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A pH Switch in Supramolecular Polymeric Capsules

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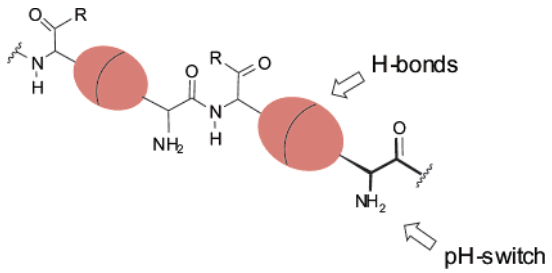
ABSTRACT



A switchable, supramolecular polymer is introduced which is held together through hydrogen bonding and reversibly precipitates–redissolves upon subtle pH control. Precipitating, it entraps and stores guest molecules within the self-assembling capsules incorporated within the polymeric chain.

A novel class of polymers has recently emerged in which monomeric units are held together by reversible forces. These are self-assembling, supramolecular polymers which form and dissipate through hydrogen bonds, metal−ligand interactions, and van der Waals forces.[1] Supramolecular polymers thus combine features of conventional polymers with properties resulting from the bonding reversibility. Structural and dynamic parameters of supramolecular polymeric materials, such as their 2D and 3D architectures, degree of polymerization, strength, liquid crystallinity, etc., can be adjusted or switched "on−off" through assembly dissociation processes. In this paper, we disclose how to switch properties of supramolecular polymers *without* breaking their unique polymeric structure. We introduce pH-switchable supramolecular polymers which take advantage of the side-chain acid-sensitive functionalities (Figure 1). These also possess multiple self-assembling capsules and precipitate together with encapsulated guests upon lowering the solution pH. Our findings thus open an opportunity to construct materials which reversibly trap, store, and then deliver chemicals to reaction mixtures.

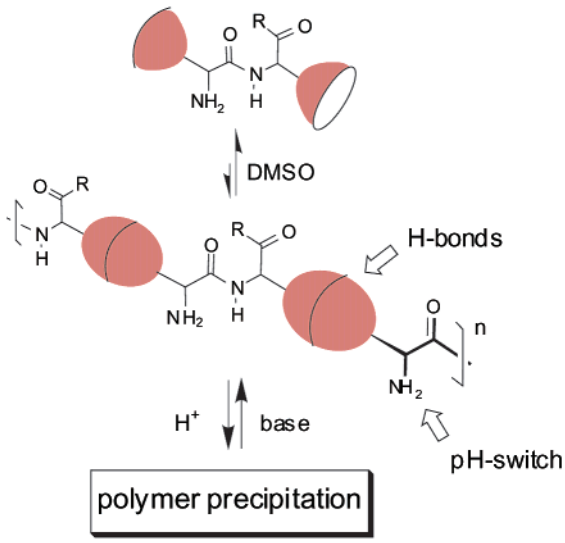


Figure 1. pH-switchable polymeric capsules.

(1) (a) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. *Chem. Rev.* **2001**, *101*, 4071−4097. (b) Ten Cate, T. A.; Sijbesma, R. P. *Macromol. Rapid Commun.* **2002**, *23*, 1094−1112. (c) Schubert, U. S.; Eschbaumer, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2892−2926. (d) Schmuck, C.; Wienand, W. *Angew. Chem., Int. Ed.* **2001**, *40*, 4363−4369.

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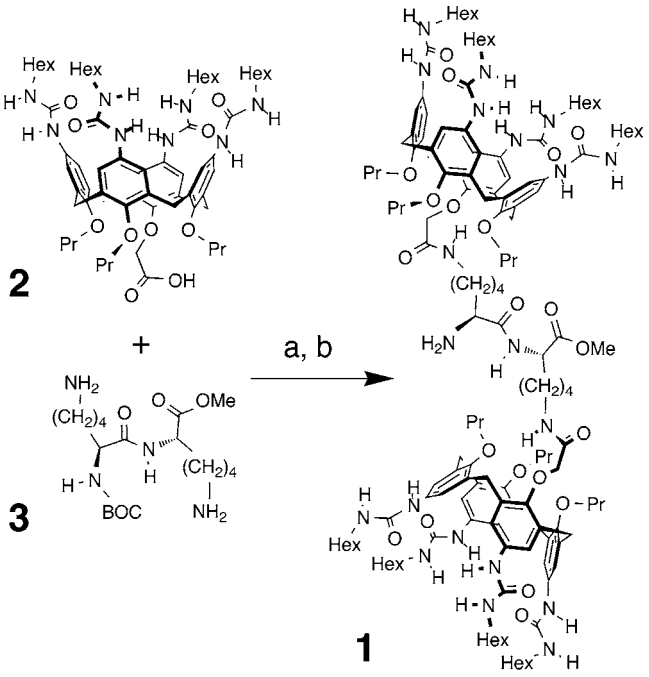
In this study, we took advantage of calixarenes as both self-assembling and cavity-forming modules.[2] Calix[4]arene tetraurea dimers were chosen, as these are probably the most studied and publicized class of capsules to date.[3] Discovered almost 10 years ago by Rebek[4] and Böhmer,[5] these capsules form in apolar solution and are held together by a seam of 16 intermolecular C═O···H−N hydrogen bonds at the upper rims. This results in a rigid cavity of ∼200 Å^3, which reversibly encapsulates one solvent molecule or a benzene-sized guest. When two calix[4]arene tetraureas are covalently linked at their lower rims, hydrogen bonding yields supramolecular polymeric capsules.[6] For this project, biscalix[4]arene **1** was designed in which two calix[4]arene tetraurea moieties are stitched together with a dipeptide chain (Scheme 1). Combining capsules with amino acids, we employed

Scheme 1[a]



[a] Key: (a) EDCI, HOBT, DMF, 56%; (b) TFA, THF, >95%.

trifunctional lysine, which possesses a carboxylic group and two amino groups of distinguishable reactivity.[7] Calixarenes were attached to the ϵ-NH_2 ends. The dilysine module orients them away from each other, in roughly opposite directions, and also prevents the intramolecular assembly. It also possesses a pH-sensitive α-NH_2 group.

Biscalix[4]arene **1** was prepared (as a TFA-salt) by conventional peptide-coupling procedure from 2 equiv of calix[4]arene tetraurea **2** and 1 equiv of di-L-lysine **3** (EDCI, HOBT, DMF, 56%) followed by the α-*N*-BOC deprotection (TFA, THF, >95%). The α-NH_2 group was then liberated with aq NaOH (Scheme 1, Supporting Information).

As expected, **1** self-assembles in apolar solution with the formation of supramolecular polymer **4** (e.g., (**1**·Solvent)$_n$, Figures 2−4, Supporting Information). Due to the lack of

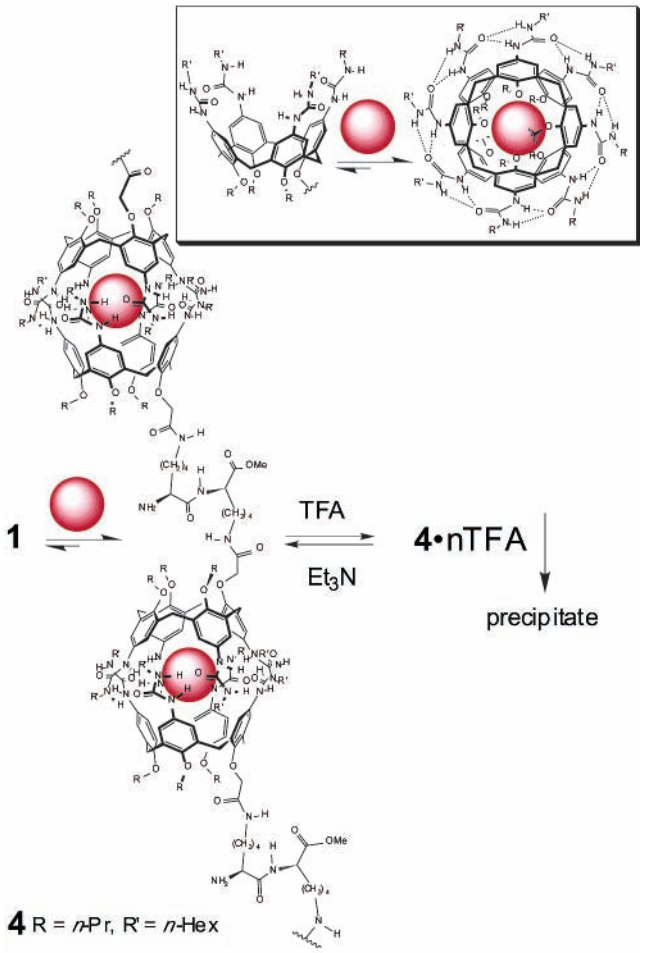


Figure 2. Switchable transformations with polymeric capsules **4**.

symmetry, a multiple set of NH urea signals was recorded in the ^{1}H NMR spectra of **4** in $CDCl_3$, $(CDCl_2)_2$, and benzene-d_6. These were shifted downfield (≥2 ppm), which is a characteristic feature[4−6] of capsule formation (for example, Figure 3A). Both proximal and distal regioisomers of the calixarene dimer can form with respect to the orientation of the acetamide $OCH_2C(O)NH$-substituents at the lower rims of each calixarene **1**.[6] Moreover, the circular array of hydrogen bonds can be arranged either clockwise

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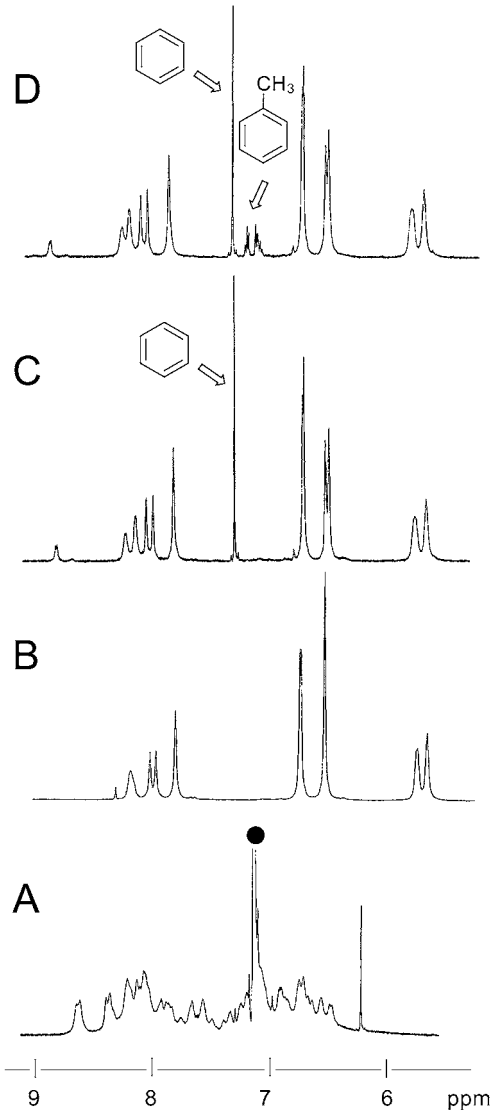

Figure 3. Selected downfield portions of the ^{1}H NMR spectra (500 MHz, 295 ± 1 K) of (A) polymer **4** in benzene-d_6; (B) biscalixarene **1** in DMSO-d_6; (C) dissociated polymer **4**·nTFA, obtained from **4** in benzene upon addition of TFA, in DMSO-d_6; (D) dissociated polymer **4**·nTFA, obtained from **4** in benzene−toluene, a 2:1 mixture, upon addition of TFA, in DMSO-d_6. The residual benzene peak is marked (•). Arrows mark the entrapped benzene and toluene signals.

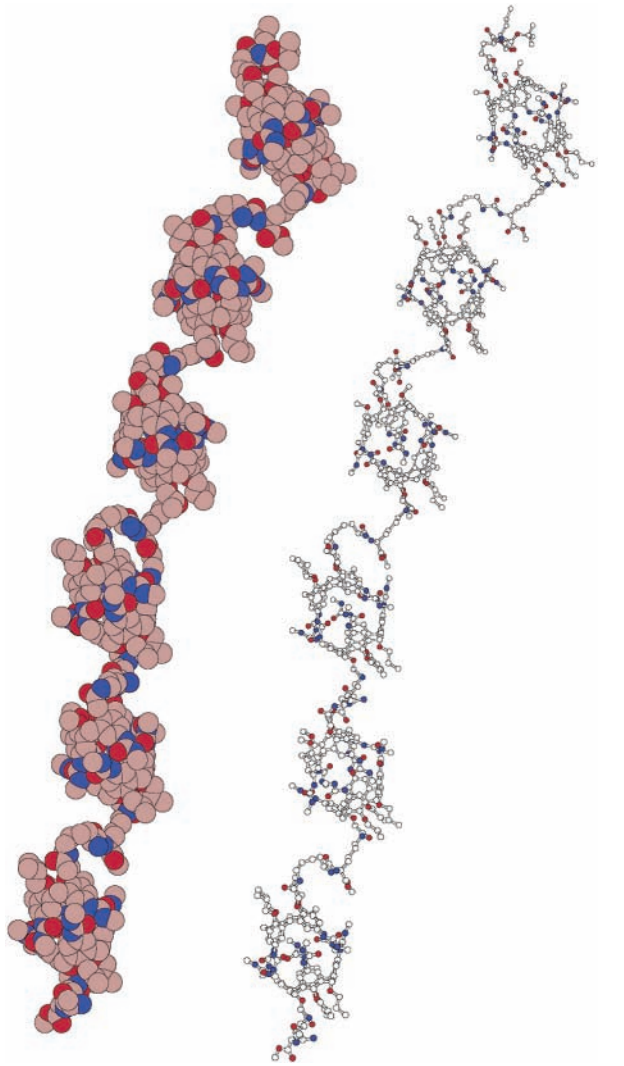

Figure 4. MacroModel 7.1 (MM2) representations of supramolecular polymer **4**: a fragment of the chain. The CH and NH hydrogens and long alkyl chains are omitted for viewing clarity.

or counterclockwise. With the dimerization constant $K_D > 10^6$ M^{-1} for each calixarene capsule,[8] the average degree of polymerization of at least 100 can be estimated for structure **4** at the NMR concentration range.[9] Due to the steric restrains in the design, no unimolecular cyclization of two calixarene tetraureas in **1** occurs.

The interiors of capsules **4** are, most probably, filled by solvent. For example, the ^{1}H NMR spectrum of **4**, recorded in benzene-d_6−benzene, 3:1 mixture, clearly exhibits the encapsulated benzene CH singlet at ∼4.1 ppm. The encapsulation of benzene in simple calixarene dimers has been observed in solution[6] and in the solid state.[5b] Polymer **4** dissociates to monomeric dipeptide **1** in a more competitive for hydrogen bonds solvent, such as DMSO-d_6. This results in a much simpler ^{1}H NMR picture, reflecting the presence of an apparent vertical symmetry plane in **1** (Figure 3B).

Addition of small quantities (5−7 equiv) of trifluoroacetic acid (TFA) to the benzene solution of **4** (e.g., (**1**·Benzene)$_n$) results in instant precipitation of material **4**·nTFA (Figure 2). Obviously, the α-NH_2 groups in **4** become protonated, and the insoluble TFA-salt formed. Being a proton donor, TFA can strongly compete for hydrogen-bond acceptors and cause the capsule dissociation. We determined that at ≤20 equiv of TFA per capsule, no significant dissociation occurs (≤30%, see the Supporting Information). Accordingly, a pH-switch can be provided at low concentrations of acids without breaking the self-assembling polymeric chain.

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(9) Martin, R. B. *Chem. Rev.* **1996**, *96*, 3043−3064. See also ref 1b.

Polymer **4**·nTFA is a colorless solid which readily dissolves in chlorinated solvents, DMSO and DMF and is insoluble in aromatic solvents. A multiple set of the downfield NH urea signals of **4**·nTFA, recorded in $CDCl_3$ and $(CDCl_2)_2$, clearly indicates the hydrogen bonding assembly of polymeric chains. Like **4**, capsules **4**·nTFA dissociate to monomers **1**·TFA in DMSO-d_6. Indeed, once the cyclic hydrogen bonds are broken, the apparent plane of symmetry in the calixarene fragment is restored. On the other hand, addition of Et_3N to the suspension of **4**·nTFA in benzene quickly regenerates **4**, which dissolves without dissociation of the capsules.

Polymer **4** exhibits, thus, unique properties. Similar to other hydrogen-bonding supramolecular polymers,[1,6] it assembles and dissipates upon varying the solvent polarity. At the same time, it changes aggregation properties upon pH changes with the polymeric chains remaining intact. This is novel.

The most interesting feature of material **4** is, probably, in its capsules. These are already preformed in apolar solution but precipitate as salt **4**·nTFA only upon protonation. While precipitating, they captivate and store guest/solvent molecules in the solid state. Thus, polymer **4** entraps benzene already in solution, upon the capsules' formation, and then precipitates with it as **4**·nTFA. The benzene is protected inside the capsules. In a preliminary test, obtained from benzene and carefully dried (0.1 mmHg, rt, 24 h) material **4**·nTFA did not release the guest when the capsules were intact. In suspension of this polymer in noncompetitive *p*-xylene-d_{10}, no traces of benzene was detected, but when DMSO-d_6 was applied, the capsules dissociated and released visible quantities of benzene—approximately one per capsule (Figure 3C). Both benzene and toluene were analogously entrapped upon precipitation from the mixture of these solvents (Figure 3D). The guest escape may be arranged even without the dissociation. Indeed, when redissolved in $CDCl_3$ or $(CDCl_2)_2$, polymer **4**·nTFA releases benzene simply because the solvent now competes for the cavities.

In summary, it is now possible to build switchable supramolecular polymers and turn "on−off" their properties without breaking polymeric chains. In this work, a pH-switch has been demonstrated, resulting in precipitation−dissolution of polymeric self-assembling capsules and trapping guest molecules inside. In principle, redox-, temperature-, light-, and other switching processes can be involved.[10] Another direction is the covalent modification of the polymeric sidechains (e.g., amino or carboxylic groups) without disrupting self-assembly. The most immediate applications, however, are in encapsulation. While polymeric capsules have been known for some time, their encapsulation complexes have not been explored. Indeed, those have only been detected in solution. Polymers **4**·nTFA·nGuest are different. We are currently testing their ability to store and deliver chemicals to reaction mixtures.

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Supporting Information Available: Procedures and spectral data for compounds **1**−**4**, their precursors, and model calixarene compounds; ^1H NMR spectroscopic characterization of self-assembling capsules. This material is available free of charge via the Internet at http://pubs.acs.org.

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