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Highly efficient non-covalent energy transfer in all-organic macrocycles

Bhasker Radaram, Joshua Potvin and Mindy Levine*

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The use of aromatic organic macrocycles as supramolecular hosts for non-covalent energy transfer is reported herein. These macrocycles lead to stronger binding and more efficient energy transfer compared to commercially available γ-cyclodextrin. This energy transfer was particularly efficient for the highly toxic benzo[α]pyrene with a fluorescent BODIPY acceptor, with up to a 5-fold increase in the fluorophore emission observed.

The complexation of small molecules in organic macrocycles is a highly active area of research, with applications including supramolecular catalysis,1 small-molecule detection,2 and macrocycle-promoted energy transfer.3 We have previously shown that γ-cyclodextrin, a well-known supramolecular host,4 promotes efficient energy transfer from several polycyclic aromatic hydrocarbons (PAHs) and polychlorinated biphenyls (PCBs) to fluorophore acceptors.5 This energy transfer occurs with up to 35% efficiency, and has significant potential applications in developing array-based detection schemes.6 The use of aromatic macrocycles as supramolecular hosts can lead to even stronger binding of aromatic guests and higher energy transfer efficiencies, as these macrocycles can bind aromatic guests via π-π stacking7 in addition to hydrophobic binding.8 Four examples of such macrocycles were synthesized (Figure 1) (synthetic details provided in the ESI). Briefly, a double Williamson etherification reaction9 followed by a double Suzuki reaction10 rapidly assembled the linear precursors. The key macrocyclization reactions were accomplished via a double etherification reaction (for compound 1)11 or via a double Mitsunobu reaction (for compounds 2-4).12 These macrocycles include three structures that are electronically-dissymmetric (1-3), with clearly defined electron-rich and electron-deficient components to the macrocycle, and one that is electronically symmetric (4). The electronically dissymmetric structures are designed to bind an electron-rich analyte near the electron-deficient component of the macrocycle, and an electron-deficient fluorophore near the electron-rich segment of the macrocycle, to form a stack of four aromatic components with alternating electronic character that will undergo efficient energy transfer. Whether such dissymmetry improves the binding and energy transfer efficiencies was tested by comparison to control macrocycle 4, which lacks this dissymmetry.

Semi-empirical PM3-level calculations of the macrocycles indicate that all of them have internal dimensions analogous to that of γ-cyclodextrin (Table 1),13 and sufficiently large to promote intra-cavity energy transfer.

![Figure 1: Structures of supramolecular hosts, with electron-rich segments highlighted in red, and electron-deficient segments in blue. Height and width dimensions are shown on macrocycle 1, and the key protons involved in NMR studies are indicated by letters “c” and “d”.](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Height</th>
<th>Width</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.1 Å</td>
<td>11.2 Å</td>
</tr>
<tr>
<td>2</td>
<td>5.0 Å</td>
<td>12.6 Å</td>
</tr>
<tr>
<td>3</td>
<td>5.7 Å</td>
<td>13.0 Å</td>
</tr>
<tr>
<td>4</td>
<td>9.7 Å</td>
<td>8.0 Å</td>
</tr>
</tbody>
</table>

Once synthesized, macrocycles 1-4 were used for two key applications: (a) as supramolecular hosts to bind aromatic PAHs; and (b) as hosts for non-covalent energy transfer from PAHs to fluorophore 7 (Figure 2).14 The binding of aromatic PAHs in macrocycles 1-4 was measured by adding concentrated solutions of the macrocycle and PAH in THF to an aqueous solution of phosphate buffered saline. The fluorescence emission spectrum of the PAH was measured in the presence of increasing amounts of the macrocycle. This experimental design resulted in a mostly aqueous solution, which maximized hydrophobic binding of the PAHs.

Table 1 Cavity dimensions of compounds 1-4 in the energy-minimized conformations

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Among all macrocycles tested, macrocycle 2 was the most efficient supramolecular host for binding benzo[a]pyrene 6, with other PAH-macrocycle combinations leading to negligible binding. This binding was quantified by measuring changes in the emission spectra of benzo[a]pyrene: the addition of 0.061 mM of macrocycle 2 to 0.029 mM solution of benzo[a]pyrene 6 resulted in a 4-fold increase in the benzo[a]pyrene emission (Figure 3a). The sharp increase in the excimer band around 500 nm with increasing amounts of the macrocycle strongly suggests a 1:2 host: guest complex, even in the presence of a ca. 2-fold excess of the supramolecular host. Fitting this data to a Benesi-Hildebrand equation for a 1:2 complex revealed an apparent binding constant 15 of this proximity-induced energy transfer depends significantly on whether the PAH donors and fluorophore acceptors bind in the macrocycle interior. Because macrocycle 2 binds benzo[a]pyrene with high affinities, the likelihood of its success as a host for supramolecular energy transfer was increased.

Table 2 1H NMR chemical shifts for macrocycle 2:6 complex

<table>
<thead>
<tr>
<th>NMR proton</th>
<th>Initial (ppm)</th>
<th>Final (ppm)</th>
<th>Change in ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak A</td>
<td>9.005</td>
<td>9.021</td>
<td>+0.016</td>
</tr>
<tr>
<td>Peak B</td>
<td>8.471</td>
<td>8.482</td>
<td>+0.021</td>
</tr>
<tr>
<td>Peak C</td>
<td>5.542</td>
<td>5.465</td>
<td>-0.077</td>
</tr>
<tr>
<td>Peak D</td>
<td>4.571</td>
<td>4.549</td>
<td>-0.022</td>
</tr>
</tbody>
</table>

The efficiency of such energy transfer was quantified in two ways:

(a) by measuring the decrease in the donor emission from adding an energy acceptor, according to Equation 1:

\[
\text{Donor decrease} = \frac{F_{DA}}{F_D}
\]

where \( F_{DA} \) and \( F_D \) are the integrated emission of the donor in the presence and absence of acceptors;19

(b) by measuring the increase in the acceptor emission from adding the energy donor, according to Equation 2:

\[
\text{Fluorophore increase} = \frac{I_{DA}}{I_A}
\]

where \( I_{DA} \) is the integrated emission of the fluorophore from analyte excitation, and \( I_A \) is the integrated emission of the fluorophore (from excitation at the same wavelength) in the absence of the analyte.

The results of macrocycle-promoted energy transfer are summarized in Table 3. These experiments were conducted under mostly aqueous conditions to maximize the favourable hydrophobic binding and \( \pi-\pi \) stacking between the aromatic PAH donor, aromatic fluorophore acceptor, and aromatic macrocycle.

Table 3 Results of macrocycle-promoted energy transfer between compound 6 and compound 7

<table>
<thead>
<tr>
<th>Host</th>
<th>Fluorophore Increase</th>
<th>Donor Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrocycle 1</td>
<td>3.3</td>
<td>0.90</td>
</tr>
<tr>
<td>Macrocycle 2</td>
<td>5.3</td>
<td>0.57</td>
</tr>
<tr>
<td>Macrocycle 3</td>
<td>2.4</td>
<td>0.80</td>
</tr>
<tr>
<td>Macrocycle 4</td>
<td>3.6</td>
<td>0.72</td>
</tr>
</tbody>
</table>

\( a \) 360 nm excitation in all cases; fluorophore increase calculated according to Equation 2 and donor decrease calculated according to Equation 1. Control experiments in the absence of a macrocycle showed no significant energy transfer.

The results clearly indicate that macrocycle 2 was the most efficient host for non-covalent energy transfer, as measured both...
by the increase in fluorophore emission more than 5-fold and by
the decrease in donor emission to 57% of its initial value (Figure
5a and 5b). The minimal amount of excimer emission observed in
these spectra strongly suggests that fluorophore 7 displaces one
molecule of benzo[α]pyrene from the macrocycle’s interior.

Interestingly, macrocycle 4 was substantially less efficient than
macrocycle 2 at promoting supramolecular energy transfer
between benzo[α]pyrene 6 and BODIPY 7 (Figure 5c and 5d).
The only difference between the two hosts is the replacement of
the perfluorophenyl ring in macrocycle 2 with a phenyl ring in
macrocycle 4, which effectively removes the electronic
dissymmetry from the structure. This direct comparison indicates
that electronic dissymmetry provides a direct benefit for
supramolecular energy transfer efficiencies.

Macrocycle 2 was also substantially more efficient at promoting
such energy transfer compared to γ-cycloedextrin.5 Using γ-
cycloedextrin as a supramolecular host resulted predominantly in
the formation of a benzo[α]pyrene excimer, with only weak
energy transfer observed. This excimer effectively obscured the
fluorophore emission peak, rendering such a system ineffectual for
benzo[α]pyrene-based energy transfer and detection. In contrast, using macrocycle 2 resulted in a strong BODIPY peak
and minimal benzo[α]pyrene excimer emission under identical
experimental conditions. The ability to use benzo[α]pyrene in
such energy transfer schemes (and detection schemes based on
such energy transfer) is particularly relevant, due to the high
toxicity and known carcinogenicity of benzo[α]pyrene.20 Control
experiments with macrocycle 2 and BODIPY 7 indicated that no
energy transfer occurred from the very weakly fluorescent
macrocycle to the BODIPY fluorophore.

In summary, reported herein is the use of aromatic organic
macrocycles as supramolecular hosts for PAH binding and non-
covalent energy transfer. One of the new macrocycles, compound
2, is substantially more efficient than known macrocyclic molecules at
binding benzo[α]pyrene and promoting energy transfer from this
toxin to a fluorophore. More generally, the ability to modify the
supramolecular host for this energy transfer via synthetic organic
chemistry provides optimal flexibility in tuning and optimizing
such non-covalent energy transfer. The scope of macrocycle-
promoted energy transfer and its use in array-based detection
scheme is currently under investigation, and results will be
reported in due course.

The reasons why macrocycle 2 is substantially more efficient
than macrocycles 1, 3, and 4 at binding PAHs and promoting
energy transfer are currently under investigation, but the
following conclusions can already be drawn: (a) The electronic
dissymmetry in macrocycle 2 led to better energy transfer efficiencies than electronically symmetric macrocycle 4; (b) the
ester linkages in macrocycle 2 led to better energy transfer efficiencies than the ether linkages of macrocycle 1; and (c) the
presence of the methoxy groups in macrocycle 3 led to less
efficient energy transfer than macrocycle 2, possibly due to the
increased steric bulk.

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