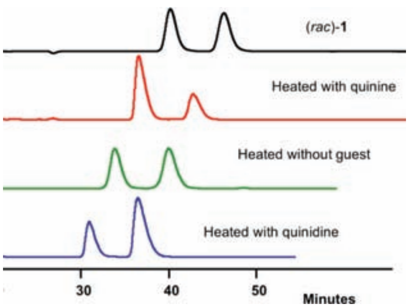

**Figure 2.** Staggered chromatograms of the chiral HPLC analyses of samples of *rac*-**1** (black line), which was sequentially heated (neat, 24 h, 125 °C) with 2 equiv of quinine (red line), without guest (green line), and with 2 equiv of quinidine (blue line). Prior to HPLC analysis, each sample of **1** was washed with 0.25 N HCl to remove the alkaloid guests and derivatized with phenyldiazomethane.

The templating abilities of other commercially available chiral alkaloids were also tested (Table 1). However, they all displayed lower chiral imprinting efficiencies than quinine and quinidine. Nicotine and sparteine showed no chiral induction. The cinchonidine and cinchonine diastereomers displayed poor templating efficiencies with low ee's (2% and 8% ee). This was surprising since cinchonidine and quinine differ by only a methoxy group. One possible explanation is that these small structural differences are magnified in the solid-state environment. Support for this hypothesis was provided by the low ee of the analogous studies carried out in solution (1,1,2,2-tetrachloroethane, TCE) (Table 1, entry 7).

**Table 1.** Chiral Imprinting Studies Monitored by Chiral HPLC

| entry | chiral guest[a] | conditions[b] | % ee of **1**[c] (major) |
|---|---|---|---|
| 1 | quinine | neat | 40 (−) |
| 2 | quinidine | neat | 40 (+) |
| 3 | cinchonidine | neat | 2 (−) |
| 4 | cinchonine | neat | 8 (+) |
| 5 | nicotine | neat | 0 |
| 6 | (−)-sparteine | neat | 0 |
| 7 | quinine | 5 mM TCE | 0 |

[a] Two equivalents of guest. [b] Experiments were conducted at 125 °C (24 h). [c] The % ee of **1** was determined by chiral HPLC (Chiralpak IC) after treatment with phenyldiazomethane.

The reversibility of the chiral templation process and the stability of the chiral products were also verified by chiral HPLC. A 40% ee sample of (−)-diacid **1** (Figure 2, red line) became racemic after heating in the absence of chiral guest (green line). This racemic sample could also be switched to the opposite enantiomer by heating with quinidine, yielding 40% ee of the (+) enantiomer (blue line).

The ability to quantitatively measure the ee of diacid **1** also enabled an accurate measure of its $C_{aryl}-N_{imide}$ rotational barrier. A sample of enantiomerically enriched **1** was heated neat at 100 °C, and the racemization was followed by chiral HPLC. The data was fitted to a first-order kinetic analysis (Supporting Information) to yield a rate constant of $6.5 \times 10^{-5}$ s$^{-1}$, which calculates to a rotational barrier of 29.6 kcal/mol.[9] This high barrier was consistent with the observed stability of the enantiomers of **1** at rt and equates to a half-life of 14 years at 23 °C. At the same time, the barrier was not too high, as isomerization could be facilitated by heating at a moderate temperature ($t_{1/2} = 14$ min at 125 °C). An almost identical barrier was measured for diacid **1** (29.4 kcal/mol) in solution (TCE). Thus, enantiomerically enriched **1** was kinetically stable both in solution and in the solid-state.[10] Control studies confirmed that enriched samples of **1** were stable at rt as they did not show any measurable change in ee after 2 months in solution ($CH_2Cl_2$ or EtOAc) or in the solid state. Similar studies established that the dibenzyl ester **2** also had a high rotational barrier ($\Delta G = 28.2$ kcal/mol), confirming that isomerization was not occurring during the HPLC analyses.

To study the mechanism of the chirality-transfer process, samples of *rac*-**1** were heated with varying stoichiometries of quinine and quinidine (Figure 3a). Both alkaloids showed very similar sigmoidal ee profiles, reaching a plateau at 2

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(8) To verify that the CD spectra were due to enantiomeric enrichment of **1** and not residual quinine or quinidine, the CD spectra of **1**/quinine and **1**/quinidine mixtures were measured (Supplementary Information). These samples had very different spectra and did not display a Cotton effect.

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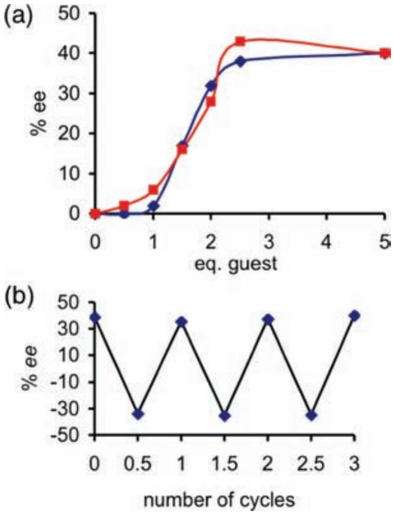

**Figure 3.** (a) Measured ee of diacid **1** when heated with varying equivalents of quinine (blue line) and quinidine (red). (b) Percent ee for three cycles of heating **1** (neat, 125 °C, 24 h) with quinidine (2 equiv) and then with quinine (2 equiv).

equiv. This is consistent with the formation of a 2:1 (guest/**1**) complex, in which the more basic bicyclic amine of two different quinoline alkaloids forms a salt with each carboxylic acid of diacid **1**. The chiral induction appears to be highly cooperative as stoichiometries lower than 1 equiv of guest gave virtually no chiral induction.[11] Thus, the corresponding 1:1 (alkaloid/**1**) complex is not very efficient in transferring chiral information. The possibility that the chiral induction was due to the formation of a highly ordered crystalline state was examined by powder XRD and DTA analyses of neat 1·(alkaloid)$_2$ mixtures (Supporting Information). All of the samples were found to be amorphous and did not undergo any phase changes on heating or cooling, suggesting that the individual alkaloid/**1** complexes were primarily responsible for the chiral induction.

Most recently, we have been able to extend the chiral imprinting process to the solution phase. Heating **1** with 2 equiv of quinine in toluene (100 °C, 3 d) yielded (−)-**1** in 47% ee. One possible explanation for the successful chiral induction in toluene and not in TCE may be the low solubility of **1**·(alkaloid)$_2$, which only dissolves on heating in toluene. On cooling, it is possible that the less soluble diastereomeric salt precipitates while the more soluble salt is still equilibrating in solution. Alternatively, the success in toluene may be related to its lower polarity, which enhances the intermolecular interactions.

Finally, the more thermally stable diacid **1** still retains its dynamic properties, as the chiral memory can be “written”, “erased”, and “rewritten.” This was demonstrated by its use as a chiral molecular switch.[4] A sample of **1** was repeatedly heated with 2 equiv of quinidine and then with 2 equiv of quinine (Figure 3b). After each heating cycle, the samples were dissolved in EtOAc and washed with 0.25 N HCl to remove the guest. An aliquot was removed for analysis by chiral HPLC, and the remaining material was used in subsequent heating cycles. After three cycles of heating with quinidine then quinine, no significant loss in material or in the efficiency of the chiral induction was observed. This study demonstrates the excellent fidelity of the switching process, which is a consequence of the simplicity of the switching process that does not involve any covalent bond-forming or -breaking steps.[12]

In summary, a chiral atropisomer **1** was designed with chiral memory. The chiral templation process is efficient as it is an example of a dynamic kinetic resolution where the enantiomeric enrichment of a host by a chiral guest is kinetically trapped by restricted rotation.[13] The templation process is also reversible, yielding products with dynamic properties that can be used in applications such as chiral molecular switches. The present system is distinguished from previous chiral memory systems in two key respects. First, atropisomeric receptor **1** is a small organic molecule, which facilitates its application to the synthesis of chiral building blocks and catalysts. Second, the guest-induced enantiomerically enriched state displays excellent kinetic stability. Finally, the ee’s of this chiral templation strategy are still moderate. Low ee’s were observed for the first reports of asymmetric transition metal and organic catalysts, which have now become well-established routes to chiral materials. We expect that the ee’s will improve with continued optimization and development of this strategy.

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**Supporting Information Available:** NMR, HPLC, DTA, and crystallographic data for **1** and diester **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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