Crescent oligoamides as hosts: conformation-dependent binding specificity†

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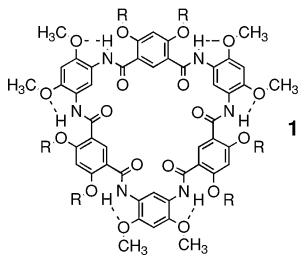
Crescent oligoamides have been found to bind substituted guanidinium ions with high specificity and affinity.

Many unnatural oligomers folding into well-defined secondary structures have been reported.[1,2] In addition to mimicking the folding of biomacromolecules, another major objective of studying foldamers is to create molecules with biomimetic or other unique functions. Although efforts have mainly been focused on structural studies, foldamers with novel functions have been reported. For example, foldamers and their derivatives acting as hosts for various guests,[3] antibiotic agents,[4] and inhibitors of protein–protein interactions,[5] are known. By introducing an intramolecular hydrogen bonding interaction that serves to limit conformational freedom,[6] we have developed aromatic oligoamides adopting crescent or helical conformations that contain large cavities with well-positioned, multiple amide O atoms.[7,8] Macrocycles **1**, derived from crescent aromatic oligoamides, were discovered by us.[9] With an internal cavity containing six introverted O atoms, macrocycles **1** were found to bind guanidinium (G) ion with nearly exclusive selectivity.[10]† In contrast, substituted guanidinium ions such as octylguanidinium (OG) ion were not recognized in comparable affinity and selectivity by these macrocycles. The specific binding of G ion by **1** prompted us to investigate the possibility of developing hosts with altered selectivity that prefers substituted guanidinium ions. Herein we describe crescent oligoamides with dramatically different binding specificities due to subtle conformational differences. These molecules represent novel hosts capable of tightly binding as well as discriminating guests of similar structures.



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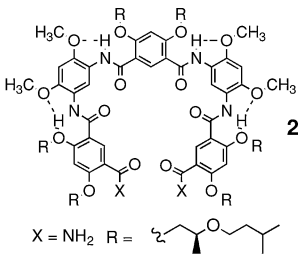

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X = NH_2 R =

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It was initially reasoned that the preference of **1** toward G over OG ion was due to the poor accommodation of the "tail" of the latter by the macrocycles. Non-cyclic, crescent-shaped **2**, derived by removing a benzene ring from macrocycle **1**,[8] may better accommodate substituted guanidinium ions, resulting in enhanced binding selectivity. A mixture containing **2**, guanidinium tetraphenylborate (G·TPB) and octylguanidinium tetraphenylborate (OG·TPB) was examined by MALDI-TOF. Compared to **1**, oligomer **2** did show improved binding to OG ion.† However, in the MALDI spectrum, the [**2**+Na^+] and [**2**+H^+] peaks due to non-specific binding to the host appeared in high intensity. This is in sharp contrast to the exclusive complexation of the G ion by **1**, suggesting that the affinities of G and OG ions for **2** were insufficient to expel small cations from the cavity.

Nevertheless, the modest improvement of binding selectivity toward OG ion by **2** was encouraging, which implied that creating a "gap" on an otherwise enclosed cavity might be a feasible strategy for developing hosts with enhanced selectivity toward substituted guanidinium ions. Fine-tuning the cavity of a host may lead to further improvement of binding selectivity. While this remains a challenge for many host systems, it can be readily realized with our crescent oligoamides. A unique feature of our system is that it not only leads to the convenient creation of different (cyclic *vs.* non-cyclic) oligomers with noncollapsible cavities of a narrow range of sizes, but also allows fine-tuning the H-bonding capability of a cavity by adjusting the distribution of the introverted amide oxygen atoms. This is achieved by incorporating different monomeric residues into the design of the oligomers. Such fine-tuning may improve the binding strength and specificity of the corresponding oligomers toward a guest.

To probe the effect of different "gaps" and numbers of amide oxygens on binding selectivity, previously synthesized oligoamides **3**, **4**, and **5a**[8], with three, four, and five amide oxygens, were examined for their binding of G·TPB. MALDI-TOF revealed that all three oligomers bound G ion.† However, significant [M + Na^+] or [M + H^+] peaks were detected for each host, suggesting that these noncyclic oligomers could not selectively bind G ion.

In the presence of OG·TPB, the MALDI spectra of **3** (Fig. 1a) and **4** (Fig. 1b) also contain [M + H^+] and [M + Na^+] peaks of significant intensities. In contrast, the spectrum of **5a** (Fig. 1c) reveals an exclusive complexation of the OG ion. In fact, in the presence of multiple cations such as Cs^+, Rb^+, K^+, Na^+, Li^+, NH_4^+, and NMe_4^+ that were in large (five-fold) excess, the exclusive binding of OG ion by **5a** remained unchanged.†

The selectivity of **5a** toward the OG ion was further demonstrated by competition experiments. In the presence of one equivalent of OG·TPB and G·TPB, **5a** only bound the OG ion (Fig. 1d). In fact, G·TPB, even with a ten-fold excess to OG·TPB, could not prevent the OG ion from binding to **5a**.† Similar binding

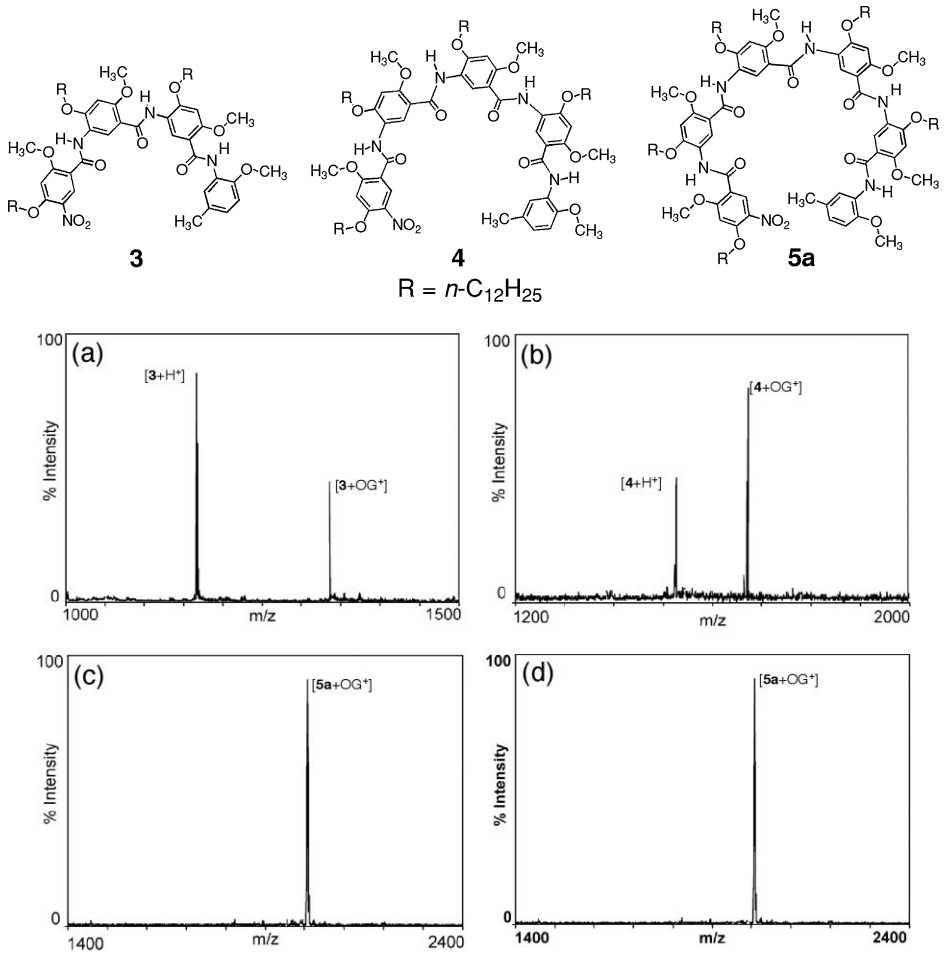

Fig. 1 MALDI spectra of (a) tetramer **3**, (b) pentamer **4**, and (c) hexamer **5a** (2 mM, 10% methanol in chloroform) in the presence of one equivalent of OG·TPB; (d) the MALDI spectrum of **5a** (2 mM, 10% methanol in chloroform) with one equivalent of each of G·TPB and OG·TPB.

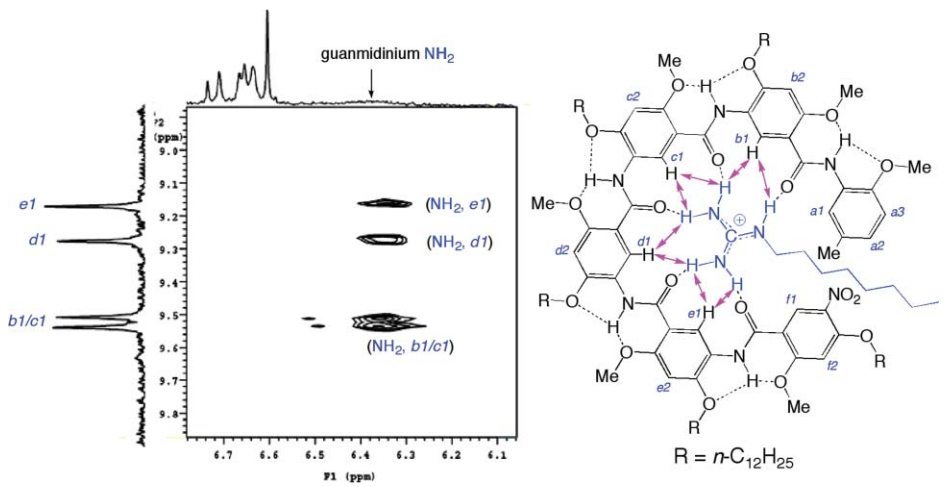

Fig. 2 NOESY spectrum of **5a** (1.2 mM) and OG·TPB (1.2 mM) (500 MHz, in 85% $CDCl_3$/15% acetone-d_6(v/v), 0 °C, mix time = 0.5 s).

preference was found for ethylguanidinium (EG) ion over the G ion,† indicating that the selectivity of **5a** is general to substituted guanidinium ions.

Two-dimensional NMR (NOESY) revealed strong NOEs between the guanidinium protons of OG·TPB and the interior aromatic protons of **5a** (Fig. 2). No NOEs between the guanidinium NH protons and the exterior aromatic protons were detected. This result clearly indicated that the guanidinium moiety of OG ion was indeed bound into the cavity of **5a**.

The behaviour of **3**, **4**, and **5a** seemed to suggest that a maximum number of H-bonds between the host and the guanidinium moiety was responsible for the exclusive binding of the OG ion by **5a**.

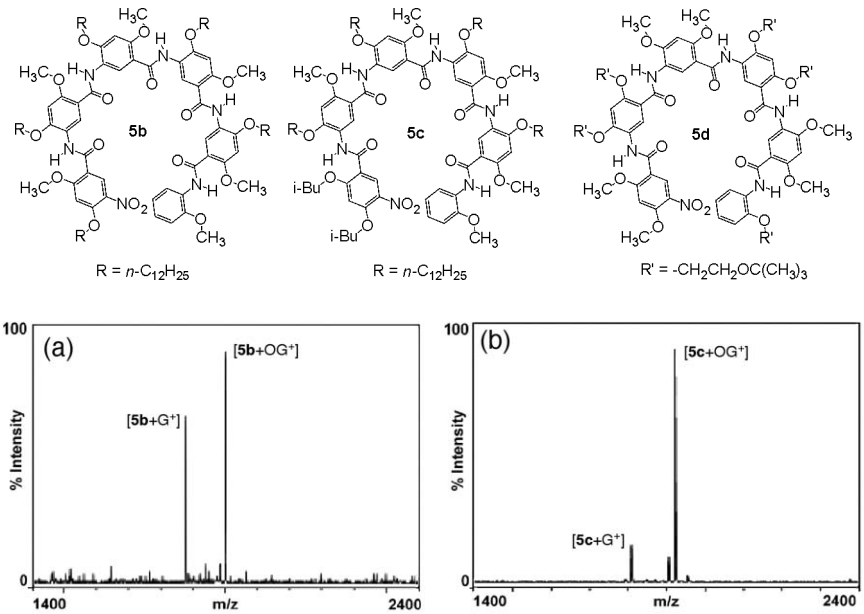

Fig. 3 (a) Hexamer **5b** in the presence of one equivalent of each of G·TPB and OG·TPB, (b) hexamer **5c**.

However, such a conclusion contradicts the fact that although **5a** can form five H-bonds with G and **2** is able to fully encircle the G ion with six H-bonds, oligoamides **2** and **5a** did not show any improved selectivity for the G ion. Thus it seemed that the alkyl tail of the OG ion also contributed to its exclusive binding to **5a**.

Examining the interaction of the OG ion with hexamer **5b** led to a surprising result. In spite of its structural similarity to that of **5a**, hexamer **5b** demonstrated a very different binding selectivity. While **5a** is an exclusive host for OG, hexamer **5b** binds both the G and OG ions similarly in the presence of G·TPB and OG·TPB (Fig. 3a). This observation suggests that the high selectivity of **5a** toward OG depended on the structures of both the host and the guest.

The different binding behaviour of **5a** and **5b**, which differ by a methyl group, was initially very surprising and perplexing. To provide insights into the observed phenomenon, the structures of **2**, **5a**, and **5b** (or **5d**) were optimized by *ab initio* computation. The optimized conformation of **2** (Fig. 4a) reveals a backbone that deviates significantly from planarity. The overall lowered selectivity of **2** toward both G and OG can be easily explained: forming H-bonds with the planar guanidinium ions is energetically costly because this requires the amide oxygens of **2** to be re-positioned in the same plane. The significant conformational change of **2** upon binding OG is confirmed by *ab initio* computation.†

The optimized structure of **5a** shows that the residue bearing the end methyl group is out of co-planarity with the rest of the backbone, creating a short dent in the otherwise flat backbone (Fig. 4b). In contrast, oligomer **5b** (or **5d**) has a planar backbone that forms a fully encircled cavity (Fig. 4c). The exclusive selectivity of **5a** to OG can be rationalized by its conformation: the mostly flat backbone provides well-positioned, coplanar amide oxygens that recognize the guanidinium moiety of OG by H-bonding, while the octyl tail extends out of the cavity *via* the short

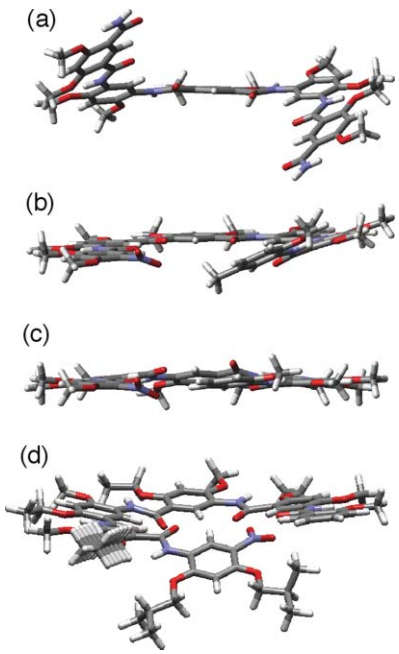

Fig. 4 Conformations of (a) **2**, (b) **5a**, (c) **5b** (or **5d**), and (d) **5c**, optimized based on *ab initio* computation at the B3LYP/6–311G(d) level. All side chains (R groups) of **2**, **5a**, and **5b** are replaced with methyl groups. To save computation time, the dodecyl side chains of **5c**, except for the one closest to the end residue bearing the isobutyl side chains, are replaced with ethyl groups.

depression without having to adopt unfavorable conformation or disturb the conformation of the host. Thus, the conformation of **5a** is predisposed for both maximum H-bonding with the guanidinium moiety and at the same time, accommodating the octyl tail. For **5b**, H-bonding with the guanidinium head would lead to steric hindrance between the octyl tail and the oligoamide

backbone of the host, which requires conformational adjustment, lowering both binding affinity and selectivity. These expectations are confirmed by *ab initio* computations on complexes **5a**·OG and **5b**·OG,† which indicate that the guanidinium moiety, along with the α-C of OG, is coplanar in the former complex but twisted in the latter.

If the above model is valid, structural modification that twists a short segment of the backbone of hexamer **5b** (or **5d**) out of planarity should lead to a hexamer with a conformation similar to that of **5a**. Such an analogous hexamer may then exhibit an enhanced binding preference toward substituted guanidinium ions. Our previous studies[7,8] on crescent oligoamides revealed that, when at least one of the two side chains flanking a backbone amide group is methyl, the two benzene rings, along with the amide group involved in three-center H-bonding, are coplanar. When both flanking side chains are bulkier than methyl, the two aromatic rings attached to such an amide linkage are always twisted out of coplanarity. Thus an otherwise planar backbone of a crescent oligoamide can be locally twisted by introducing bulky alkoxy groups onto adjacent aromatic units linked to the same amide group.

To probe the possibility of tuning conformation by incorporating bulky side chains, hexamer **5c**, with one of its backbone amide groups being flanked by a dodecyloxy group and an isobutoxy group, was designed. *Ab initio* computation revealed that **5c** adopts a conformation in which the end residue bearing the isobutoxy group is out of co-planarity with the rest of the backbone (Fig. 4d). Although sharing the same backbone with **5b**, hexamer **5c** has an optimized conformation that bears close similarity to that of **5a**, with a small depressed segment being created in the otherwise flat backbone.

Hexamer **5c** was then examined for binding the OG ion in the presence of the G ion. As revealed by MALDI, a significant preference toward the OG ion was observed for **5c** (Fig. 3b). This result demonstrates that adjusting the conformation of a crescent oligoamide can indeed lead to the tuning of binding specificity.

While direct measurement of the binding constants (K_a's) of oligomers **5a–c** with the G and OG ions was frustrated by limited solubility and serious ^{1}H NMR line-broadening upon dilution, hexamer **5d**, which shares the same backbone with **5b**, showed high affinities toward the G and EG ions. Using Cram's extraction method,[11] the K_a's of G and EG ions with **6** in water-saturated $CHCl_3$ were found to be $1.33 \pm 0.78 \times 10^8$ M^{-1} and $1.27 \pm 1.73 \times 10^7$ M^{-1}, respectively.†

In summary, an initial attempt to probe the effect of factors such as the number and distribution of H-bonding sites on the binding of guanidinium and substituted guanidinium ions by crescent oligoamides, has led to hosts with high binding selectivity. The presence of an end methyl group in **5a** leads to a conformation capable of accommodating substituted guanidinium ions, which represents an unexpected, rare example of binding selectivity determined by the conformation of a host. This model, based on conformation-dependent binding specificity, was confirmed by the behaviour of the rationally designed **5c**. This work points to a new possibility of developing simple molecular hosts with tailored specificity by evolving and tuning the number of bonding sites, shape of cavity and especially, the conformation of a host. Crescent oligoamides, with their demonstrated shape- and conformation-persistency as well as ready tunability of conformation, structure, dimension, and shape,[2] offers a systematically modifiable platform for developing highly specific hosts capable of recognizing different guest species. Given the efforts made in developing receptors for guanidinium ion[12] and the important biological roles associated with substituted guanidinium ions such as methylated arginines,[13] the ability to created hosts with high affinity and tailored specificity toward these ions should attract wide interest.

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