A polyaromatic nanocapsule as a sucrose receptor in water

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Selective recognition of saccharides by artificial receptors in water is a challenging goal due to their strong hydrophilicities and complex molecular structures with subtle regio- and stereochemical differences. We report the selective and efficient encapsulation of α-sucrose within a coordination-driven molecular capsule from natural saccharide mixtures in water (~100% selectivity, >85% yield, and ~10^3 M\(^{-1}\) binding constant). Unlike previous artificial receptors and natural receptors that rely on multiple hydrogen-bonding interactions, theoretical calculations and control experiments indicate that the observed unique selectivity arises from multiple CH–π interactions between the sucrose hydrocarbon backbone and the shape-complementary polyaromatic cavity (~1 nm in diameter) of the capsule.

INTRODUCTION

Hydrogen bonds are a ubiquitous and indispensable tool in the selective binding of guest substrates by enzymes and biological receptors (1). Even in water, where hydrophilic natural compounds such as saccharides are fully solvated by water molecules through extensive hydrogen bonds (1–3), the protein surfaces and active sites precisely discriminate subtle stereo- and regiochemical differences in the complex structures (Fig. 1A) (4–6). The Davis group demonstrated that isophthalamidobased organic cages can efficiently accommodate monosaccharides such as D-glucose (binding constant: \(K_a = \) up to 190 M\(^{-1}\)) (7) and disaccharides such as D-cellobiose (\(K_a = \) up to 3300 M\(^{-1}\)) (8, 9) in water through hydrogen bonds and CH–π interactions. Similar cooperative interactions (10), reversible covalent bonds (11), coordinative interactions (12), and ion-dipole interactions (13) were also used for the recognition of natural saccharides in water. However, strict discrimination of saccharides in water remains an extremely hard task for synthetic molecular receptors (14–16). To further develop artificial receptors as novel sensing devices (17) and to provide mechanistic insights into biological recognition events such as taste (18–20), here we demonstrate a new recognition motif using a molecular cavity enclosed by polyaromatic frameworks (Fig. 1B) that exclusively bind α-sucrose in water. α-Sucrose is one of the most common natural compounds in our daily life, yet the relatively large and bulky structure (a ~1 nm length and ~300 Å\(^3\) volume) prevents it from full encapsulation by traditional covalent hosts (7–16). On the other hand, coordination-driven molecular cages and capsules (21–25) are available in a much wider range of cavity sizes and shapes, suitable for large guest substrates. However, because of the lack of effective bonding motifs, the recognition and binding of saccharides within coordination host compounds remain very rare, even in organic media (26, 27).

The encapsulation of polyaromatic fullerene guests by saccharide-based molecular hosts, that is, cyclodextrin dimers, in water has been reported by several groups (28–30). The intriguing host-guest complexes prompted us to invert the relationship and use a polyaromatic-shelled host (31, 32) for the selective recognition of saccharide guests. We used coordination-driven molecular capsule 1, which has a spherical cavity (~1 nm in diameter and ~580 Å\(^3\) in volume) surrounded by polyaromatic anthracene panels (Fig. 1, C and D) (33). Although the host capability of 1 toward various hydrophobic compounds (for example, adamantanes, pyrenes, and fullerene C\(_{60}\)) is well known (33–36), the potential for binding

Fig. 1. Cartoon representation of saccharide recognitions and structures of a polyaromatic nanocapsule and saccharides. Recognition of α-glucose (A) in a hydrogen-bonding cavity modeled after the binding site of sucrose hydrolase (E322Q-glucose complex) from Xanthomonas axonopodis pv. glycines (6) and (B) in a polyaromatic cavity. (C) Coordination-driven polyaromatic nanocapsule 1 and (D) its slice through the center of the crystal structure [space-filling model; substituents (R) are replaced by hydrogen atoms for clarity]. (E) α-Sucrose (2a), glucose derivatives 3a to 3c, and α-fructose (3d) used as guest molecules.
highly hydrophilic biomolecules in the hydrophobic cavity of 1 was rather unexpected. Nevertheless, we report here that nanocapsule 1 can effectively encapsulate D-sucrose (2a; \( K_a \geq 1100 \text{ M}^{-1} \)) from mixtures of 2a and other natural disaccharides in water with perfect selectivity. Theoretical host-guest calculations and control binding experiments with D-glucose derivatives 3a to 3c (Fig. 1E) indicate that the observed unique selectivity stems from multiple CH–π interactions between the hydrocarbon framework of 2a and the shape-complementary polyaromatic cavity of 1.

RESULTS

Encapsulation of monosaccharides

We initially examined host-guest interactions between nanocapsule 1 and natural monosaccharides, such as D-glucose (3a), D-fructose (3d), and D-mannose, in water. For example, when a mixture of 1 (0.39 \( \mu \text{mol} \)) and slight excess 3a (2.0 \( \mu \text{mol} \)) was stirred in D_2O (0.5 ml) at 60°C for 30 min (scheme S1), neither new peaks nor peak shifts (expected for host-guest interactions) were observed in the proton nuclear magnetic resonance (\(^1\)H NMR) and electrospray ionization–time-of-flight (ESI-TOF) mass spectrometry (MS) spectra of the resultant solution (Fig. 2, A and B). No interactions were also observed for the other monosaccharides (figs. S1 and S2). These results are explicable by usual hydrophilic and hydrophobic properties: The highly hydrophilic saccharides preferentially exist in the aqueous phase rather than the hydrophobic cavity of 1.

In contrast, one molecule of pentamethylated \( \alpha \)–D-glucose 3b was quantitatively encapsulated within capsule 1 under the same conditions (Fig. 2A, right, and scheme S2) (37), although 3b is very soluble in water (>50 mM). The 1:1 host-guest complex 1 \( \supseteq \) 3b exhibited \(^1\)H NMR signals derived from the methyl groups of encapsulated 3b ranging from −0.45 to 1.03 parts per million (ppm) (Fig. 2C, left, and figs. S3 and S4). These signals are significantly shifted upfield (\( \Delta \delta_{\text{max}} = −3.86 \text{ ppm} \)), compared with free 3b in D_2O, because of the shielding effects of the nearby anthracene rings. Close contact between 1 (protons H_{1\text{IP}1}) and 3b (CH_3 groups) in the cavity was confirmed by one-dimensional (1D) nuclear Overhauser effect spectroscopy (NOESY) NMR studies (fig. S5). The noncovalent host-guest 1 \( \supseteq \) 3b complex is highly stable in water; we estimated the binding constant at >10^9 M\(^{-1}\) from \(^1\)H NMR and MS analyses under high-dilution conditions (5.0 \( \mu \text{M}; \) figs. S6 and S7) (37). The ESI-TOF MS spectrum only displayed prominent peaks from the intact host-guest structure [for example, mass-to-charge ratios (m/z) of 1995.4 for [1 \( \supseteq \) 3b − 2NO_3\(^{−} \)]\(^{4+}\), 1309.6 for [1 \( \supseteq \) 3b − 3NO_3\(^{−} \)]\(^{4+}\), and 966.7 for [1 \( \supseteq \) 3b − 4NO_3\(^{−} \)]\(^{4+}\); Fig. 2C, right, and fig. S8]. The optimized structure of 1 \( \supseteq \) 3b indicates that the four CH_3 groups of 3b are in close proximity (−3.6 Å) to the anthracene panels of 1 (fig. S9). The strong host-guest interactions observed between 1 and 3b are mainly caused by hydrophobic CH–π (polyaromatic) interactions in the confined cavity (38–41). Pentamethylated \( \alpha \)–D-glucose 3c was also bound by capsule 1 in 81% yield (figs. S1C and S2C). These unusual binding affinities prompted us to further examine host-guest interactions between the polyaromatic capsule and natural disaccharides.

Encapsulation of disaccharides

We next investigated aqueous binding for common disaccharides, D-sucrose, D-lactose, D-maltose, and D-trehalose (scheme S3), and thereby, efficient encapsulation by capsule 1 was observed for only D-sucrose (2a). Upon mixing 1 (0.39 \( \mu \text{mol} \)) with 2a (2.0 \( \mu \text{mol} \)) in D_2O (0.5 ml) for 30 min at 60°C, 1:1 host-guest complex 1 \( \supseteq \) 2a was formed in 86% yield (Fig. 3A, right, and figs. S10 and S11). In the \(^1\)H NMR spectrum, all signals for the host and guest were assigned by 2D NMR studies (figs. 3B and figs. S12 to S15). The methine signals H_{A,\text{E},1} and methylene signals H_{E,\text{LK}} of encapsulated 2a were found in the range of −1.14 to 1.29 ppm due to aromatic shielding (\( \Delta \delta_{\text{max}} = −4.64 \text{ ppm} \)). Broadening of the anthracene signals H_{\text{C,1}} at (6.5 to 7.2 ppm) suggests restricted motion of the polyaromatic panels upon encapsulation of the relatively large guest 2a. The number of host proton signals of 1 \( \supseteq \) 2a is the same as that of empty 1, indicating full inclusion of 2a in the capsule cavity. The \(^1\)H diffusion–ordered spectroscopy (DOSY) NMR spectrum revealed the presence of a single host-guest species (Fig. 3C and fig. S16). A 1:1 host-guest composition was unequivocally confirmed by the ESI-TOF MS analysis, which showed prominent peaks at m/z values of 2041.7, 1340.5, and 989.9 assignable to [1 \( \supseteq \) 2a − nNO_3\(^{−} \)]\(^{4+}\) species (n = 2, 3, and 4, respectively; Fig. 3E and fig. S17). Host-guest interactions were undetected for 1 and the other disaccharides in water (fig. S18). Furthermore, the formation of the ternary complex 1 \( \supseteq \) (3a+3d) was not observed upon combination of 1 and an equimolar mixture of 3a and D-fructose (3d) (5 eq each), which are components of 2a, even under various conditions (Fig. 3A, left, and D).

To elucidate detailed host-guest interactions, we estimated theoretical binding free energies of 1 \( \supseteq \) 2a and the related host-guest complexes in water by comparing the solvation free energies of the saccharide guests and intermolecular host-guest interactions (42). The binding energy of 1 \( \supseteq \) 2a is lower than that of host-guest complexes such as 1 \( \supseteq \) (d-trehalose) and 1 \( \supseteq \) (D-lactose) (−10.2 and −37.2 kcal mol\(^{−1}\), respectively) and higher than that of 1 \( \supseteq \) 3b (11.0 kcal mol\(^{−1}\)) (table S1). These results are consistent with the \(^1\)H NMR–binding experiments. In the optimized structure (Fig. 3F and figs. S19 and S20), encapsulated 2a adopts a spherical conformation in the spherical cavity of 1. The conformation is supported by the NOESY NMR analysis, where correlation signals are observed between the pyranose and furanose moieties (H_{2g}–H_{1g} and H_{2g}–H_{2g}) of 2a (fig. S13). The three CH_2 groups of 2a are in close contact (<3.8 Å) with the polyaromatic panels of 1 in the optimized
structure (Fig. 3F). Thermodynamic parameters for the host-guest interactions of $1 \supseteq 2a$ in water were determined by a van’t Hoff plot (Fig. 3G) using temperature-dependent $^1$H NMR analysis (fig. S21 and table S2). The obtained positive value of entropy (8.00 cal mol$^{-1}$ K$^{-1}$) and negative value of enthalpy ($-1.90$ kcal mol$^{-1}$) indicate that the encapsulation process is driven mainly by enthalpic stabilization. The binding constant was also calculated to be 1170 ± 120 M$^{-1}$ at 25°C (fig. S22 and table S3).

Selective recognition of D-sucrose

Nanocapsule 1 is a working sucrose receptor and selectively binds D-sucrose even from mixtures of natural disaccharides in water. To illustrate this instance, the $1 \supseteq 2a$ complex exclusively formed from a D$_2$O solution containing 1 and a mixture of 2a and D-trehalose (2b) (5 eq each) for 30 min at 60°C (Fig. 4A). The upfield region $^1$H NMR spectrum of the resultant solution displayed only peaks when corresponding to encapsulated 2a (Fig. 4, B and C). The host-guest complex could be isolated as a pale yellow solid (in 80% yield; Fig. 4D and fig. S23) from the aqueous solution by salting out with a grain of KNO$_3$. The sucrose-bound capsule $1 \supseteq 2a$ was selectively obtained from all competitive binding experiments with 2a and other disaccharides [that is, D-lactose (2c), D-maltose (2d), D-cellobiose (2e), and D-lactulose (2f); Fig. 4, E and F], as revealed by $^1$H NMR analysis (fig. S24). On the basis of the present experimental and theoretical studies, we postulate that the observed strict discrimination stems from an effective steric match and multiple CH-π interactions between the

Fig. 3. Encapsulation of D-sucrose within capsule 1 in water. (A) Schematic representation of host-guest interactions between capsule 1, D-glucose (3a), and D-fructose (3d) (left) and the encapsulation of D-sucrose (2a) within 1 (right). (B) $^1$H NMR and (C) $^1$H DOSY NMR spectra (500 MHz, D$_2$O, room temperature) of $1 \supseteq 2a$. (D) $^1$H NMR spectrum (500 MHz, D$_2$O, room temperature) of a mixture of 3a and 3d with 1. (E) ESI-TOF MS spectrum (H$_2$O, room temperature) of $1 \supseteq 2a$. (F) Structure of $1 \supseteq 2a$ in water (left) and its slice through the center (right) (substituents and counterions are omitted for clarity). (G) van’t Hoff plot for the thermodynamic parameters of $1 \supseteq 2a$.

Fig. 4. Selective recognition of D-sucrose and structures of disaccharides and artificial sugars. (A) Schematic representation of the selective encapsulation of D-sucrose (2a) from a mixture of 2a and d-trehalose (2b) by capsule 1. $^1$H NMR spectra (500 MHz, D$_2$O, room temperature) of (B) 2a and 2b, (C) a mixture of 1:2a, 2a, and 2b, and (D) isolated $1 \supseteq 2a$. (E) D-Lactose (2c), D-maltose (2d), D-cellobiose (2e), D-lactulose (2f), sucralose (4a), and aspartame (4b) used as guest molecules and (F) their optimized structures [density functional theory (DFT), B3LYP/6-31G(d); conductor-like polarizable continuum model (CPCM; H$_2$O) level].
hydrocarbon backbone of sucrose and the polyaromatic interior surface of capsule 1.

Note that the artificial cavity of capsule 1 could quantitatively and strongly bind artificial sugar substitutes such as sucralose (4a) and aspartame (4b) in water (Fig. 4, E and F, figs. S25 to S27, and scheme S4) (42, 43). The competitive encapsulation experiments revealed the binding preference in the order of (400 MHz) and ASCEND-500 (500 MHz). The 1H NMR and 2D NMR analyses (fig. S22 and table S3). The thermodynamic parameters (fig. S21, and table S2) were estimated to be 24,200 and 13,000 M−1 with a binding constant of 1.02 (J = 9.5 Hz, 1H, 2a), −0.75 (d, J = 9.5 Hz, 1H, 2a), 0.32 (d, J = 12 Hz, 1H, 2a), 0.04 to 0.09 (m, 2H, 2a), 0.22 (m, 1H, 2a), 0.34 to 0.45 (m, 2H, 2a), 0.62 (d, J = 9.5 Hz, 1H, 2a), 0.76 (d, J = 14 Hz, 1H, 2a), 1.29 (m, 2H, 2a), 2.43 to 2.48 (s, 2H, 4H, 1), 3.07 (m, 16H, 1), 3.40 (s, 12H, 1), 3.88 to 4.20 (m, 1H, 1), 4.47 (m, 4H, 1), 4.62 (m, 4H, 1), 4.63 (s, 4H, 1), 6.45 (br, 8H, 1), 6.73 (br, 8H, 1), 7.01 (d, J = 9.0 Hz, 8H, 1), 7.15 (br, 8H, 1), 7.53 (dd, J = 9.0, 7.0 Hz, 8H, 1), 7.71 (d, J = 9.0 Hz, 8H, 1), 7.77 (br, 8H, 1), 8.09 to 8.27 (d, 16H, 1), 8.32 (dd, J = 8.0, 5.5 Hz, 8H, 1), 8.54 (d, J = 8.0 Hz, 8H, 1), 9.21 (d, J = 5.5 Hz, 8H, 1). 1H NMR (500 MHz, D2O, 60°C): δ −1.12 (t, J = 9.5 Hz, 1H, 2a), −0.66 (d, J = 12 Hz, 1H, 2a), 0.02 (d, J = 9.0 Hz, 1H, 2a), 0.09 (d, J = 12 Hz, 1H, 2a), 0.19 (m, 1H, 2a), 0.29 to 0.43 (m, 3H, 2a), 0.58 (t, J = 9.5 Hz, 1H, 2a), 0.73 (d, J = 14 Hz, 1H, 2a), 1.27 (t, J = 9.0 Hz, 1H, 2a), 1.30 (s, 1H, 2a), 2.45 to 2.49 (s, 2H, 1), 3.08 (m, 16H, 1), 4.57 to 4.58 (m, 8H, 1), 6.15 to 6.26 (s, 4H, 1), 6.34 to 6.45 (m, 8H, 1), 6.56 to 6.66 (br, 8H, 1), 6.92 (d, J = 8.5 Hz, 8H, 1), 7.05 to 7.21 (br, 8H, 1), 7.48 (dd, J = 9.0, 7.0 Hz, 8H, 1), 7.65 (d, J = 9.0 Hz, 8H, 1), 7.74 (dd, J = 9.0, 7.0 Hz, 8H, 1), 7.95 to 8.04 (m, 8H, 1), 8.30 (dd, J = 9.5, 5.5 Hz, 8H, 1), 8.45 to 8.52 (m, 8H, 1), 9.16 to 9.20 (m, 20H, 1). 1H DOSY NMR (500 MHz, D2O, 25°C): D = 1.48 × 10−18 m2 s−1. FT-IR (KBr, cm−1): 2926, 2883, 2828, 1638, 1337, 1257, 1195, 1150, 1061, 1031, 945, 821, 768, 706, 671, 639, 617. ESI-TOF MS (H2O, room temperature): m/z 2041.7 [1\{2a−2\nO3\}]+, 1340.5 [1\{2a−3\nO3\}]+, 989.9 [1\{2a−4\nO3\}]+. Selective encapsulation of 2a by 1 from mixed disaccharides

Pt capsule 1 (1.5 mg, 0.39 μmol) and d-sucrose (2a; 0.7 mg, 2.0 μmol) were added to a glass test tube containing D2O (0.5 ml). The mixture was stirred for 30 min at 60°C. The selective formation of 1\{2a\} was confirmed by 1H NMR analysis. When a grain of KNO3 was added to 1\{2a\}, 2f was also observed from mixtures of 2a/2c, 2a/2d, 2a/2e, and 2a/2f under the same conditions. Theoretical calculation of host-guest complexes

The universal force field (UFF) model (46) was used for intramolecular potential models and nonelectrostatic interactions, unless otherwise specified. The atomic charges of molecular capsule 1 (R = \_OCH3) were determined by the charge equilibration method (47) implemented in the FORCITE module at the geometry of the crystal structure, whereas the atomic charges of saccharides [that is, d-sucrose (2a), d-trehalose (2b), d-lactose (2c), and pentamethylated α-d-glucose (3b)] were taken from the GLYCAM06j force field (48). The geometry optimizations of all the molecules were performed with the FORCITE module of Materials Studio and the Sander module of an Amber14 suite (49). The 10-ns-long annealing simulations of the hydroxy groups on the saccharides from 1000 to 10 K were performed to optimize their orientations before the full-geometry optimizations with the Sander module. The final optimized structures of the molecular capsule and the saccharides were obtained by performing the geometry optimizations implemented in the FORCITE program (fig. S19). Relative binding energies were evaluated with gas-phase binding energies and solvation energies of the saccharides in aqueous solutions on the assumption that differences in solvation energies between the host-guest complexes with the different saccharides are negligible. Given that
The capsular hosts isolated the sugars from bulk water environment, and conformations of the host frameworks in contact with the bulk water molecules were not greatly altered upon the encapsulations, the solvation energies of the host-guest complexes with the different saccharides can be expected to be almost identical. First, the gas-phase binding energies were calculated with the UFF model. Then, the solvation free energies, $\Delta G_{soln}$, were calculated by the finite-difference linearized Poisson-Boltzmann method for electrostatic contributions and the solvent-accessible surface area model for nonpolar contributions. The molecular dynamics simulation was performed with the modified pmemd module in the Amber14 suite (49), where the intramolecular geometries were fixed at their optimized structures and the capsule and saccharides were treated as a rigid body (52). We used the cubic unit cell of the 44.31 Å edge length, which contained capsule 1 ($R = -\text{OC}H_3$), 2a, and 2723 TIP3P (transferable intermolecular potential with 3 points) waters (fig. S20).

**SUPPLEMENTARY MATERIALS**

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/3/8/e1701126/DC1

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