ORGANIC LETTERS

2007
Vol. 9, No. 12
2349−2352

Reconfigurable Four-Component Molecular Switch Based on pH-Controlled Guest Swapping

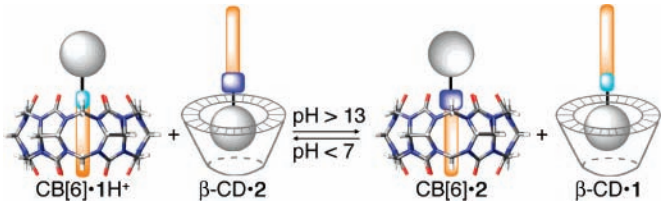
Sriparna Chakrabarti,[†] Pritam Mukhopadhyay,[†] Shirley Lin,[‡] and Lyle Isaacs*,[†]

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, and Department of Chemistry, United States Naval Academy, Annapolis, Maryland 21402

LIsaacs@umd.edu

Received March 25, 2007

ABSTRACT



The four-component ensemble comprising CB[6], β-CD, and guests 1 and 2 forms complexes CB[6]·1H$^+$ and β-CD·2 at pH < 7 but swaps partners forming complexes CB[6]·2 and β-CD·1 at pH > 13. The intermolecular nature of the switching process suggests application as a basis for stimuli-responsive reconfigurable systems.

A major thrust in chemistry over the past several years has been the development of molecular scale devices that perform useful functions in response to environmental stimuli. For example, a wide variety of colorimetric or fluorescence sensing or computational systems have been developed that display useful levels of selectivity and sensitivity toward molecular and ionic analytes.[1] Of more direct relevance to the work reported in this paper, however, is the quest for systems that perform mechanical work by controlling linear (e.g., molecular shuttles or muscles) and unidirectional rotary motion within molecular and supramolecular systems.[2] As the toolbox of available molecular devices increases, so does the need to develop methods to interconnect these parts to allow the preparation of multicomponent molecular machines. We envisioned that it would also be desirable to reconfigure the connectivity of these parts in response to environmental stimuli to create different systems as needed. Toward this goal, we and others have been investigating the behavior of multicomponent systems that undergo self-sorting processes in water and organic solvents.[3,4] In this paper, we

[†] University of Maryland.
[‡] United States Naval Academy.

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10.1021/ol070730c CCC: $37.00
Published on Web 05/15/2007

report the preparation of a four-component system whose guests undergo an intermolecular shuttling process in response to changes in pH.

To prepare a system that is capable of intermolecular guest swapping, we relied on the well-defined recognition properties of the cyclodextrins[5] (CD) and the cucurbit[*n*]uril family[6] (CB[*n*]) of macrocycles. Figure 1 shows the structures of

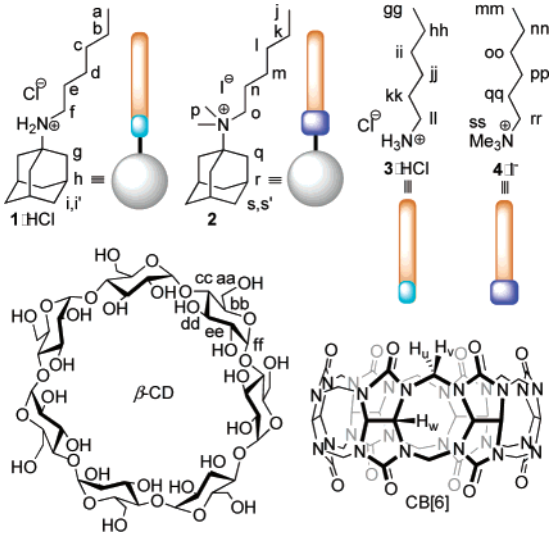

Figure 1. Compounds used in this study.

the compounds used in this study. As our hosts, we selected CB[6] for its large binding constants, high preference for cationic over neutral guests,[7] and precedent for its use as a bead in the preparation of molecular switches.[8] β-CD was selected because it mainly distinguishes between guests based on hydrophobic size rather than charge. As guests, we selected **1**−**4** that all contain alkylammonium tails suitable for binding to CB[6]. We refer to compounds **1** and **2** as two-faced guests[3d] because they also contain adamantane groups that are complementary to the cavity of β-CD. Compounds **1** and **3** contain cationic ammonium groups that undergo deprotonation at high pH, whereas quaternary ammonium salts **2** and **4** remain cationic across the full pH range.

Initial proof-of-principle experiments focused on the three-component ensemble comprising CB[6], **3**, and **4** (Figure

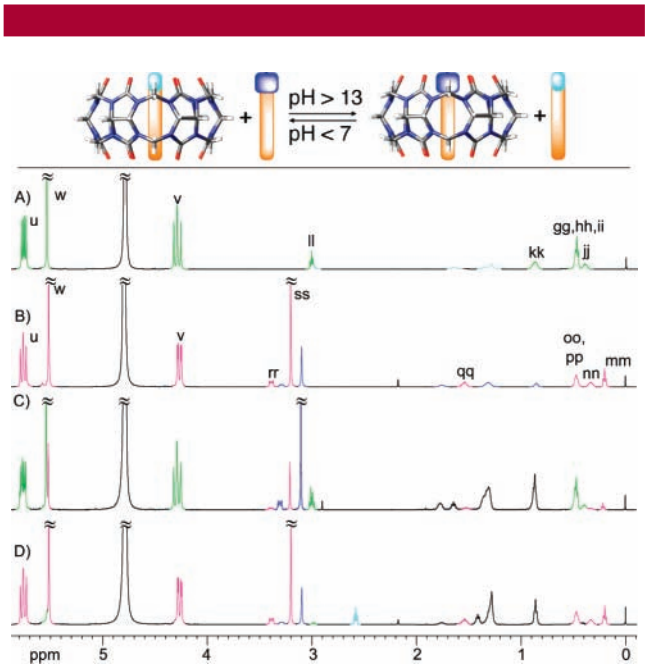

Figure 2. ^{1}H NMR spectra recorded (400 MHz, 298 K, 8 mM Na_2SO_4 in D_2O) for (A) CB[6]·**3**H$^+$ with excess **3** at pH 7.0; (B) CB[6]·**4** with excess **4** at pH = 13.0; (C) CB[6] (2.5 mM), **3** (3.0 mM), and **4** (3.0 mM) at pH 7.0; (D) CB[6] (2.5 mM), **3** (3.0 mM), and **4** (3.0 mM) at pH 13.0. Color code: free **3**, aqua; free **4**, blue; CB[6]·**3**, green; CB[6]·**4**, pink. Some resonances are unlabeled because of spectral overlap.

2). We took advantage of the slow chemical exchange commonly exhibited by CB[*n*]·guest complexes[7a] to monitor the concentration of CB[6]·**3**H$^+$ and CB[6]·**4** as a function of pH by ^{1}H NMR (Supporting Information). At pH 7 (Figure 2C), a CB[6]·**3**H$^+$:CB[6]·**4** ratio of 73:27 is achieved, which reflects preferential binding of **3** within CB[6] presumably due to favorable NH···O═C H-bonds that are not present within CB[6]·**4**. As the solution is made basic (pH 13.0, Figure 2D), **3**H$^+$ is deprotonated to **3**, which now binds less tightly than **4** to CB[6]; the ratio of CB[6]·**3**H$^+$:CB[6]·**4** is now 17:83, a complete reversal of the situation at pH 7.0. Figure 3A shows a plot of the concentration of CB[6]·**3**H$^+$ and CB[6]·**4** versus pH, which illustrates the efficiency of the switching process.[9]

To extend this system toward a pH-controlled guest swapping, we increased the complexity by working with both CB[6] and β-CD along with two-faced guests **1** and **2**. We hypothesized that **1**H$^+$, **1**, and **2**—with their common adamantane binding epitope—would exhibit comparable values of K_a toward β-CD and that the pH-induced changes in K_a for CB[6]·**1**H$^+$ could be used to simultaneously swap guests **1** and **2** between CB[6] and β-CD. Figure 4A−F shows ^{1}H NMR control experiments recorded for two-component systems at pH 7.0 or 13.0; Panels G and H of Figure 4 show the ^{1}H NMR spectra for equimolar mixtures of CB[6], β-CD, **1**, and **2** at pH 7.0 and 13.0, respectively. Figure 3B shows a plot of concentration versus pH based

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(9) The pH switching experiments performed with mixtures of CB[6], **1**, and **2** showed comparable efficiency (Supporting Information).

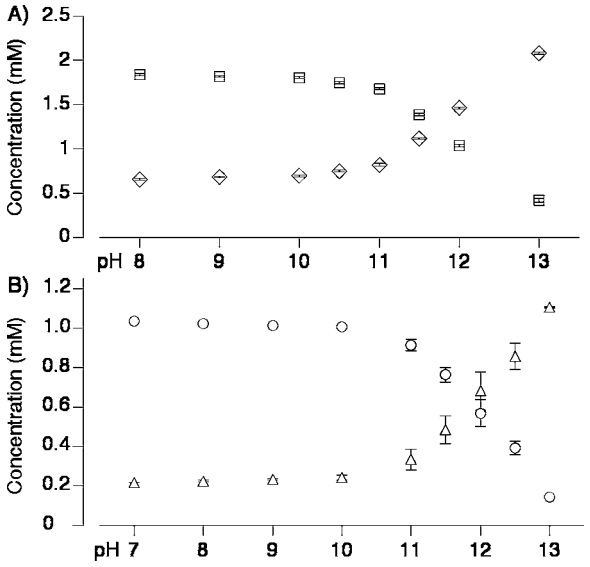

Figure 3. Plots of concentration versus pH for (A) three-component mixture comprising CB[6] (2.5 mM), **3** (3 mM), and **4** (3 mM); (B) four-component mixture comprising CB[6] (1.25 mM), β-CD (1.25 mM), **1** (1.25 mM), and **2** (1.25 mM). Key: ○, CB[6]·**1**; △, CB[6]·**2**; □, CB[6]·**3**; ◇, CB[6]·**4**.

on integration of the spectra recorded across the full pH (7.0−13.0) range. At pH 7.0, CB[6] prefers **1**H$^+$ over **2** by a factor of 84:16; mass balance dictates β-CD exhibits an equal but opposite preference for **2** over **1**.[10] As the solution is made basic (pH 13.0), **1**H$^+$ is deprotonated, which reduces its affinity toward CB[6] relative to **2** which remains cationic and therefore exhibits relatively constant affinity toward CB[6] as a function of pH resulting in an 11:89 CB[6]·**1**H$^+$:CB[6]·**2** ratio.[11] As CB[6] swaps partners, so does β-CD with equal but opposite efficiency.

To understand the fundamental thermodynamic requirements underpinning the successful swapping of guests **1** and **2** between hosts CB[6] and β-CD in response to changes in pH, we performed simulations of a hypothetical system comprising two hosts (CB[6] and β-CD) and two guests (**G** and **G2**) with the program GEPASI. GEPASI uses starting concentrations, equilibrium constants, and an interaction model as input and determines equilibrium concentrations as output.[12] Figure 5A,C shows the equilibria that we considered and the values of K_a that we assumed. We allow guest **G** to exist in the **G** or **G**H$^+$ forms to mimic the

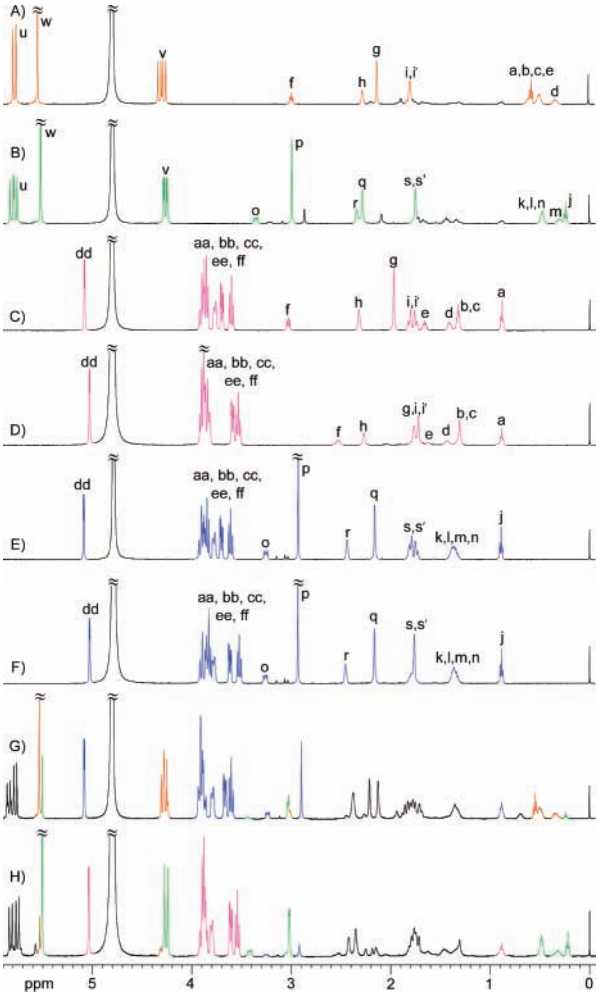

Figure 4. ^{1}H NMR spectra recorded (400 MHz, 298 K, 8 mM Na_2SO_4 in D_2O) for (A) CB[6]·**1** (1.25 mM/1.5 mM) at pH 7.0; (B) CB[6]·**2** (1.25 mM/1.5 mM) at pH 7.0; (C) β-CD·**1** (1.25 mM/1.5 mM) at pH 7.0; (D) β-CD·**1** (1.25 mM/1.5 mM) at pH 13.0; (E) β-CD·**2** (1.25 mM/1.5 mM) at pH 7.0; (F) β-CD·**2** (1.25 mM/1.5 mM) at pH 13.0; (G) equimolar mixture of CB[6], β-CD, **1**, and **2** (1.25 mM, pH 7.0); (H) equimolar mixture of CB[6], β-CD, **1**, and **2** (1.25 mM, pH 13.0). Color code: CB[6]·**1**, orange; CB[6]·**2**, green; β-CD·**1**, pink; β-CD·**2**, blue. Resonances for free **1** and **2** and overlapped regions are not labeled.

behavior of **1** and **3**. Figure 5B shows a thermodynamic cycle connecting CB[6] and its **G** and **G**H$^+$ complexes, which respond to pH changes. In the simulations (Figure 5D),[13] we systematically increase the difference between K_{G+H} and $K_{6\cdot G+H}$ (highlighted in green) from 0 to 4 pK_a units.[14] The magnitude of the difference between K_{G+H} and $K_{6\cdot G+H}$

(10) Fast exchange between the β-CD complexes and significant spectral overlap made independent determination of [β-CD·**1**] and [β-CD·**2**] challenging. The equal but opposite preference of β-CD based on mass balance considerations assumes the concentration of free β-CD is small, which seems reasonable given its high affinity toward adamantane derivatives (ref 5).

(11) The CB[6]·**1**H$^+$ complex remains protonated at pH 13 because of the large pK_a shift observed for CB[6] complexes. For pK_a shifts in CB[*n*] complexes see: Mohanty, J.; Bhasikuttan, A. C.; Nau, W. M.; Pal, H. *J. Phys. Chem. B* **2006**, *110*, 5132−5138.

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(13) The changes in the concentration of CB[6]·**G2** and β-CD·**G2** as a function of pH are not shown in Figure 5D for purposes of clarity; the trends are parallel but opposite to those shown for the CB[6] and β-CD complexes of **G** and **G**H$^+$ (Supporting Information).

(14) Because the species in Figure 5B are connected by a thermodynamic cycle, the ratio of the equilibrium constants highlighted in green must equal that of those highlighted in red. To fully define the system, we also fix $\log\{(K_{6\cdot GH})(K_{6\cdot G})\} = \log\{(K_{6\cdot G2})(K_{6\cdot G2}) = 14\}$; this choice disposes $K_{6\cdot GH}$ and $K_{6\cdot G}$ symmetrically around $K_{6\cdot G2}$ (e.g., $K_{6\cdot G} = 10^6$ M^{-1}, $K_{6\cdot GH} = 10^8$ M^{-1}; or $K_{6\cdot G} = 10^5$ M^{-1}, $K_{6\cdot GH} = 10^9$ M^{-1}).

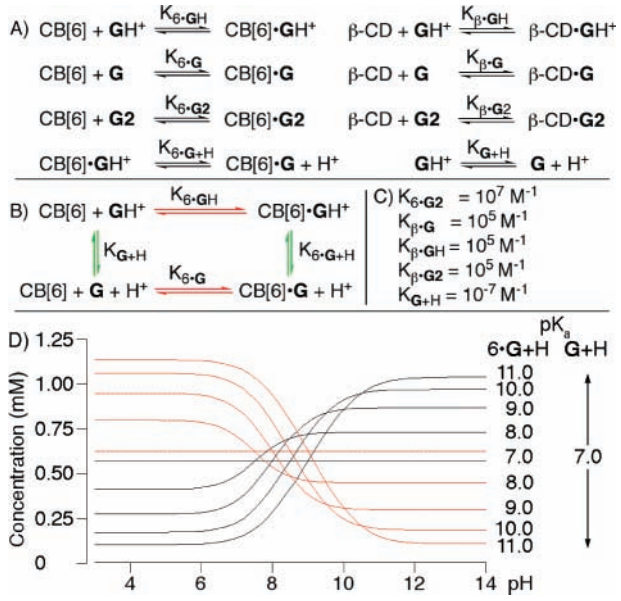

Figure 5. (A) Equilibria considered, (B) thermodynamic cycle for CB[6]·**G** complexes, (C) input equilibrium constants, and (D) plot of concentration versus pH (CB[6]·**G** + CB[6]·**G**H$^+$, red lines; β-CD·**G** + β-CD·**G**H$^+$, black lines) as a function of $K_{6\cdot G+H}$. [CB[6]] = [β-CD] = [**G**] = [**G2**] = 1.25 mM.

represents the pK_a shift that occurs upon binding of **G**H$^+$. It is this pK_a shift that provides the change in ΔG, which is the driving force for the pH swapping process. When there is no pK_a shift (pK_a(G+H) = pK_a(6·**G**+H) = 7.0; ΔpK_a = 0), the system does not respond to changes in pH and **G** and **G**H$^+$ form host−guest complexes with CB[6] and β-CD in nearly equal amounts. As the difference in pK_a is increased (pK_a(6·**G**+H) = 11.0; ΔpK_a = 4), the fidelity of the guest swapping process increases dramatically; the swapping fidelity observed experimentally (~5:1, Figure 3B) corresponds to a pK_a shift of 2−3 units.

Although the simulation shown in Figure 5D uses fixed values of $K_{\mathbf{G}\cdot H}$ (pK_a(**G**+H) = 7), $K_{\beta-GH} = K_{\beta-G} = K_{\beta-G2}$ = 10^5 M^{-1}, and $K_{6\cdot G2} = 10^7$ M^{-1}, the fidelity of the guest swapping process does not depend significantly on these choices; instead, it is the magnitude of the pK_a shift and the distribution of $K_{6\cdot GH}$ and $K_{6\cdot G}$ relative to the fixed value of $K_{6\cdot G2}$ that controls the overall behavior of the system.[15] For example, as the pK_a of **G**H$^+$ becomes more (less) positive the inflection points of the swapping curves move to higher (lower) values of pH (Supporting Information). Interestingly, when log{($K_{6\cdot GH}$)($K_{6\cdot G}$)} is greater (less) than log{($K_{6\cdot G2}$)-($K_{6\cdot G2}$)},[13] the swapping efficiency decreases at high (low) pH (Supporting Information).

In conclusion, we have demonstrated a four-component system comprising CB[6], β-CD, **2**, and pH-responsive two-faced guest **1** that undergoes controlled inter-aggregate guest swapping in response to changes in pH. GEPASI simulations provide insights into two deficiencies of the current system that simultaneously provides guidance for the future designs: (1) incomplete switching even at pH 13 is due to the high pK_a of **G**H$^+$ and even higher pK_a of CB[6]·**G**H$^+$, and (2) a pK_a shift of 2−3 units is sufficient to drive a swapping process of only modest fidelity, which suggests the need to couple the protonation/deprotonation of two or more pH-responsive groups (e.g., carboxylic acid to carboxylate and imidazolium to imidazole) to achieve efficient swapping. Most significantly, the thermodynamic cycle shown in Figure 5B establishes the conceptual equivalency of changes in binding constant (e.g., $K_{6\cdot GH}$ vs $K_{6\cdot G}$)—that has been implicitly used in as the driving force in the H-bonded or $\pi-\pi$ interaction-based molecular shuttles[2] in polar organic media—with a pK_a shift that will be critical for the development of biomimetic systems that operate in aqueous solution. Last, in contrast to the majority of single-component molecular shuttles and devices which undergo intramolecular conformational change,[2] the intermolecular nature of the swapping process described here is particularly well-suited for the reconfiguration of the components of multiple interconnected molecular devices that together constitute a more complex molecular machine in response to external stimuli.

Acknowledgment. We thank the National Science Foundation (CHE-0615049), the National Institutes of Health (GM61854), and the United States Naval Academy for financial support.

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for **2**, experimental procedures and ^{1}H NMR spectra for the pH swapping experiments, and the GEPASI model file used for the simulations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The behavior of the system remains similar when the common value of K_b is sufficiently large to ensure complete complexation at the concentrations of β-CD employed in the simulations (e.g., [β-CD] = 1.25 mM; K_b = 10^5 M^{-1}; K_b^{-1} = 0.01 mM). When $K_b \approx 10^4$ M^{-1}, decomplexation begins to become an issue.