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# Dual-Action Acid/Base- and Base/Acid-Controllable Molecular Switch

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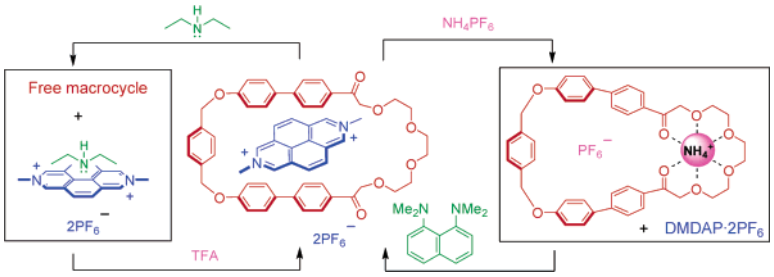
## ABSTRACT




**We report a molecular switch that not only can be switched between its complexed and decomplexed states through the sequential addition of an acid and a base ($NH_4^+$ and Proton Sponge, respectively) but also can be operated equally through the sequential addition of basic and acidic reagents ($Et_2NH$ and TFA, respectively).**

The synthesis of molecular actuators and switches continues to attract much attention because these machinelike molecules[1] have potential applicability in mesoscale molecular electronics devices.[2] Because of the need for reversibility in the operation of these machinelike molecules, chemically controllable molecular switches are generally operated through the addition and removal of electrons,[3] metal ions,[1a,4] or protons.[1c,5] Although many elegant acid/base-controllable molecular switches[5] have been developed, their switching mechanisms are all similar conceptually: proton receptors comprise parts of the molecular structure of the host or guest molecule, and the switching process is driven generally by charge repulsion or hydrogen bonding interactions that arise

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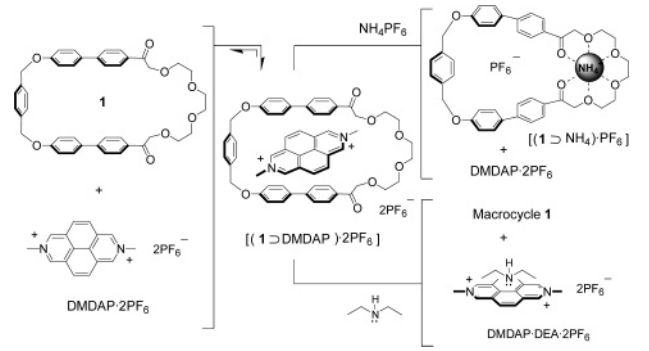


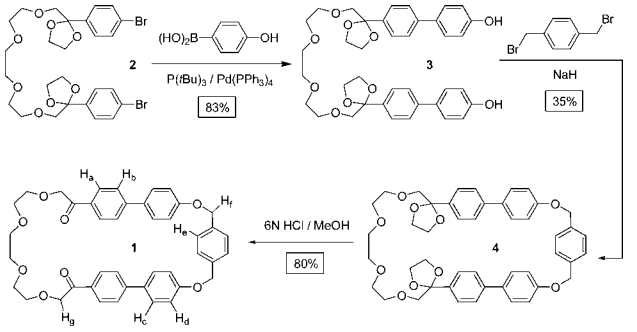

**Figure 1.** Structural representation of a complex that can be dissociated using either an acid or a base.

from protonation of these components. Such designs provide simple two-directional operation of acid/base-controllable molecular switches; i.e., an "acid" turns the molecular switch "on" and a "base" turns it "off", or vice versa, even when different acid/base pairs are applied. Because of the increasing need for molecular sensors that exhibit high guest specificity and for logic gates that provide a number of inputs and versatile functions, we became interested in preparing a pH-controllable molecular switch that could be controlled only when using specific acid/base reagent pairs. To the best of our knowledge, molecular switches that can be switched on and off through the action of specific acid/base and base/acid reagent pairs have yet to be reported, possibly because of the difficulty in adjusting the values of p$K_a$ of the proton receptors to avoid complicated formations of acid/base equivalents between the different proton receptors. Herein, we report a unique dual-action supramolecular complex that can be switched between its complexed and uncomplexed states through the use of not only an acid/base reagent pair but also a base/acid pair.

A potential approach toward a molecular switch that responds to the presence of both acids and bases, but without the complications arising from the issue of balancing the values of p$K_a$ of the proton acceptors, is to avoid the use of proton acceptors within the molecular structures of either the host or the guest. We wished to design a molecular switch in which the incoming acid and base compete with the guest or host moieties to cause the dissociation of their original complex. If different binding sites exist for the incoming acid and base in the molecular structure of the host and guest, such a supramolecular complex should be switchable between its complexed and uncomplexed states through the addition of both acid/base and base/acid reagent pairs. On the basis of this concept, we designed macrocycle **1**, which comprises a ring-expanded [18]crown-6 (18C6) unit, for binding to ammonium ions, and a $\pi$-electron-rich aromatic system, for binding to $\pi$-electron-deficient units, such as the dimethyldiazopyrenium (DMDAP) ion. We expected macrocycle **1** to form a [2]pseudorotaxane-like complex with DMDAP in solution. Dissociation of this complex should be possible through the addition of an acid, e.g., $NH_4^+$ ions binding to macrocycle **1**[6], or a base, e.g., an alkylamine binding to the DMDAP ion.[7] In this example, regeneration of the complex in solution would be possible through the addition of a suitable base to deprotonate the $NH_4^+$ ions or an acid to protonate the alkylamine (Figure 1).

We synthesized macrocycle **1** from dibromide **2** in three steps (Scheme 1). Suzuki coupling of the dibromide **2** with

**Scheme 1.** Synthesis of Macrocycle **1**




4-hydroxyphenylboronic acid gave the biphenol **3**. Macrocycle **4** was obtained after [1+1] macrocyclization of **3** with α,α′-dibromo-*p*-xylene. Removal of the ketal protecting group of macrocycle **3** under acidic conditions afforded macrocycle **1**.

The $^1$H NMR spectrum of an equimolar (2.5 mM) mixture of **1** and DMDAP·2PF$_6$ in $CD_3CN/CDCl_3$ (4:1) at room temperature displays significant changes in the chemical shifts of the protons of the complex relative to those of its free components (Figure 2). In the spectrum of the complex, pronounced upfield shifts in the signals of the aromatic protons of macrocycle **1** ($H_a$, $H_b$) and DMDAP ($H_i$, $H_j$)

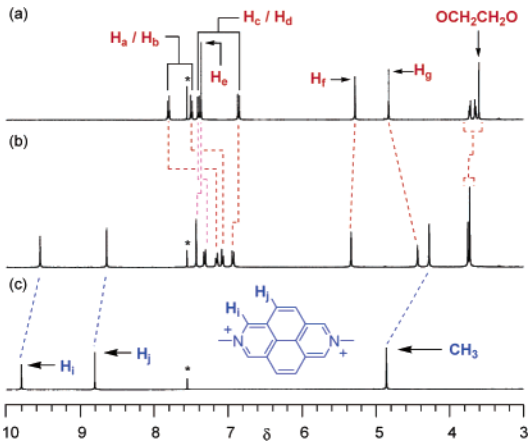



**Figure 2.** Partial $^1$H NMR spectra [400 MHz, $CD_3CN/CDCl_3$ (4:1), 298 K] of (a) macrocycle **1**, (b) an equimolar mixture of **1** and DMDAP·2PF$_6$ (2.5 mM), and (c) DMDAP·2PF$_6$.

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suggest that stacking occurs between these electronically complementary aromatic rings. A Job plot, based on $^1$H NMR spectroscopic data obtained in $CD_3CN/CDCl_3$ (4:1), provided conclusive evidence for 1:1 complexation (see the Supporting Information). From an $^1$H NMR spectroscopic dilution experiment,[8] we determined the association constant ($K_a$) for this complex in $CD_3CN/CDCl_3$ (4:1) to be 630 ± 20 $M^{-1}$, which is ca. 30-fold stronger than that for the complex formed between **1** and the *N*,*N*′-dimethyl-4,4′-bipyridinium (viologen) ion in the same solvent ($K_a$ = 19 ± 3 $M^{-1}$).

The lowest-energy structure of **1**⊃DMDAP obtained from MD simulations is shown in Figure 3.[9] Statistically, the

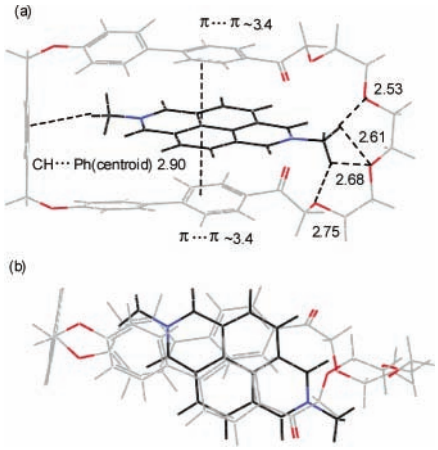



**Figure 3.** (a) Side and (b) top views of the lowest-energy structures of **1**⊃DMDAP obtained from MD.

calculated binding energy of **1**⊃DMDAP is 19.13 kJ $mol^{-1}$ stronger than that of **1**⊃viologen; this value correlates with that observed experimentally, i.e., the association constant of the former complex is 30-fold stronger than that of the latter. Although the gains in the electrostatic energy are larger for **1**⊃viologen ($\Delta\Delta E_{electrostatic}$ = 10.55 kJ $mol^{-1}$), the overall greater stability of **1**⊃DMDAP possibly arises from the higher van der Waals contribution ($\Delta\Delta E_{vdw}$ = 30.49 kJ $mol^{-1}$) resulting from the larger degree of surface contact between **1** and DMDAP (see the Supporting Information for the structure of **1**⊃viologen and a Table of calculated energies). The lowest-energy structures indicate that the long axes of the two guest molecules and one of the biphenyl units of **1** are aligned almost parallel. In each structure, the

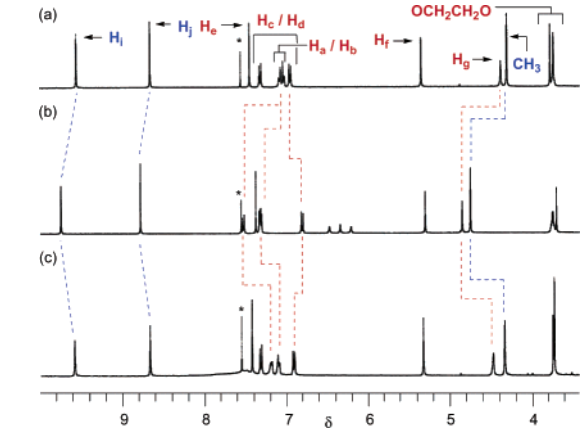


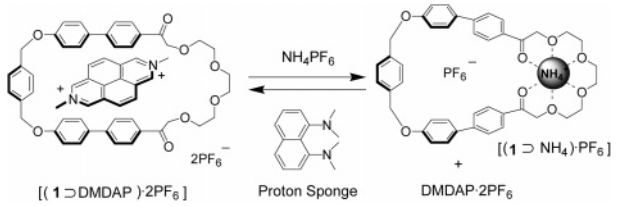

**Figure 4.** Partial $^1$H NMR spectra [400 MHz, $CD_3CN/CDCl_3$ (4:1), 298 K] of (a) an equimolar mixture of **1** and DMDAP·$2PF_6$ (2.5 mM), (b) the mixture obtained after adding $NH_4PF_6$ (1.5 equiv) to solution a, and (c) the mixture obtained after adding Proton Sponge (3 equiv) to solution b.

two biphenyl units of **1** are offset by a twist of ca. −33°; [C−H···O], [C−H···$\pi$], and $\pi-\pi$ interactions are formed in the binding geometry of these complexes.

The $^1$H NMR spectra in Figure 4b indicate that the addition of 1.5 equiv of $NH_4PF_6$ to an equimolar mixture of macrocycle **1** and DMDAP·$2PF_6$ caused the migration of the DMDAP signals back to their free original positions; i.e., it dissociated the complex **1**⊃DMDAP. The addition of up to 15 equiv of triethylamine or hexylamine to this mixture failed to switch the system back to the original complex. The addition of large excesses of small alkylamine bases is not practical for switching this system back to the original complex because they themselves complex with the already-disassociated DMDAP ions.[7]

1,8-Bis(dimethylamino)naphthalene[10] (Proton Sponge, Scheme 2) seemed to be a possible candidate for successful

**Scheme 2.** Acid/Base-Controllable Switching




switching not only because is it more basic than triethylamine but also because its amino groups' lone pairs of electrons are less nucleophilic relative to those of normal alkylamines. Indeed, the addition of 3 equiv of Proton Sponge to the solution of macrocycle **1**, DMDAP·$2PF_6$, and $NH_4PF_6$

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(8) Connors, K. A. *Binding Constants*; Wiley: New York, 1987.

(9) Stochastic molecular dynamics simulations were performed using MacroModel V 9.0 with an all-atom Amber* force field in the gas phase. Charges for the molecules were obtained through CHELPG electrostatic potential fitting using Gaussian 03 at the HF/6-31g* level. See the Supporting Information for further details.

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resulted in an $^1$H NMR spectrum (Figure 4c) similar to that of the original mixture of macrocycle **1** and DMDAP·2$PF_6$ (Figure 4a); i.e., the original complex **1**⊃DMDAP had regenerated in this solution. Thus, the sequential addition of $NH_4PF_6$ and Proton Sponge to a solution of macrocycle **1** and DMDAP·2$PF_6$ can be used to switch the two components between uncomplexed and complexed states; this complex behaves as an acid/base-controllable molecular switch.

The calculated binding energy of **1**⊃$NH_4^+$ from MD is ca. 36 kJ/mol stronger than the interaction of **1** with DMDAP. The low-energy structures indicate that the $NH_4^+$ ion binds with the 18C6 unit of **1** through a series of [N−H···O] interactions, involving both the carbonyl and the ether oxygen atoms ([N−H···O] distances ranged from 1.66 to 2.04 Å; see the Supporting Information). The ammonium ion sits on the rim of the 18C6 unit, in common with the binding of 18-crown-6 observed in solid-state structures. Binding of the $NH_4^+$ ion reduces the cavity size between the two biphenyl units of **1**, allowing $\pi-\pi$ interactions to occur between these two groups (see the Supporting Information). This conformational change triggers the expulsion of the guest in the **1**⊃DMDAP complex.

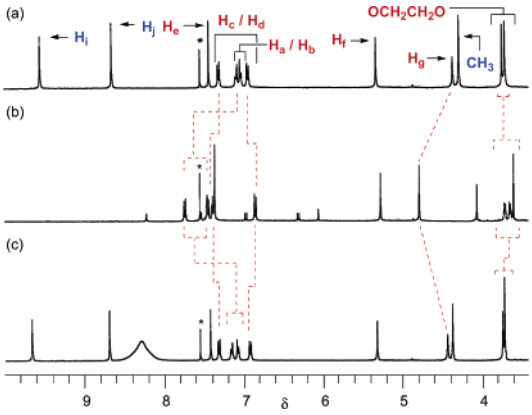
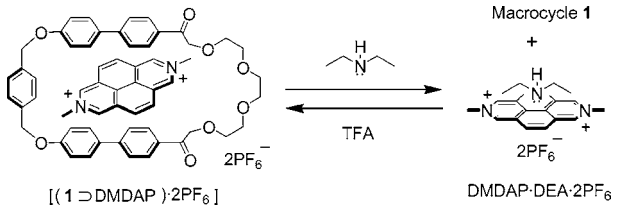



**Figure 5.** Partial $^1$H NMR spectra [400 MHz, $CD_3CN/CDCl_3$ (4:1), 298 K] of (a) an equimolar (2.5 mM) mixture of **1** and DMDAP·2$PF_6$, (b) the mixture obtained after adding $Et_2NH$ (15 equiv) to solution a, and (c) the mixture obtained after adding TFA (15 equiv) to solution b.

Next, we investigated the reverse approach: base/acid-controlled switching. The addition of hexylamine to an equimolar mixture of macrocycle **1** and DMDAP·2$PF_6$ dissociated the complex **1**⊃DMDAP, as evidenced by the appearance of signals for the free macrocycle **1** in the $^1$H NMR spectrum. Subsequent addition of trifluoroacetic acid (TFA) did not reproduce an $^1$H NMR spectrum similar to that of the original mixture of macrocycle **1** and DMDAP·2$PF_6$. In a control experiment, in which equimolar (2.5 mM) hexylamine, TFA, and macrocycle **1** were mixed in $CD_3CN/CDCl_3$ (4:1), we found that the hexylammonium ion is capable of complexing with macrocycle **1** (see the Supporting Information); this binding is probably the reason the original complex was not regenerated. Triethylamine and DABCO form less-stable complexes with DMDAP, relative to the one between DMDAP and hexylamine, and thus, they cannot efficiently dissociate the **1**⊃DMDAP complex in solution.[7a] Figure 5b indicates that 15 equiv of diethylamine (DEA) is capable of almost completely dissociating the complex **1**⊃DMDAP in this solution;[11] the subsequent addition of 15 equiv of TFA to the mixture resulted in an $^1$H NMR spectrum (Figure 5c) similar to that of the original solution of macrocycle **1** and DMDAP·2$PF_6$ (Figure 5a). This result suggests that the original complex **1**⊃DMDAP was regenerated in the solution and implies that complexation between the diethylammonium ion and macrocycle **1** is weak. Therefore, the molecular complex **1**⊃DMDAP can be switched reversibly between its complexed and noncomplexed states through the sequential addition of $Et_2NH$ and TFA; i.e., this supramolecular complex also behaves as a base/acid-controllable molecular switch (Scheme 3).

**Scheme 3.** Base/Acid-Controllable Switching




In this paper, we report a molecular switch that not only can be switched between its complexed and decomplexed states through the sequential addition of an acid and a base ($NH_4^+$ and Proton Sponge, respectively) but also can be operated equally through the sequential addition of a base and an acid ($Et_2NH$ and TFA, respectively). This dual-action acid/base- and base/acid-controllable molecular switch operates through the disruptive acid or base serving as a competitive guest or host to dissociate the original host−guest complex; subsequent deprotonation (of the disruptive acid) or protonation (of the disruptive base), with appropriately chosen reagents, regenerates the original host−guest complex.

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**Note Added after ASAP Publication.** Due to a production error, the caption of Figure 5 was incorrect in the version published ASAP June 21, 2006; the corrected version was published ASAP June 28, 2006.

**Supporting Information Available:** Synthetic procedures and characterization data for all new compounds; molecular simulation data of the complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The disappearance of the signal of the aromatic protons of DMDAP in the $^1$H NMR spectrum after formation of the DMDAP−amine complexes is consistent with literature observations; see ref 7a.