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Aromatically Functionalized Pseudo Crown Ethers with Unusual Solvent Response and Enhanced Binding Properties

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Conformational flexibility in the host's structure is often considered detrimental to its binding. Flexible pseudo crown ethers with aromatic donor/acceptor groups at the chain ends, however, displayed enhanced binding affinity and selectivity, particularly when the direct binding interactions were compromised by unfavorable solvents.

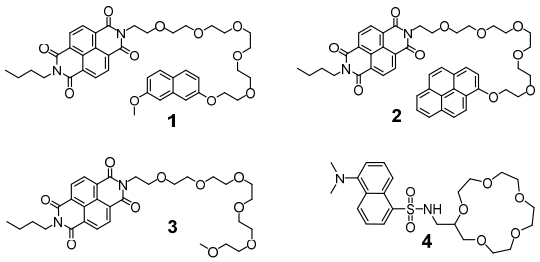
Biopolymers such as proteins have rich conformational dynamics essential to their functions. Foldamers are synthetic mimics of these biopolymers with controlled conformational changes.[1-5] Foldamer-based supramolecular hosts differ from conventionally preorganized hosts because guest-induced conformational change is often an inherent property of the host,[6-9] sometimes leading to unusual molecular motions during binding.[10] Extreme sensitivity to the environment can be easily obtained from the conformational mobility.[11-14] Meanwhile, due to their highly programmable structures, foldamers can be designed to bind complex organic molecules with high structural precision.[15-18]

Guest-induced conformational change traditionally is considered detrimental to the binding affinity because the energetic cost associated with the change is assumed to be paid out of the binding energy.[19] Intuition also suggests that flexible hosts, being so accommodating, would be less selective in its binding. Although this has been the dominant view in supramolecular chemistry, it is puzzling that conformationally mobile biofoldamers can obtain extremely high binding affinity and selectivity far better than rigid synthetic hosts.[20]

In recent years, an alternative strategy to achieve strong and selective binding has been proposed[21-23] and experimentally verified.[24-30] Representative examples include the anion-binding peptidic bismacrocycle by Kubik and Otto,[24] the crown ether-like receptor by Carrillo and co-workers,[25-27] and our glutamic acid-functionalized oligocholate foldamer.[28] Rational designs are also possible.[29, 30] In these hosts, disengaged noncovalent interactions within the host are "turned on" by the guest. Because these guest-triggered intrahost interactions (together with the solvation/desolvation changes) also contribute to the binding equilibrium, binding becomes stronger than what can be obtained from the direct binding interactions alone. As a result, binding in these receptors is delocalized over the entire host structure instead of being confined at the host–guest interface.[21]

Herein, we report two oligoether hosts with aromatic donor/acceptor (D/A) groups at the chain ends. The aromatic groups not only could preorganize the chain into a pseudo crown ether but also interacted more strongly in the presence of the guest. The result was usually strong binding for the guest, particularly in unfavorable solvents. Despite its conformational flexibility, such receptors could possess good binding selectivity.

Our study involved four receptors (**1**–**4**). Receptors **1** and **2** are podands[31-35] with an electron-rich naphthyl and pyrenyl group, respectively, that can interact with the electron-deficient



naphthalene diimide (NDI) on the other end of the chain. We chose aromatic rings as the intrahost-interacting groups because they can be tuned easily in strength and can be monitored spectroscopically.[36-39] The *direct* binding groups are oligo(ethylene oxide), akin to an open-chain crown ether that can bind a sodium ion through electrostatic interactions (vide infra for the binding of other alkali metal ions).[40, 41] Receptor **3** replaces the electron donor of **1** and **2** with a methyl group and thus is devoid of the aromatic interactions needed for the proposed intramolecular enhancement. Crown ether derivative **4** is a covalent control, preorganized in the conventional

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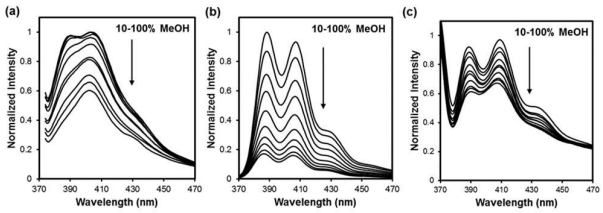

Fig 1. Normalized fluorescence emission spectra of compounds **1** (a), **2** (b), and **3** (c) in mixtures of methanol and DCM. [**1**] = 2.0 μM. [**2**] = 20 μM. [**3**] = 30 μM. λ_{ex} = 358 nm for compounds **1** and **3**. λ_{ex} = 278 nm for compound **2**.

manner to bind sodium. Its dansyl group on the side chain makes it easy for us to study the binding by spectroscopy.

Syntheses of **1**–**3** are reported for the first time and the details are given in the Electron Supplementary Information (ESI). Compound **4** was synthesized according to a literature procedure.[42]

Figure 1a,c shows the emission spectra of **1**–**3** in mixtures of methanol and dichloromethane (DCM).[43] Compounds **1** and **3** were excited at λ_{ex} = 358 nm, where naphthyl had no absorption. Although quenching was observed in both compounds, the emission peaks changed in shape in **1** but mostly decreased in intensity in **3**, presumably due to the NDI–naphthyl interactions in the former. When the emission intensity of NDI at ~390 nm was plotted against solvent polarity (Figure 2a), compound **1** afforded a sigmoidal curve (◆) but compound **3** a straight line (●). It is likely that the linear decrease in emission intensity in **3** was from a generic solvent effect on the NDI, as no other fluorophore was present in this compound. The sigmoidal transition in **1**, on the other hand, is a hallmark of cooperative conformational changes.[44]

As shown in Figure 2, the fluorescence data for compound **1** (◆) fit well to the two-state transition model (unfolded ⇆ folded), which assumes the compound only exists in the folded or unfolded form and the free energy for the conformational change is linearly related to solvent polarity.[44] Two-state conformational changes are frequently observed in foldamers stabilized by solvophobic interactions.[12, 45-47] In our case, higher

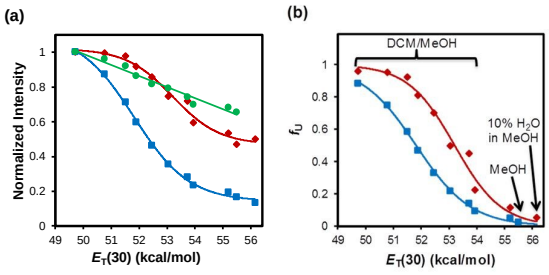

Fig 2. (a) Normalized fluorescence emission intensity at 390 nm as a function of solvent polarity for compounds **1** (◆), **2** (■), and **3** (●). The emission intensity of compound 3 fit well to a linear relationship with R = 0.995. (b) Unfolded fraction as a function of solvent polarity for compound 1 (◆) and 2 (■). Details of fitting are found in ESI.

methanol in the solvent—i.e., larger E_T(30)—should strengthen the aromatic interactions between NDI and naphthyl[48-50] and thus help the compound fold. Intermolecular aggregation was ruled out by a dilution study (Figure S1 in ESI)

Pyrene emits much more strongly than NDI and the emission spectrum of **2** is dominated by the pyrene emission (Figure 1b). Upon addition of methanol, significant quenching occurred and the quenching profile was a partial sigmoidal curve (Figure 2a, ■). The curve also fit well to the two-state model, which shows a higher population of folded conformer in **2** than in **1** at any given solvent composition (Figure 2b). Aromatic donors and acceptors tend to stack face-to-face and solvophobic interactions are known to be the major contributor to the binding interactions, especially in polar solvents such as methanol.[48-50] Since the larger-sized pyrenyl group in **2** is expected to provide a stronger solvophobic driving force to the folding, better folding in **2** is expected.

The binding properties of compounds **1**–**3** were determined by UV titrations using sodium thiocyanate as the guest. The UV absorptions of these compounds displayed very little change during the solvent titration (in DCM/methanol mixtures) and thus better reflects the effect of binding than the changes in emission.[51] As shown by the titration curves (Figures S2 and S3), the UV absorbance (at 358 nm for **1** and 382 nm for **2**) fit well to a 1:1 binding isotherm, from which the binding constant could be determined.

Figure 3a shows the relationship between log K_a of compounds **1**, **2**, and **4** and the solvent composition. The binding for sodium by **3** was hardly measurable in methanol/DCM mixtures and thus was not included.

The preorganized receptor (**4**, ▲) displayed a monotonous decrease in log K_a with increasing solvent polarity (larger E_T(30))—this is the conventional solvent effect for the binding. Because methanol solvates both the binding functionalities (oxygen atoms on the ether chain) and the sodium guest, higher methanol in the solvent increases the desolvation cost of the binding. In addition, the higher dielectric constant of methanol over DCM screens the electrostatic interactions between the host and the guest and also weakens the binding.

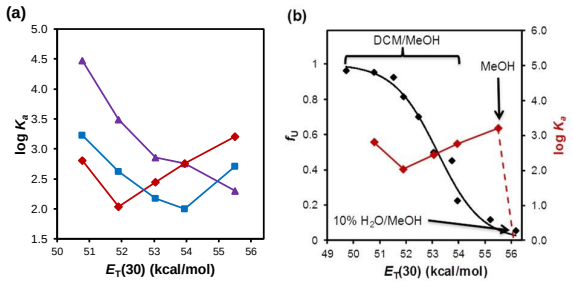

Fig 3. (a) Binding constant of compounds **1** (◆), **2** (■), and **4** (▲) for sodium determined by UV-vis titrations against solvent polarity in methanol/DCM mixtures. The binding constants were averages from triplicate titrations at 90% confidence level. Titrations curves are reported in the ESI (Figures S2–S5) and binding constants in Table S1. (b) Unfolded fraction of **1** as a function of solvent polarity (black line) and log K_a of **1** for NaSCN (red line). The solid smooth curve was from nonlinear least-squares fitting of the intensity to the two-state transition model.

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Both the naphthyl–NDI (**1**, ◆) and pyrenyl–NDI receptor (**2**, ■) behaved differently, showing a decrease in binding followed by increasing $E_T(30)$ (Figure 3a). In low-polarity solvents, log K_a followed the order of **4** > **2** > **1**. This trend supports the importance of preorganization in this solvent region. Receptor **4** has the best preorganization among the three, being covalently formed. The D–A aromatic interactions in **1** and **2** serve to preorganize the compound into a pseudo crown ether and the stronger D–A interactions in **2** makes it better preorganized for binding sodium.

The inflection points in the log K_a curves suggest that a different binding mechanism began to dominate in more polar solvents for **1** and **2** (Figure 3a). Several pieces of evidence support that the guest-triggered D–A interactions dominated after the inflection points.

First, since the direct binding force between oligo(ethylene oxide) and Na^+ was weakened continuously by polar solvents (evident from the weaker binding of the control receptor **4**), the increase in log K_a for **1** and **2** beyond the inflection points must have other sources. Better preorganization by methanol to strengthen the D–A interactions *cannot* explain the trend, as the order of binding reversed for **1** and **2** after the inflection points. As mentioned above, the stronger D–A interactions in the pyrenyl receptor (**2**) should better preorganize the compound for binding. Interactions between the imide carbonyls and sodium could not explain the reversal either. (Besides, even with the imide carbonyls, **3** always displayed weak binding.)

Second, the key feature of intramolecular enhancement is that guest-triggered intramolecular interactions become part of the overall binding energy. Such enhancement is expected to occur only if the donor and acceptor are *not* fully engaged prior to the guest binding. Given that **2** folded almost fully in methanol (Figure 2b), it is quite likely that the pyrenyl and NDI were simply bound too well prior to guest-binding so that further improvement from the guest binding was minimal. Weaker naphthyl–NDI interactions in **1**, on the other hand, made it possible for the guest to strengthen the D–A interactions. Thus, the model of intramolecular enhancement correctly predicts the weaker binding of **2** than **1** after the inflection points.

Third, when 10% water was added to methanol, a precipitous drop in binding was observed for **1** (K_a < 10 M^{-1}, Figure 3b, red dashed line) while **4** was barely affected (K_a went from 200 to 180 M^{-1}). Thus, the small amount of water did not change the direct binding force significantly but completely shut down the intramolecular enhancement. Addition of water served to increase the solvophobic interactions between the donor and acceptor, evident from the enhanced charge-transfer band near 450 nm for **1** (Figure S6). Once the D–A pair became tightly bound before the guest binding, the very basis of intramolecular enhancement—guest-triggered strengthening of intrahost interactions—was removed. Similar observation was made in other intramolecularly enhanced receptors.[28-30]

Fourth, the sodium-enhanced D–A interaction was confirmed spectroscopically. As shown by UV-vis spectroscopy, when sodium was added to **1** in methanol, the charge-transfer band near 450 nm increased steadily, supporting a closer contact between the donor and acceptor induced by the guest (Figure S7). Receptor **1** displayed no NOE signals between the NDI and the naphthyl protons in methanol at 213 K, suggesting that the naphthyl and NDI are separated by a significant distance in the NMR sense (Figure S8). Addition of sodium significantly enhanced the naphthyl–NDI contact and numerous naphthyl–NDI cross peaks appeared (Figure S10). The NDI protons also became closer to the ethylene oxide protons, supporting the sodium-triggered "ring closure" in **1**. Our fluorescence data indicate that the population of folded 1 was over 90% in methanol (Figure 2b). The CT band in the UV-vis spectrum (Figure S6) indicates that some of the naphthyl and NDI groups were in reasonable proximity. Taken together, the spectroscopic data support a loosely bound donor–acceptor pair, hypothesized to be essential to the cooperatively enhanced binding.

Fifth, although by itself not conclusive, the extremely weak binding of **3** was consistent with the intramolecular enhancement. Without an appropriate donor, intramolecular D–A interactions do not exist in this compound. Without the D–A interactions, neither preorganization nor intramolecular enhancement could operate and the weak binding was an expected result.

Figure 3a also shows that the onset of intramolecular enhancement was earlier for **1** than for **2**. The most likely reason for this is the interplay between the preorganization and intramolecular enhancement. In general, very strong D–A interactions favor preorganization but a weakly bound D–A pair with "room for improvement" is best for intramolecular enhancement. In the case of **2**, the stronger pyrenyl–NDI interactions serve to better preorganize the oligo(ethylene oxide) chain for binding, and thus can promote the principle of preorganization and make it last longer.

To be selective in binding, preorganized receptors typically are fairly rigid so that only the best-fitted guest can enter the binding site to engage the largest number of binding interactions possible. Intramolecularly enhanced receptors obtain their binding selectivity in a different way—by having the best guest turn on the largest number of intrareceptor interactions while maintaining as much direct binding interaction as possible.[29, 30]

Receptor **1** indeed displayed significant binding selectivity, despite its flexibility.[52, 53] In methanol, among common alkali metal ions, it showed insignificant binding for Li^+, bound Na^+ with $K_a = 1.6 \times 10^3$ M^{-1}, and bound K^+ with $K_a = 4.2 \times 10^2$ M^{-1} (Figure S12). The Na/K ratio in the binding affinity was nearly 4:1. In contrast, the binding constants of 15-crown-5 for Na^+ and K^+ are reported to be 1.7×10^3 and 2.7×10^3 M^{-1}, respectively, with a Na/K ratio of 1:1.5—18-Crown-6 has a Na/K ratio of 1:54.[54] Therefore, at least in this example, the flexible intramolecularly enhanced receptor **1** actually displayed a higher binding selectivity for sodium than the traditionally preorganized crown ether.

In summary, flexible structures with intramolecular enhancement offer an interesting strategy to strong and selective receptors. As shown by Figure 3a, they become particularly competitive when the direct binding forces are weakened by unfavorable solvents. Binding selectivity, meanwhile, does not have to suffer. These are very useful properties and could help chemists design a new generation of biomimetic receptors.

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Notes and references

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† Electronic Supplementary Informa on (ESI) available: syntheses and characterization of materials, experimental procedures for the binding studies, additional data and Figures. See DOI: 10.1039/c000000x/.

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