Molecular Recognition

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# Acid/Base- and Anion-Controllable Organogels Formed From a Urea-Based Molecular Switch**

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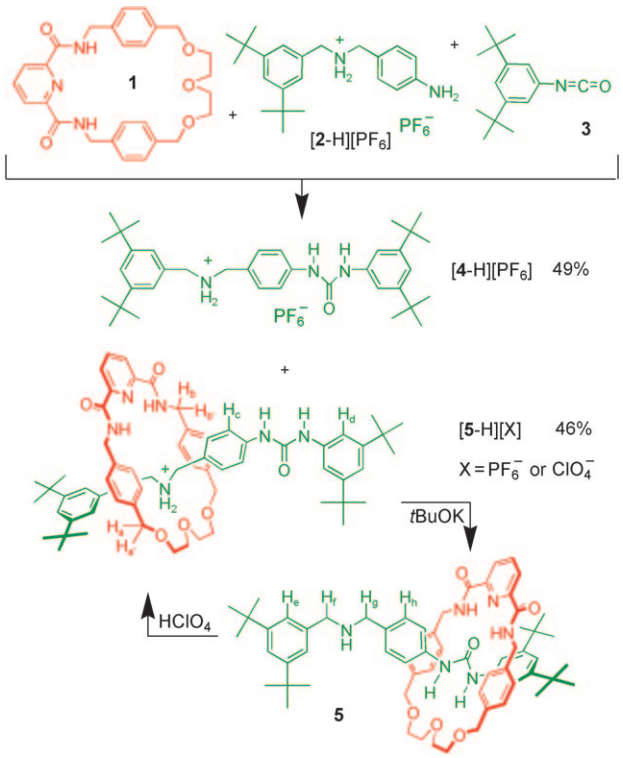
Low-molecular-weight organogels have applications in several fields, including molecular sensing,[1] nanostructure assembly,[2] and drug delivery.[3] Ideally, these materials would switch reversibly between their solution and gel states through the addition or removal of heat, electrons, or ions.[4] Although these modes of operation are similar to those employed for switches based on interlocked molecules, organogels formed from pseudorotaxane- or rotaxane-type gelators are rare. Indeed, we are aware of only a few previously reported examples, all of which feature long alkyl chains or cholesterol units incorporated into the molecular structures to assist the gelation process.[5] Predicting the molecular structures of potential gelators and their preferred solvents remains difficult, and developing new rotaxane-based gelators that do not feature commonly used types of gelation units (e.g., long alkyl chains, steroids) in their structures is particularly challenging. Herein we report the serendipitous discovery of a urea-based [2]rotaxane that behaves as both a molecular switch and an organogelator; both functions are mediated by acid/base and anion control.

The reaction of the macrocycle **1**,[6] the amino-terminated salt [**2**-H][$PF_6$],[7] and the isocyanate **3** in $CH_3NO_2$ gave the dumbbell-shaped salt [**4**-H][$PF_6$] and the [2]rotaxane [**5**-H][$PF_6$] in 49 and 46% yield, respectively (Scheme 1). The binding constant for the assembly formed from the macrocycle **1** and dibenzylammonium hexafluorophosphate ((DBA)$PF_6$) in $CD_3NO_2$ is $(300 \pm 30)\,M^{-1}$, and **1** interacts only negligibly with diphenylurea derivatives in this solvent.[6,8] Therefore we suspected that the interlocked macrocycle in the [2]rotaxane [**5**-H][$PF_6$] would prefer to encircle the $DBA^+$ station, rather than the diphenylurea station, when dissolved in $CD_3NO_2$. Indeed, the 2D NOESY spectrum of the [2]rotaxane [**5**-H][$PF_6$] in $CD_3NO_2$ shows cross-signals between the ethylene glycol protons of the macrocyclic unit and the aromatic protons of the 3,5-di-*tert*-butylphenyl stopper adjacent to the $DBA^+$ center, however, no cross-signals are seen between the macrocyle and the stopper unit adjacent to the urea station.




***Scheme 1.*** Synthesis and switching of the [2]rotaxane [**5**-H][$PF_6$].

As expected, addition of potassium *tert*-butoxide (1 equivalent) to a solution of the [2]rotaxane [**5**-H][$PF_6$] ($CD_3NO_2$, 13.6 mM) resulted in significant shifts in the locations of many of the signals in the $^1$H NMR spectrum (Figure 1). The significant downfield shift of the signal for the macrocyle NH protons, and the appearance of signals for the formerly severely broadened urea protons suggested the formation of hydrogen bonds to the carbonyl group of the urea station (Figure 1b). The addition of perchloric acid (70% in $H_2O$, 1 equivalent) to this solution afforded a spectrum similar to that of the original [2]rotaxane. These observations suggest that the [2]rotaxane [**5**-H][X] is an acid/base-controllable molecular switch;[9] the interlocked macrocyclic unit can be

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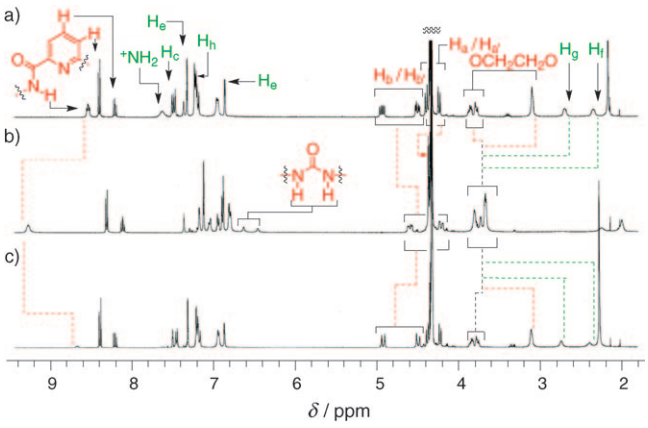



***Figure 1.*** Partial $^1$H NMR spectra (400 MHz, $CD_3NO_2$, 298 K) of a) the [2]rotaxane [**5**-H][$PF_6$], b) the mixture obtained after adding *t*BuOK (1 equiv) to the solution in (a), and c) the mixture obtained after adding aqueous $HClO_4$ (1 equiv) to the solution in (b).

positioned selectively at the $DBA^+$ or urea station after the addition of *t*BuOK or $HClO_4$, respectively. When we used $Et_3N$/trifluoroacetic acid (TFA) as the operating acid/base pair, we observed similar reversible switching of the rotaxane [**5**-H]$^+$ in $CD_3NO_2$ (see the Supporting Information).

We grew single crystals suitable for X-ray crystallography by liquid diffusion of hexanes into a solution of [**5**-H][$PF_6$] in $CH_3CN/CHCl_3$ 1:1. The solid-state structure[10] (Figure 2)

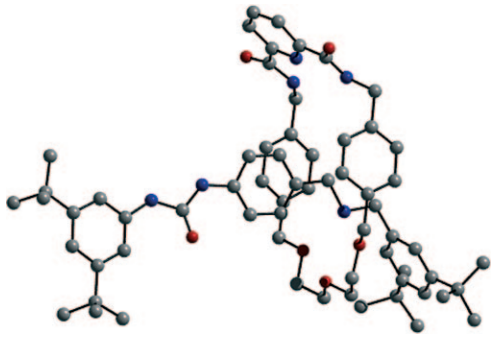


***Figure 2.*** Ball-and-stick representation of the solid state structure of the [2]rotaxane [5-H]$^+$. C gray, O red, N blue.

shows the expected [2]rotaxane molecular geometry, in which the macrocycle resides on the $DBA^+$ unit of the dumbbell-shaped component. We did not observe any intermolecular hydrogen bonds between the [2]rotaxane units in the solid state.

We observed gelation behavior for the [2]rotaxane [**5**-H][$PF_6$] in several solvent systems, including hexanes/EtOAc 1:1, ethyl caproate, and 1-pentanol. The addition of [**5**-H][$PF_6$] (12 mg) to 1-pentanol (0.6 mL) and subsequent sonication led to gelation of the solvent;[11] the solution state was regenerated after adding 1 equivalent of *t*BuOK. Interestingly, the addition of aqueous $HClO_4$ (1 equivalent) to the latter solution returned the system to a gel state; one such gel–sol phase transition cycle is shown in Figure 3 a. Migration of the interlocked macrocyclic unit from the $DBA^+$ station to the urea station and back again was also evident in $^1$H NMR

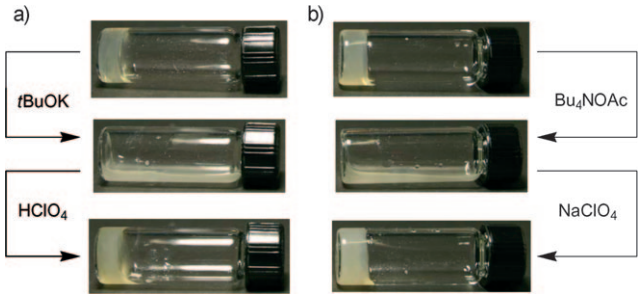
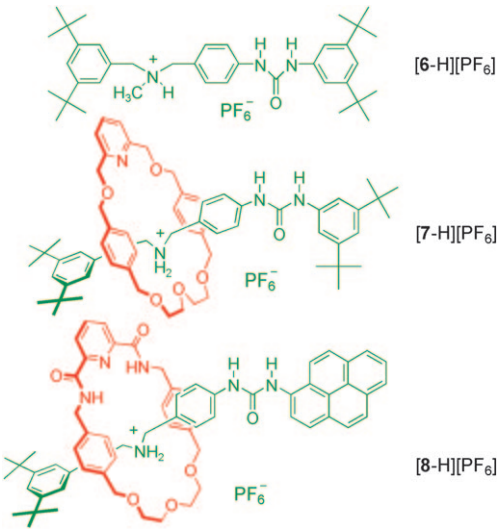



***Figure 3.*** Sol–gel phase transitions of the [2]rotaxane [**5**-H][$PF_6$] in 1-pentanol (2.4 wt%) upon sequential additions of a) *t*BuOK (in 1-pentanol) and aqueous $HClO_4$ and b) $Bu_4NOAc$ (in 1-pentanol) and $NaClO_4$ (in 1-pentanol).

spectra after sequential addition of *t*BuOK and $HClO_4$ to a solution of the [2]rotaxane [**5**-H][$PF_6$] in $CD_3OD$ (see the Supporting Information). It therefore appears that the sol–gel phase transitions of [**5**-H][$PF_6$] in 1-pentanol are related to the location of the interlocked macrocyclic unit. The intermolecular accessibility of the urea station presumably plays the major role in effecting the aggregation of these [2]rotaxanes through intermolecular hydrogen bonds and the subsequent sol–gel phase transitions.[12]

Addition of the dumbbell-shaped salt [**4**-H][$PF_6$] (4.0 mg) or an equimolar mixture of **4** and the macrocycle **1** (2.7 mg) to 1-pentanol (0.4 mL) gave suspensions in solution, rather than organogels, after sonication. As the solubility of the salt [**4**-H][$PF_6$] in 1-pentanol is relatively low, we also investigated the gelation behavior of the methylated derivative [**6**-H][$PF_6$] (Scheme 2), which is more soluble, as well as the neutralized forms of these two ammonium salts (i.e., **4** and **6**). None of these urea-containing derivatives formed organogels in 1-pentanol, either alone or mixed with a stoichiometric amount of the macrocycle **1**, after sonication. This result suggested that the interlocked structure of the [2]rotaxane [**5**-H]$^+$ played an important role influencing its gelation process.




***Scheme 2.*** Molecular structure of the dumbbell-shaped salt [**6**-H][$PF_6$] and the [2]rotaxanes [**7**-H][$PF_6$] and [**8**-H][$PF_6$].

We used TEM and AFM to gain insight into the gelation behavior. TEM images of the gels prepared from dilute and concentrated [**5**-H][$PF_6$] in hexanes/1-pentanol (1:1) exhibited nerve-like (Figure 4a) and network (Figure 4b) features,

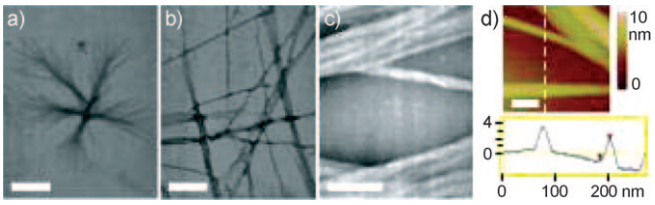
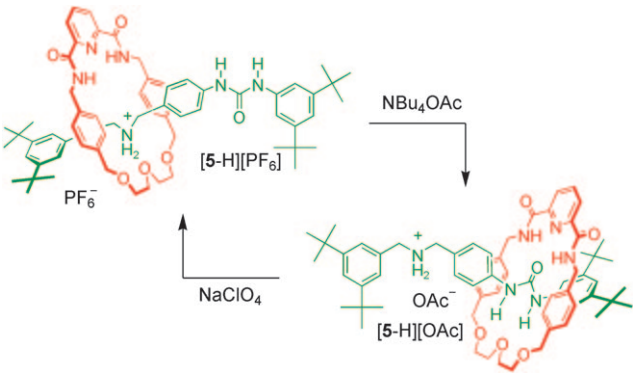



***Figure 4.*** Microscopy images of the gels formed from the [2]rotaxane [**5**-H][$PF_6$]. TEM micrographs of a) nerve-like fibers and b) fiber bundles. c) High-magnification TEM image. d) AFM image of the gel and a section profile of the dashed line in it. The samples for TEM imaging were stained with 2% phosphotungstic acid. The samples for AFM imaging were prepared through spin-coating of [**5**-H][$PF_6$] (1.2 wt% in 1-pentanol) on graphite. Scale bars: a, b) 1 μm; c) 100 nm; d) 50 nm.

respectively, with fiber widths of 20–40 nm and lengths of up to 20 micrometers. The high-resolution TEM image of the [2]rotaxane [**5**-H][$PF_6$] in 1-pentanol (Figure 4c) shows that the fibers in the gel were helical bundles. Unfortunately, further magnification did not provide images of satisfactory contrast to characterize the fine structures of the fibers. From the AFM image (Figure 4d), we determined the minimum height and width of the fibers to be approximately 2.8 and 10 nm, respectively. Therefore, the gelation effect of the [2]rotaxane [**5**-H][$PF_6$] appears to occur through steric immobilization of the organic solvent by formation of interwoven structures from numerous fiber bundles.

To avoid introducing water into the [**5**-H][$PF_6$] sol–gel system during the acidification process, we used $Et_3N$ and TFA as the operating acid/base pair, which resulted in smooth sol–gel phase transitions. We found, however, that the gel state could not be regenerated when we added an excess of TFA or when large amounts of the corresponding triethylammonium salt accumulated in the system. We suspected that this behavior was due to the recognition of the TFA anion by the urea and/or $NH_2^+$ stations of the [2]rotaxane [**5**-H]$^+$, thereby disturbing the alignment of the [2]rotaxanes in the gel state by disrupting the intermolecular hydrogen bonds to the urea unit. If this hypothesis were valid, the sol–gel phase transitions of mixtures of the [2]rotaxane [**5**-H]$^+$ and 1-pentanol should be operable through the addition and removal of the appropriate anions (Scheme 3)

Firstly, we tested whether the interaction of shape-complementary acetate anions with the urea units would dissolve the organogel. We found, however, that the addition of tetrabutylammonium acetate to a solution of [**5**-H][$PF_6$] in $CD_3NO_2$ actually switched the location of the interlocked macrocyclic unit to the urea station, presumably because of the tighter binding of the acetate ion to the $DBA^+$ center under these conditions (Scheme 3). The addition of 3 equivalents of $NaClO_4$ to this solution resulted in a $^1$H NMR spectrum similar to the original spectrum of [**5**-H][$PF_6$] (see the Supporting Information), thus suggesting that the macrocyclic unit had returned to its preferred $NH_2^+$ station,



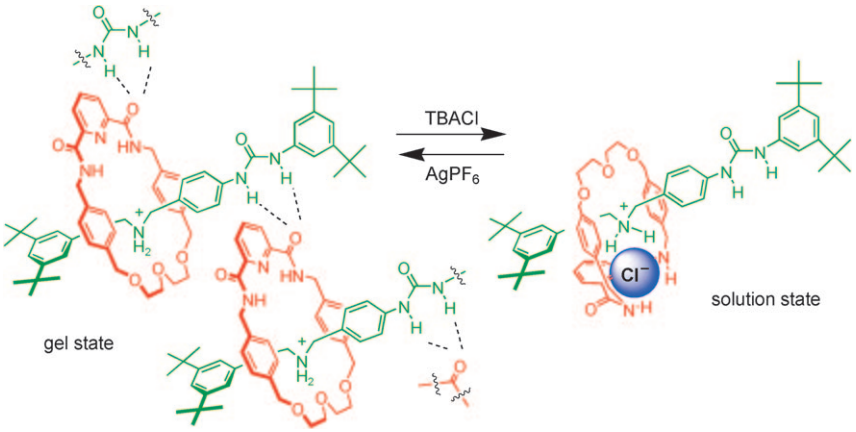

***Scheme 3.*** Anion-induced switching of the [2]rotaxane [**5**-H]$^+$.

presumably through the precipitation of the acetate anions in the form of NaOAc.[13] Addition of 2 equivalents of $Bu_4NOAc$ to the gel formed after sonication of the mixture of 1-pentanol (0.6 mL) and [**5**-H][$PF_6$] (12 mg) switched the system to the solution state (Figure 3b). Subsequent addition of $NaClO_4$ (3 equivalents) to this solution returned it to the gel state. As exposure of the urea station appeared to be necessary for the acid-mediated gelation process to occur in 1-pentanol, we suspected that the addition/removal of acetate anions would also induce sol–gel transitions for mixtures of [**5**-H][$PF_6$] and 1-pentanol through control over the availability of the urea station (Scheme 4).

We also achieved the same sol–gel phase transition of the mixture of [**5**-H][$PF_6$] and 1-pentanol upon sequential addition of TBACl (or TBABr, 1 equivalent) and $AgPF_6$ (1 equivalent). However, the addition of equimolar amounts of these TBA salts to $CD_3OD$ solutions of the [2]rotaxane [**5**-H][$PF_6$] did not cause noticeable shifts in signals ($^1$H NMR) that correspond to the movement of the macrocycle **1** from the $NH_2^+$ station to the urea station; instead, we observed significant downfield shifts of the macrocycle amide protons, thus suggesting that these two spherical anions ($Cl^-$ and $Br^-$) dissolved the organogel without changing the location of the macrocycle unit in [**5**-H][$PF_6$]. We suspect that these anions might interact with the amide NH units of the macrocycle **1**, as these units are stabilized through both hydrogen bonding and electrostatic attraction to the $NH_2^+$ center. These binding interactions might induce conformational changes of the pyridinediamide units of the [2]rotaxane [**5**-H][$PF_6$] and, thus change the orientation of their C=O units and disrupt potential intermolecular hydrogen bonding (Scheme 4). If gel formation relies on the formation of intermolecular hydrogen bonds between the amide C=O groups of one [**5**-H][$PF_6$] unit and the urea station of another in the gel state, then it might be reasonable to expect that the sol–gel phase transitions could be controlled either by translating the position of the interlocked macrocycle (from the $NH_2^+$ center to the urea station, or vice versa) or by changing the orientation of the C=O groups of the macrocycle.[14]

To confirm this hypothesis, we synthesized the [2]rotaxane [**7**-H][$PF_6$], which lacks the two C=O groups in its interlocked macrocyclic unit (Scheme 2). As expected, a mixture of 1-pentanol and the [2]rotaxane [**7**-H][$PF_6$] did not gel after sonication. This result supports our proposed model and




***Scheme 4.*** Proposed molecular aggregation of [**5**-H]$^+$ in the gel state and its halogen anion-induced phase transition.

confirms the importance of the C=O groups of the pyridine-diamide unit in the gelation of [**5**-H][$PF_6$] in 1-pentanol. We also suspected that the terminal 3,5-di-*tert*-butylphenyl stoppers played an important role in this gelation process, because they would retard the crystallization of the [2]rotaxanes or increase the solubility of their aggregates. This hypothesis was supported by our observation that the [2]rotaxane [**8**-H][$PF_6$], in which the 3,5-di-tert-butylphenyl stopper at the urea end of [**5**-H][$PF_6$] is replaced by a pyrene unit, did not form a gel in 1-pentanol formed a precipitate after a sonicated homogeneous solution was left at ambient temperature for few hours.

We have prepared a urea-based [2]rotaxane gelator [**5**-H][$PF_6$], which does not feature long alkyl chains or cholesterol units in its structure and can reversibly transition between solution and gel states under both acid/base and anion-exchange control. The [2]rotaxane [**5**-H][$PF_6$] also acts as a two-way-controllable molecular switch: the degree of solvent exposure of the hydrogen-bond-donating urea station (and, therefore, the degree of intermolecular hydrogen bonding) and the orientation of the hydrogen-bond-accepting C=O groups of the interlocked macrocycle appear to be responsible for the observed gel–sol transitions in 1-pentanol. The concept might be useful for the design of functional molecular aggregates based on interlocked molecular switches.

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**Keywords:** host–guest chemistry · molecular recognition · molecular switches · organogels · rotaxanes

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[10] Crystal data for [**5**-H][$PF_6$] ($C_{72}H_{104.5}O_{7.5}N_6F_6P$): $M_r = 1319.09$; orthorhombic; space group $P2(1)2(1)2$; $a = 14.5997(2)$; $b = 39.8352(6)$; $c = 12.1622(2)$ Å; $V = 7073.32(19)$ Å$^3$; $\rho_{calcd} = 1.239\ g\,cm^{-3}$; $\mu(Mo_{K\alpha}) = 0.946\ mm^{-1}$; $T = 295(2)$ K; colorless cubes; 10,052 independent measured reflections; $F^2$ refinement; $R_1 = 0.0819$; $wR_2 = 0.2330$. CCDC 782554 (excluding structure factors) for the [2]rotaxane [**5**-H][$PF_6$] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[14] We estimated the molecular length of the dimer of [**5**-H][$PF_6$], associated through the proposed amide–urea hydrogen bonding interactions, to be 3 nm by using CS Chem. 3D computer simulation. This value is reasonably close to the thickness of the fibers observed using AFM (Figure 4d).

  