Molecular playdough: conformationally programmable molecular receptors based on restricted rotation

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Received 14th May 2009, Accepted 21st July 2009
First published as an Advance Article on the web 14th August 2009
DOI: 10.1039/b909567e

A new method for rapidly tailoring molecular properties is presented in which the three-dimensional shape of a malleable framework is controlled by heating with a template molecule.

Introduction

The most attractive and powerful aspect of organic chemistry is the ability to control molecular properties. Using organic synthesis, chemists are able to tailor the properties of pharmaceutical agents, chemical adhesives, and dyes. Despite the advances in organic synthesis, the bond-by-bond assembly of organic structures remains the slow step in most organic chemistry projects.[1,2] Thus, organic chemists have been exploring new approaches such as combinatorial libraries and self-assembly that accelerate the synthesis and screening processes.[3-6] We have also been developing a new paradigm for controlling molecular properties, which relies on controlling the three-dimensional shape of a molecule. A malleable framework is moulded into a desired shape by heating with an appropriate templating agent (Scheme 1).[7-13] The strategy is synthetically efficient as it does not involve any bond forming or breaking reactions. The strategy is also versatile as a molecule can be moulded into different shapes by heating with different templating agents. Finally, the products possess dynamic properties as the conformational moulding process is reversible. Heating the products in the absence of the templating agent returns the system to its equilibrium state, and thus the products can be repeatedly reshaped for different applications.

We have applied the conformational moulding strategy to prepare molecular receptors with dynamic recognition properties.[14,15] An induced-fit mechanism provides an efficient means of controlling the shape of a malleable host framework at elevated temperatures.[16,17] This conformational bias is preserved on cooling to rt. The moulding process is more efficient and precise than the traditional computer-aided design process for molecular receptors, which typically requires multiple rounds of synthesis and evaluation. This is because the guest physically selects the highest affinity structures from the pool of equilibrating conformers. This ensures the formation of a matched receptor in a single optimization cycle.

The conformational moulding approach is actually an example of a dynamic combinatorial library (DCL) that is made up of conformers.[3,4,18,19] The earliest examples of conformational DCLs were by Eliseev *et al.* (Scheme 2a) and Huc *et al.* (Scheme 2b) who developed receptors with isomerizable C=C and C=N double bonds that could adapt their shapes in the presence of guanidine and barbiturate guests, respectively.[20,21] More recently, Hayashi *et al.* (Scheme 2c) and Shinkai *et al.* (Scheme 2d) have designed dynamic receptors based on porphyrin frameworks that can adapt and maintain new recognition properties when equilibrated with a

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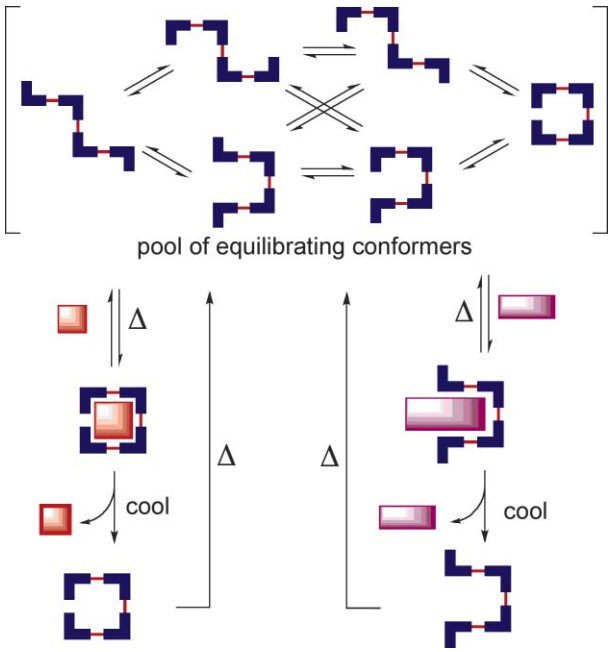


Scheme 1 Representation of the conformational moulding process where a malleable molecular framework can be shaped and reshaped by heating with a template molecule.

guest molecule.[22,23] These systems have demonstrated the viability of the conformational moulding strategy. However, the wider applicability of the approach has been limited by the kinetic instability of the products. In most cases, the templated conformers were stable for only minutes or hours at rt, which greatly limited their utility in sensing, separation, and catalytic applications.

Atropisomeric N-arylimides

Our goal has been to develop a framework with improved conformational stability at rt. Our strategy has been to connect rigid aromatic units together by single bonds that display restricted rotation.[24] For example in Fig. 1, the rigid aryl units are connected to the central diimide surface by single bonds,

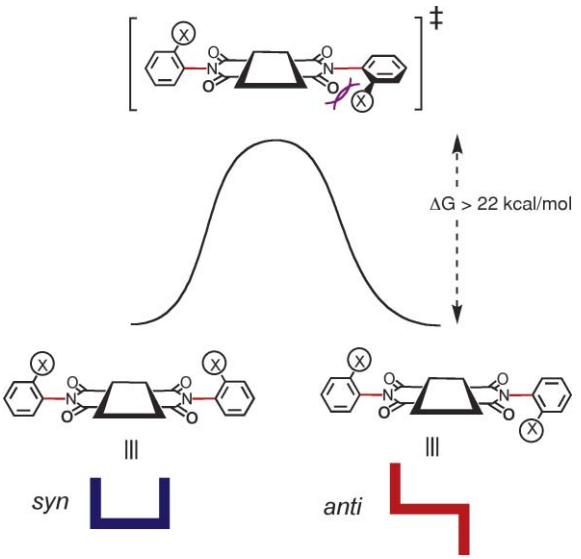
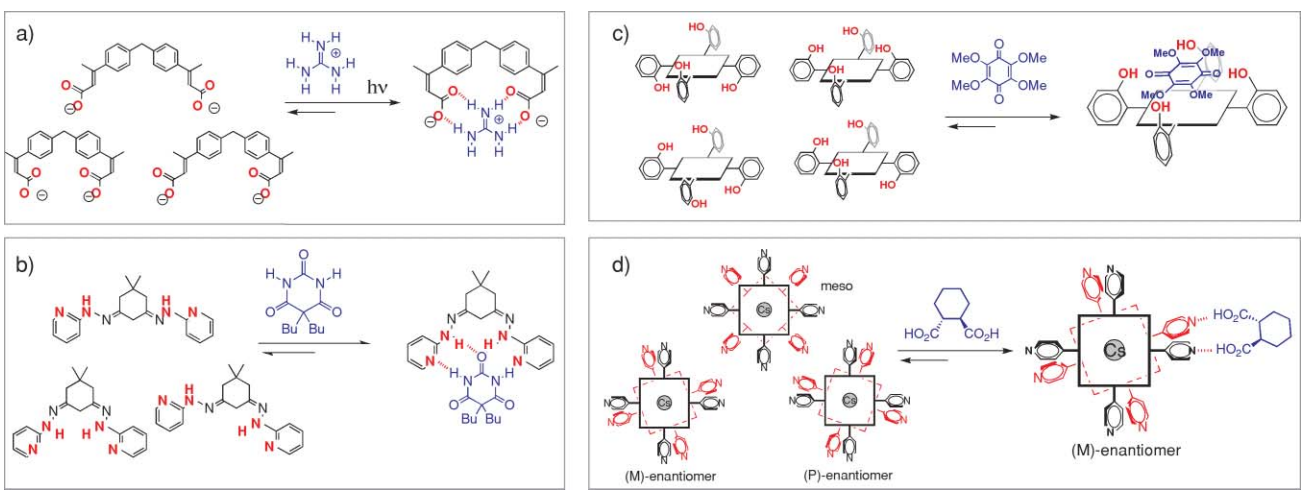


Fig. 1 Example of an atropisomeric N,N′-diaryldiimide framework with restricted rotation about two C_{aryl}–N_{imide} single bonds, leading to the formation of room temperature stable *syn*- and *anti*-isomers.

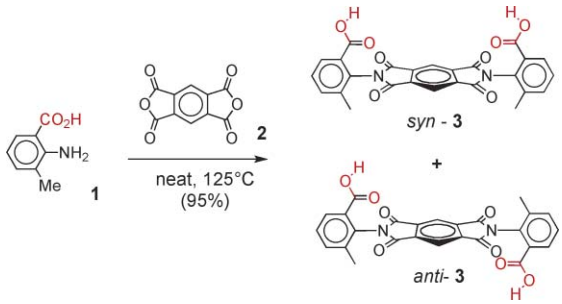
which are highlighted in red, with high rotational barriers. Thus, these atropisomeric frameworks possess the ability to switch between flexible and rigid states by heating or cooling. Above room temperature, free rotation about the single bonds allows the framework to adopt multiple three-dimensional shapes. On cooling to room temperature, the framework becomes locked into a specific conformation due to restricted rotation. The stability of these systems can be easily controlled *via* the size and number of *ortho*-aryl substituents (X-groups in Fig. 1). The rotational barriers of the atropisomeric systems are very sensitive to small structural changes due to the severe steric interactions in their planar transition states.

The major challenge was finding a synthetically accessible atropisomeric framework. We selected N-arylimides because they can be prepared in high yields *via* thermal condensation of an *ortho*-substituted aniline with cyclic anhydride.[25,26] The reaction proceeds even with highly hindered anilines and does not require



Scheme 2 Examples of conformational dynamic combinatorial libraries from the literature.

additional reagents or catalysts.[27] For example, N,N′-diaryldiimide **3** was prepared in 95% yield by heating 2,6-disubstituted aniline **1** with 1,2,4,5-benzene dianhydride **2** in DMF or neat (Scheme 3). The resulting diastereomeric *syn*- and *anti*-atropisomers[28] were stable at room temperature. This was demonstrated by separating the two isomers using flash chromatography and individually characterizing their structural and recognition properties.[29,30]



Scheme 3 Synthesis of a representative N,N′-diaryldiimide building block (diacid **3**).

The thermal imidization reaction possesses all the hallmarks of a "click" reaction, as it is high yielding and functional group tolerant.[31] Thus, a myriad of structures could be quickly assembled *via* different combinations of the readily available aniline and cyclic anhydride precursors (Chart 1). The tolerance of the condensation reaction to polar functional groups on the aniline allowed incorporation of carboxylic acid (**3**, **7**, **8**), pyridine (**4**), cyano (**5**), phenol (**6**), quinoline (**9**), and phosphine (**10**) recognition groups. The ability to use different cyclic anhydride precursors provided access to a diversity of rigid frameworks including: monoimides **8-10**, diimides **3-7**, 5-membered imides (**3**, **8-10**) and 6-membered imides (**4-7**).

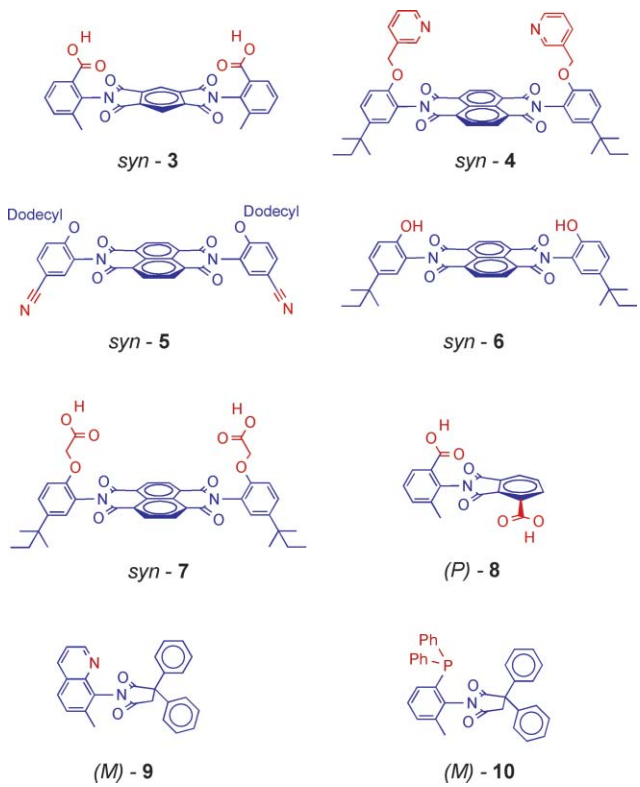
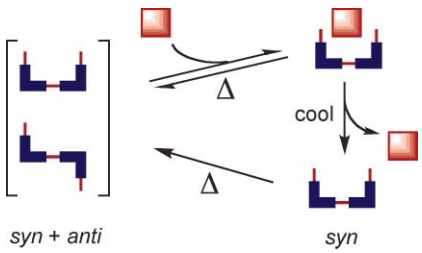


Chart 1 Examples of atropisomeric receptors based on the N-arylimide framework with the recognition groups highlighted in red.[24,27,28,31] In each case, multiple stable atropisomers were formed but only one isomer is shown for viewing clarity.

Conformational programming

Our first demonstrations of the conformational moulding strategy examined the ability of guests to control simple two-state (*syn*- and *anti*-) atropisomeric systems (Scheme 4). Initially, the *syn*- and *anti*-isomers are present in an approximately 1:1 ratio. Heating in the presence of a guest shifts the *syn–anti* equilibrium in favor of the complementary isomer. This conformational bias is "saved" on cooling to room temperature, allowing the templating agent to be removed. The *syn*-enriched product can then be used in molecular device and recognition applications. Finally, the conformational bias can be "erased" by heating without a guest, which returns the system back to its equilibrium 1:1 *syn*/*anti* ratio.



Scheme 4 Conformational moulding of a simple two-state (*syn* and *anti*) atropisomeric system *via* heating in the presence and absence of a guest molecule (red square).

The above strategy relies on finding guests with different affinities for the *syn*- and *anti*-isomers.[32,33] Luckily, the distinct shapes of the isomers gives rise to large differences in recognition properties, analogous to the *folded* and *unfolded* states of a protein. The *syn*-isomer forms strong complexes because its convergent recognition groups can cooperatively bind a guest molecule. The *anti*-isomer, in contrast, forms weak complexes due to its divergent recognition groups. For example, *syn*-diacid **3** formed a strong hydrogen bonded complex with an adenine guest ($K_a = 1100\ M^{-1}$) (Fig. 2).[13] The formation of a discrete 1:1 complex, and the participation of both carboxylic acids in *syn*-**3** was confirmed by X-ray crystallography. By comparison, *anti*-**3** had very low affinity for the adenine guest ($K_a < 5\ M^{-1}$). Another example of the different recognition properties of the *syn*- and *anti*-isomers is the metal binding properties of bis(pyridine) **4**. The *syn*-**4** was able to chelate metals in a *trans*-spanning fashion with both pyridine groups.[9,34]

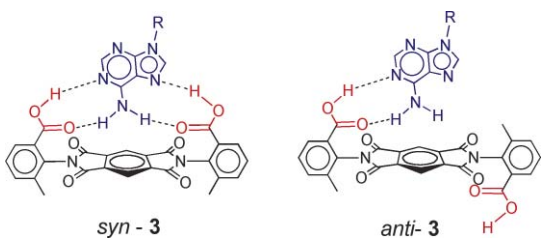
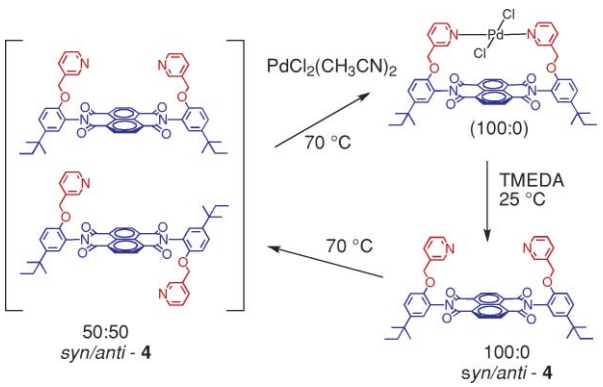


Fig. 2 Hydrogen bonded complexes of the *syn*- and *anti*-isomers of diacid **3** with ethyl adenine-9-acetate (R = $CH_2CO_2CH_2CH_3$).

The *anti*-isomer, in contrast, was not able to form a discrete molecular complex and instead formed oligomeric structures.

Our first successful demonstration of the conformational moulding approach utilized strong metal ligand interactions to control isomeric *syn*/*anti* ratios. A 1:1 *syn*/*anti*-mixture of **4** was heated with $PdCl_2$ (Scheme 5). The formation of the *syn*-**4**·$PdCl_2$ chelate quantitatively shifted the equilibrium to the *syn*-isomer.[9] Cooling to rt locked the structure in the *syn*-isomer, allowing the metal template to be removed by treatment with TMEDA without isomerization. The *syn*-**4** was stable for days at rt and could be utilized as a normal ligand or base. However, the enhanced binding properties of *syn*-**4** could also be "erased." Heating *syn*-**4** in the absence of the metal template returned the system to the equilibrium state (50:50, *syn*/*anti*).



Scheme 5 Conformational moulding cycle using Pd(II) as a template to form *syn*-**4**.

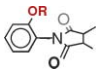
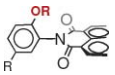
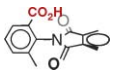
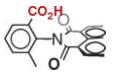
Adapting the approach to organic guests proved to be more difficult because they form weak hydrogen bonding and arene–arene complexes that are not stable at elevated temperatures. Ultimately, we found that the strong hydrogen bonding interactions of adenine guests for diacid receptors **3** and **7** were of sufficient strength to control the *syn–anti* equilibrium. Heating an 47:53 (*syn*/*anti*) mixture of diacid **3** with ethyladenine-9-acetate yielded 95:5 mixture of *syn*-enriched **3**. The basic adenine template was removed by washing with aqueous acid, yielding rt stable *syn*-enriched **3**.[13]

Rotational barriers

A key to the success of the above studies was the ability to tune the rotational barriers of the N-arylimides.[35] Ideally, the rotational barriers should be between 22 to 30 kcal/mol (Table 1). The lower limit of 22 kcal/mol is the minimum barrier required to achieve restricted rotation at rt (23 °C), which is defined as systems with half-lives > 1000 s.[36] The upper limit of 30 kcal/mol is based on being able to access free rotation with moderate heating (125 °C). By variation of the number and size of the *ortho*-aryl substituents, the barriers of the N-arylimides could be manipulated to fall within this range.[35] For example, N-arylimides **4**, **5**, and **8** all had rotational barriers of 27.0, 27.0, and 29.6 kcal/mol.

Control over the conformational stability of the N-arylimides was possible because of the extreme sensitivity of their rotational barriers to small structural and steric variations. For example, barriers of the cyclic 5-membered imides were significantly lower

Table 1 Comparison of the rotational barriers of 5- and 6-membered N-arylimides with varying number and sized *ortho*-substituents

	Rotational barrier (kcal/mol)	Half-life @ 23 °C	Half-life @ 75 °C	Half-life @ 125 °C
	20	36 s	0.2 s	
	27	65 d	1.4 h	31 s
	29	5.4 y	25 h	6.6 min
	34	27,000 y	4.0 y	2.6 d

than the analogous cyclic 6-membered imides by ~7 kcal/mol.[32] These differences appear to be due to the smaller N–C=O bond angles of the 6-membered N-arylimides, which forces their C=O oxygens in closer steric contact with the opposing *ortho*-aryl substituents. Due to these differences, the 5-membered imides such as in receptor **3** require two *ortho*-aniline substituents to achieve restricted rotation at rt. The 6-membered imides, in contrast, require only one *ortho*-aniline substituent to achieve restricted rotation at rt such as in receptor **4**.

The magnitude of the rotational barriers of the N-arylimides presented a characterization challenge. Their rates of interconversion ($k_{forward}$ and $k_{reverse}$ in eqn 1) were too slow to be measured by common dynamic methods such as NMR peak shape analysis or dynamic HPLC.[37,38] Instead, the rates of isomerization (k_{isom} in eqn 2) were measured. A sample enriched in one isomer was heated, and the change in isomeric ratio was monitored *via* HPLC or ^{1}H NMR as it approached equilibrium. The rate of isomerization (k_{isom}) was calculated from the negative slope of the plot of ln $((R - R_e)/(R + 1))$ *versus* time, where R and R_e are the ratios of isomers ([isomer 2]/[isomer 1]) at times t and at equilibrium.[39] The linearity of the plots confirmed that the isomerization reactions were first order, which is consistent with a unimolecular process. The $k_{forward}$ and $k_{reverse}$ was calculated from the measured k_{isom} using eqns 3 or 4 for systems with one or two rotatable bonds, respectively. The additional factor of 2 in eqn 4 corresponds to the two-fold increase in rate of isomerization of systems with two rotatable bonds as rotation of either bond will lead to isomerization. The rotational barrier ($\Delta G^{\dagger}$) was calculated from the Eyring equation (eqn 5), and the half-life ($t_{1/2}$) was calculated using eqn 6.

$$\text{isomer 1} \underset{k_{reverse}}{\overset{k_{forward}}{\rightleftharpoons}} \text{isomer 2} \quad (1)$$

$$\text{isomer 1} \xrightarrow{k_{isom}} \text{isomer 1} + \text{isomer 2} \quad (2)$$

$$k_{forward} = (k_{isom})/(1 + 1/K_{eq}); k_{reverse} = (k_{isom})/(1 + K_{eq}) \quad (3)$$

$$k_{forward} = (k_{isom})/(2 + 2/K_{eq}); k_{reverse} = (k_{isom})/(2 + 2K_{eq}) \quad (4)$$

$$k_{forward\ or\ reverse} = \frac{k_B T}{h} e^{(-\Delta G/RT)} \quad (5)$$

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

Applications

A unique feature of the conformational moulding process is the dynamic properties of the products, which can be repeatedly reshaped simply by heating under different conditions. We focused on applications that exploit these dynamic properties including a molecular switch, a self-optimizing receptor, a chiral memory molecule, and a molecular spring.

The first application that we examined was a molecular switch.[40,41] The reversibility of the moulding process provides a means to switch ON and OFF recognition properties. For example, repeatedly heating diacid **7** in the presence and absence of guest (ethyl adenine-9-acetate) switched the *syn*/*anti* ratio back and forth from 95:5 (ON) to 55:45 (OFF).[11] The switching process proceeds with high fidelity as it simply involves host–guest complexation and bond rotation. This was demonstrated by switching diacid **7** ON and OFF through multiple cycles without any significant decrease in amplitude (Fig. 3). This *syn*-*anti* switching process was also demonstrated with diacid **3** and bis(pyridine) **4**.[9,13] These systems are examples of conformational chemical switches similar to those present in biological systems as the change in conformation occurs only on heating in the presence or absence of the adenine guest.

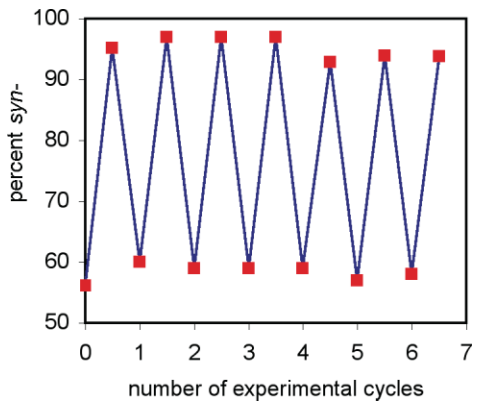
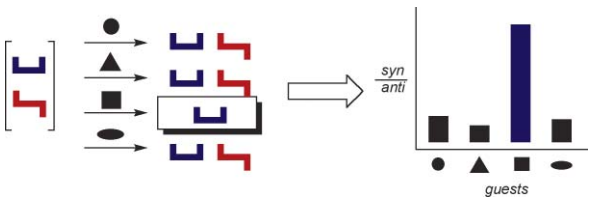


Fig. 3 Multiple switching cycles of atropisomeric diacid **7**, which was heated in the absence (OFF) and presence (ON) of a template molecule, ethyl adenine-9-acetate.

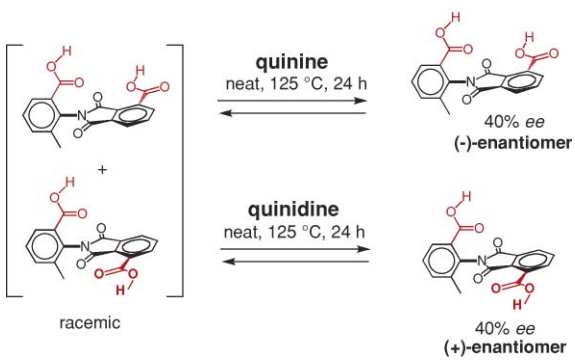
The atropisomeric molecular switches are distinguished from traditional supramolecular switches by their conformational memory.[42] The atropisomers are able to maintain their ON and OFF states even after the removal of the external stimuli (*i.e.* the guest molecule). This is in contrast to most supramolecular switches that require the constant presence of the guest molecules to maintain their ON states. This conformational memory allowed us to more accurately readout the *syn*/*anti* ratios of our molecular switches because the ON and OFF *syn*/*anti* ratios were very stable and were not sensitive to differences in solvent environment, guest concentration, and the presence of competing guests.

Next, the switching and memory capabilities of the atropisomeric receptors were used to develop a self-optimizing receptor that could rapidly identify complementary guests. New receptors are usually screened against a library of guests to identify high affinity guests. This is a slow process as it involves a multipoint titration for each receptor–guest pairing. Our atropisomeric receptors have a built in signal, the *syn*/*anti* ratios, which can identify high affinity guests in a single experiment (Scheme 6). This was demonstrated by heating diacid receptor **7** with 12 different basic guests and measuring the resulting *syn*/*anti* ratios by HPLC.[12] The majority of guests, which included nucleosides, monoamines, and diamines, showed poor differential affinity for diacid **7** as seen by their low, near unity *syn*/*anti* ratios. However, the three guests that had an adenine recognition group produced high *syn*/*anti* ratios (>15). This high affinity of the adenine guests for *syn*-**7** was separately verified using ^{1}H NMR titration experiments. The rapid screening process also identified cinchonidine alkaloids as excellent guests for diacid **3** as they induced *syn*/*anti* ratios of 10.



Scheme 6 Representation of the rapid screening strategy for the atropisomeric receptors where complementary guests are identified by their ability to shift the isomeric *syn*/*anti* ratios.

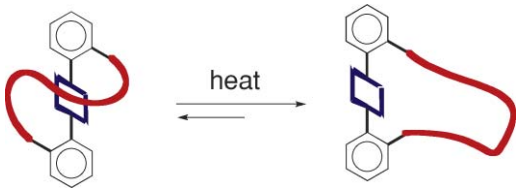
Restricted rotation in the N-arylimides can also generate enantiomeric rotamers, opening up the possibility of chiral applications. For example, N-arylimides **8-10** in Chart 1 are all axially chiral with rt stable enantiomers, which allowed them to be utilized as chiral NMR shift reagents[43] and asymmetric catalysts.[44] For example, chiral phosphine **10** was used as a chiral ligand in a Pd-catalyzed allylic alkylation reaction.[44] Unlike most chiral building blocks, the chirality of the N-arylimides can be switched back and forth between enantiomerically enriched and racemic states. These dynamic properties can be used as an efficient route to enantiomeric enrichment. For example, racemic diacid **8** (Scheme 7) was enantiomerically enriched (40% *ee*) simply by heating with a chiral alkaloid guest (quinine or quinidine).[45] This is a very direct and efficient route to enantiomerically enriched molecules as it does not involve a bond forming reaction and the chiral guest can be quantitatively recovered. Diacid **8** was also utilized as a chiral molecular switch. The optical activity of diacid **8** was switched ON and OFF by heating in the presence and absence



Scheme 7 Representation of the enantiomeric enrichment of diacid **8** *via* heating with chiral guests quinine and quinidine.

of a chiral guest. Alternatively, diacid **8** can be switched from one enantiomer to the other by heating with quinine or quinidine, as the pseudoenantiomeric alkaloids yield opposite enantiomers of **8**.

Finally, we used the atropisomers as 'molecular springs'.[46] Normally, the *syn*/*anti* ratios are near 1:1 at equilibrium as the *ortho*-recognition groups are too far apart to have steric or form non-covalent interactions. However, connecting *ortho*-substituents *via* a short linker biased the system toward the *syn*-isomer due to steric strain in the *anti*-isomer, which acted similar to a mechanical spring. For example, the carboxylic acids of atropisomer **3** were bridged by a short diamine linker shown representationally in Scheme 8. In the *anti*-macrocycle, the short linker is twisted around the central diimide spacer in a chiral configuration like a coiled spring. Although the *anti*-macrocycle is less stable, it can be separated and isolated at room temperature as this molecular spring is kinetically trapped in this high energy state due to restricted rotation. The energy can be released by heating the *anti*-isomer which unwinds into the more stable *syn*-isomer (7:1, *syn*/*anti*).

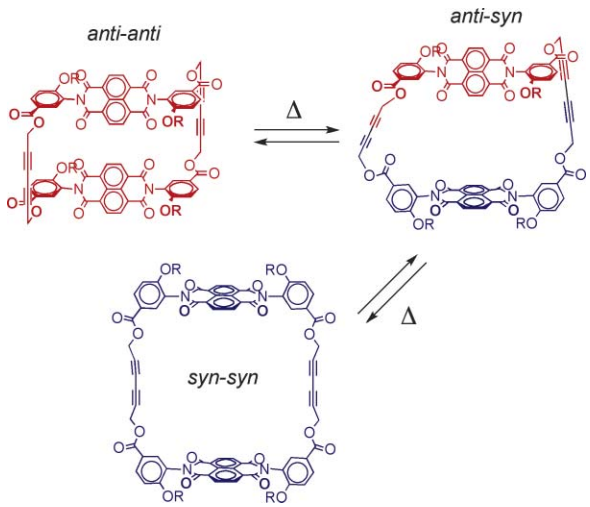


Scheme 8 Representation of a molecular spring based on macrocyclic *anti*- and *syn*-atropisomers.

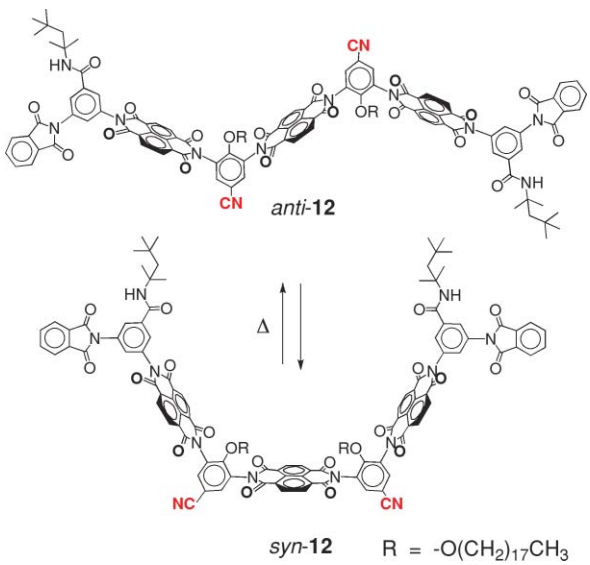
Extension to more complex systems

While the above studies have demonstrated the viability and potential of the conformational moulding strategy, they were restricted to atropisomeric systems that only adopt two shapes. Malleable frameworks that can adopt a greater diversity of shapes are also expected to access a wider range of physical properties. Our strategy is to link together multiple atropisomeric N-arylimide building blocks, yielding up to 2^n conformers. The first example in this series of oligomeric atropisomers is shown in Scheme 9. Macrocycle **11** was formed from the dimerization of two atropisomeric N,N'-diaryldiimide units.[8] Therefore, macrocycle **11** could adopt three distinct configurations: *syn–syn*, *syn–anti*, and *anti–anti*. Each isomer was stable at room temperature and was readily separable due to large differences in polarity, dipole, and hydrodynamic volume.

A second limitation of our initial studies was our focus on molecular recognition properties. The conformational moulding process can also be used to control other chemical properties because molecular shape is important in determining molecular dipole, solubility, and viscosity.[10,47] For example, differences in molecular dipole between the *syn*- and *anti*-isomers of dicyano **12** was used to control the conformational equilibrium (Scheme 10).[10] Heating **12** in a non-polar solvent such as toluene favored the smaller dipole *anti*-isomer yielding a 1:2, *syn*/*anti* ratio. Alternatively, heating **12** in a polar solvent such as DMSO masked the differences in dipole producing a 1:1 *syn*/*anti* mixture. The relationship between solvent polarity and isomeric ratio provided



Scheme 9 Three stable isomers of a macrocycle **11** composed of two atropisomeric diimide units.



Scheme 10 Solvent control of the *syn*/*anti* ratios of dicyano **12**.

precise and predictable control over the *syn*/*anti* ratios simply by heating in a solvent of appropriate polarity. Again, the unique aspect of this system was not its responsiveness to different solvents, but the ability to remember and save the solvent-induced conformational preferences. At rt, dicyano **12** could be transferred to other solvents without isomerization. In addition to control over molecular dipole and recognition properties, our studies with dicyano **12** also showed that the conformational moulding strategy could be used to control hydrodynamic volume.[10] The longer *anti*-**12** was significantly larger in hydrodynamic volume as measured by GPC than the more compact *syn*-**12**.

Conclusions

In summary, we have demonstrated the ability to tailor the properties of a molecule by control over its three-dimensional shape. The conformational moulding strategy is synthetically efficient as it avoids covalent bond forming reactions. The key to the successful implementation of the strategy was the development

of a playdough-like molecular framework with the proper balance of malleability and rigidity. This was achieved by incorporation of atropisomeric C_{aryl}–N_{imide} single bonds within a rigid aromatic framework. The N-arylimide based frameworks were readily accessible, which enabled rapid variation of their structure and conformational stabilities. The conformational preferences were controlled using a molecular template, generating an ideally matched molecular receptor. In this manner, the recognition properties could be controlled, tailored, and attenuated. While the necessity for an atropisomeric framework presents some limitations, it also endows the products with unique dynamic properties. The ability to repeatedly erase and reprogram molecular properties has applications in molecular switching and memory applications. Our future studies in this area are focused in two areas. First, we are currently exploring the extension of the molecular moulding strategy to control other molecular properties beyond recognition properties such as chirality, catalytic activity, and colour. Second, we are constructing larger more complex atropisomeric frameworks, which will provide access to a greater diversity of molecular properties.

Acknowledgements

This research was supported by the NSF grants CHE 0316395 and CHE 0616442.

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