Molecular Shuttles

Shuttling through Anion Recognition**

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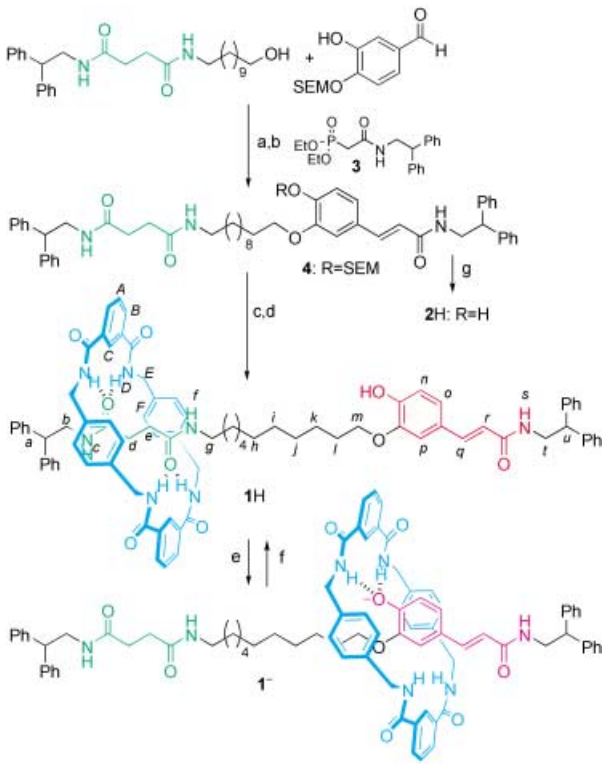
The reversible hydrogen bonding of anions is a key feature of many biological processes, including the remarkable trigger of molecular (and, ultimately, macroscopic) motion in photoactive yellow proteins (PYPs).[1,2] The photoisomerization-induced protonation of a hydrogen-bonded cinnamate anion in PYPs coincides with a large conformational change in the protein, which acts as the signal for *E. halophilia* and other bacteria to swim away from harmful blue light. Despite considerable advances[3–5] in the understanding of noncovalent anion binding in recent years, its application in synthetic systems beyond sensors[4] and templating[5] is still rare. Here we describe the use of anion hydrogen bonding to induce translocation of a macrocycle in a bistable molecular shuttle.[6]

The polarity of the N–H bond, combined with its relatively high pK_a value, makes secondary amides excellent hydrogen-bond donors for neutral[7] functional groups (particularly amides, sulfoxides, nitrones, and phosphane oxides) and anions[8] which are insufficiently basic to deprotonate the amide. Isophthalamide groups, in particular, bind strongly to halides[9] and oxyanions[10] in a variety of solvents and such observations have been exploited to template the synthesis of rotaxanes through isophthalamide-anion hydrogen bonding where the anion is either consumed (phenolate as the template[10]) or retained (chloride as the template[11]) during the synthesis. Although there is limited data or theory with which to reliably compare the hydrogen-bonding ability of anions with neutral functional groups,[12] it seemed plausible that such strong anion binding might be able to translocate an isophthalamide-based macrocycle from a neutral hydrogen-bonding station in a molecular shuttle.

Rotaxane **1**H contains a thread which features two potential hydrogen-bonding stations for a benzylic amide macrocycle. The succinamide group (Scheme 1, green) has previously been shown[13] to be an excellent geometrical and electronic fit for benzylic amide macrocycles. The second station is related to the cinnamate group found in PYPs and is weakly hydrogen bonding as either a donor or acceptor in the phenol form (red) but a powerful hydrogen-bond acceptor as the phenolate anion (purple).

The shuttle was prepared according to Scheme 1. The rotaxane-forming reaction was unusually low yielding (19%) as a result of a difficult chromatographic separation of the rotaxane from the unconsumed thread. Deprotonation of the rotaxane and thread phenol groups to form **1**$^-$ and **2**$^-$, respectively, could be accomplished with a variety of bases (for example, HO^-, $tBuO^-$, DBU, and Schwesinger's P_1 base[14]). Since the xylylene units of the macrocycle shield the encapsulated regions of the thread, the position of the ring in rotaxanes **1**H and **1**$^-$ could be readily determined from the chemical-shift differences of the protons in the corresponding threads, **2**H and **2**$^-$ (Figure 1). In the neutral form, the succinic methylene protons are shielded by >1.2 ppm in the rotaxane in a range of solvents ($CDCl_3$, CD_2Cl_2, [D_3]MeCN, [D_7]DMF),[15] which indicates that the macrocycle resides preferentially on the succinamide station. Remarkably, this is true even in DMF (>95% succinamide-bound translational isomer, 298 K, [D_7]DMF, Figure 1a and b) where the solvent is comparable, and probably slightly superior, in terms of hydrogen-bond basicity to the succinamide amide groups.[16]

^{1}H NMR confirms that deprotonation of the phenol provides an excellent alternative hydrogen-bonding station for the macrocycle. The shielding of the protons of **1**$^-$ (Figure 1d) and **2**$^-$ (Figure 1c) in [D_7]DMF (298 K, P_1H^+ counterion) show the ring is now located overwhelmingly over the phenolate anion (H_p shifted by $\delta = -0.6$ ppm in the rotaxane anion compared to the thread anion) and the adjacent parts of the alkyl chain (relative shifts of H_m $\delta =$



Scheme 1. Synthesis of the bistable molecular shuttle **1**H/**1**$^-$ (SEM = $Me_3SiCH_2CH_2OCH_2$-): a) Diisopropylazodicarboxylate (DIAD), PPh_3, 70%; b) **3**, NaH, THF, 85%; c) isophthaloyl dichloride, *p*-xylylene diamine, Et_3N, $CHCl_3$, 19%; d) tetrabutylammonium fluoride (TBAF), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 4Å molecular sieves, 75%; e) various bases, DMF; f) CF_3CO_2H (1 equiv), DMF; g) TBAF, DMPU, 4Å molecular sieves, 61%. Full experimental procedures can be found in the Supporting Information.

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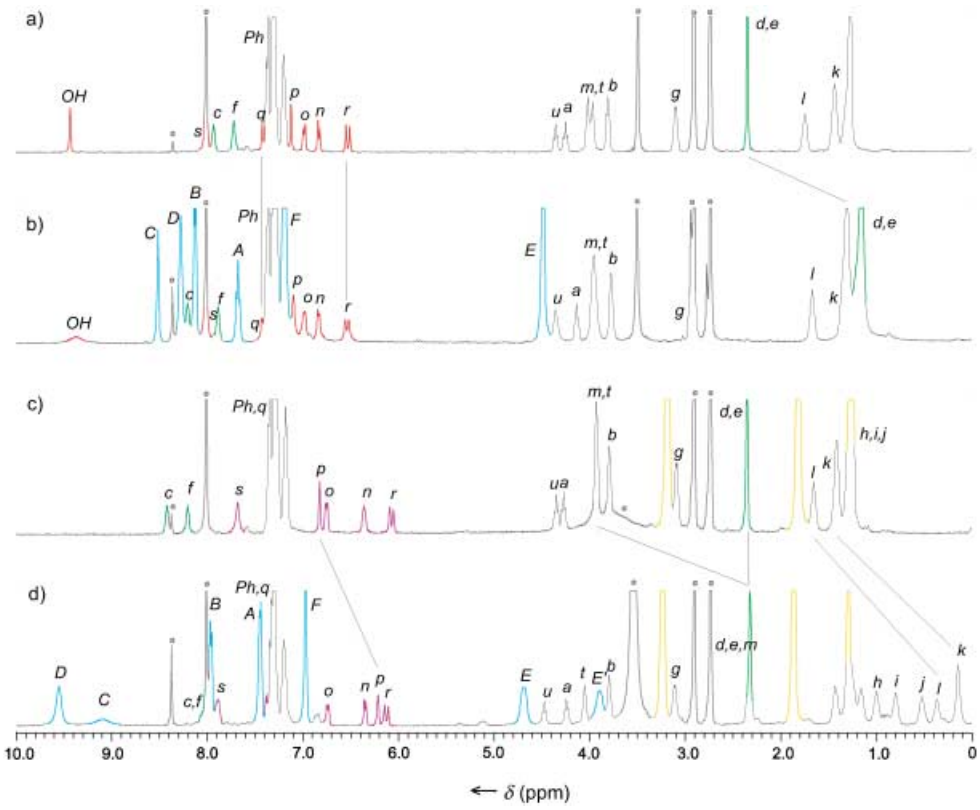

Figure 1. 400 MHz ^{1}H NMR spectra ([D$_7$]DMF, 298 K) of a) thread **2**H; b) rotaxane **1**H; c) thread **2**$^-$ with the P$_1$H$^+$ counterion; d) rotaxane **1**$^-$ with the P$_1$H$^+$ counterion. The color coding and assignments correspond to those indicated in Scheme 1. The resonances of P$_1$H$^+$ ions are shown in orange and those of the residual solvent and H$_2$O in grey (°).

−1.7 ppm, H_l $\delta = -1.3$ ppm, H_k $\delta = -0.8$ ppm, H_j $\delta = -0.7$ ppm, H_i $\delta = -0.4$ ppm). Note also the virtually unchanged chemical-shift values of the succinic methylene protons $H_{d,e}$ in **1**$^-$ and **2**$^-$. The shuttling is reversible and protonation of **1**$^-$ with CF_3CO_2H smoothly regenerates **1**H, which returns the macrocycle to the original succinamide station.

The anion-induced shuttling is highly solvent dependent. Normally hydrogen-bonded molecular shuttles work best in nonpolar solvents where the designed intercomponent hydrogen bonding is strongest.[13] For **1**$^-$, however, the opposite is true. The degree of discrimination of the macrocycle for the phenolate station over succinamide is excellent in [D$_7$]DMF, [D$_3$]MeCN, and [D$_4$]MeOH but not in $CDCl_3$ or CD_2Cl_2, where the ^{1}H NMR spectra shows that intramolecular folding occurs but the macrocycle remains located over the succinamide station.[17] This is presumably because the phenolate anion only provides a hydrogen-bonding site for one of the two isophthalamide units of the macrocycle. Good hydrogen-bond-accepting solvents are able to adequately solvate the second isophthalamide site (and, equally important, the succinamide groups of the thread) and induce shuttling, but $CDCl_3$ and CD_2Cl_2 cannot. It is indicative of the strength of the anion hydrogen bonding in **1**$^-$ that the isophthalamide–phenolate interaction can displace the macrocycle from the succinamide binding site in [D$_3$]MeCN, a solvent of modest hydrogen-bond basicity ($\beta_2^H = 0.45$[12b]) compared to an amide ($\beta_2^H \sim 0.66$[12b]).

The proton-mediated translocation of the macrocycle in **1**H/**1**$^-$ was investigated in the presence of other ions.[18] First, shuttling was found to be independent of the base used. The same ^{1}H NMR chemical shifts were observed using various bases capable of deprotonating the phenol (LiOH, NaOH, KOH, CsOH, Bu_4NOH, *t*BuOK, DBU, phosphazine P$_1$) but not bases that do not generate the rotaxane anion (Et_3N, pyridine). Although the strength of anion hydrogen bonding can be strongly influenced by the nature of the accompanying cation,[19] the co-conformation adopted by rotaxane anion **1**$^-$ is unaffected by the counterion.

Second, not only is the macrocycle observed to switch with excellent positional integrity between the different stations in **1**H and **1**$^-$ in the presence of strong alternative neutral hydrogen-bond acceptors (e.g. [D$_7$]DMF), the shuttling also proved unaffected by competition from anionic hydrogen-bond acceptors. The addition of up to 10 equivalents of Bu_4NX ($X = F^-$, Cl^-, Br^-, I^-, HO^-, NO_3^-, AcO^-) had no effect on the degree of translational isomerism exhibited by either rotaxane.[18] The shuttling in **1**$^-$ can therefore be considered to result from a precise recognition event rather than an unselective anion interaction with the amide groups in the macrocycle or thread.

In conclusion, we have demonstrated the reversible control of translation motion in a rotaxane through hydrogen bonding to an anion. The shuttle has several remarkable features, including that translocation of the macrocycle only occurs in solvent systems where the designed hydrogen-

bonding interactions are relatively weak (and competing hydrogen-bonding interactions weaker still), and that under these conditions shuttling is unaffected by the nature of the countercation or the presence of alternative anionic hydrogen-bond acceptors. This adds to the range of methods already developed for switching the position of macrocycles in bistable molecular shuttles and provides a new type of model system for probing anion hydrogen-bonding interactions.

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[17] The chemical shifts of $H_{d,e}$ are virtually unchanged between rotaxanes **1**H and $\mathbf{1}^-$ in $CDCl_3$ or CD_2Cl_2 (see Supporting Information), which shows that the macrocycle of $\mathbf{1}^-$ is preferentially located over the succinamide station in these solvents. Similarly, with the exception of H_m, the alkyl chain protons are shielded by < 0.2 ppm in $\mathbf{1}^-$ compared with $\mathbf{2}^-$, which confirms that the alkyl chain near the phenolate unit is not encapsulated by the macrocycle. However, there are significant shifts in the amide protons of the macrocycle (≈ 1.2 ppm, which indicates their involvement in stronger hydrogen bonding in the deprotonated rotaxane), H_c, H_m, and some of the phenolate resonances in $\mathbf{1}^-$ compared to **1**H, all consistent with a folded, hydrogen-bonded structure for $\mathbf{1}^-$ where the macrocycle is situated over the succinamide station while simultaneously hydrogen bonding to the phenolate anion.
[18] The standard experimental set up for all our experiments, from which one variable was changed or another component added, was: rotaxane or thread (0.009 mmol), P_1 base (0.010 mmol), and [D_7]DMF (0.6 mL) as solvent at 298 K. The base-induced shuttling in the rotaxane is rapid on the NMR timescale (the spectrum shown in Figure 1d is immediately apparent and not time dependent). Shuttling away from a succinamide binding site in a similar rotaxane has been shown to occur on the microsecond timescale.[13a,b]
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