Peptide-Based Molecular Shuttles

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The inherent restrictions in rotational and translational freedom imposed on the components of mechanically-interlocked molecules[1] make them particularly attractive architectures for precisely controlling the *positioning* of functional units/substituents with the possibility of *switching* their relative separation and orientation.[2,3] Such control has been elegantly demonstrated through π-donor−acceptor interactions in the "molecular shuttles"[2] initially developed by Stoddart *et al.* and metal ion coordination in the catenates[3a−c] and pseudorotaxanes[3d] prepared by Sauvage and co-workers. However, although hydrogen bonding has been used to synthesize a variety of simple and polymeric rotaxanes,[4] translocation of macrocycles between specific sites ("stations") in the threads of hydrogen bond-assembled systems has not previously been demonstrated—*i.e.*, such rotaxanes have not been elaborated into shuttles.

Peptide rotaxanes[4i] can be prepared by the condensation of appropriate aromatic diacid chlorides and benzylic diamines in the presence of dipeptide derivatives which template the formation of benzylic amide macrocycles around them. In nonpolar solvents the hydrogen bonding motif responsible for peptide rotaxane formation is maintained, but in polar solvents the intramolecular hydrogen bonding between isophthaloyl[5] benzamide macrocycles and the peptide is "switched off" leading to nonspecific location of the macrocycle along the peptide backbone. Medium effects[6] often influence the stability of intermolecular interactions[6a] and have previously been shown to alter intramolecular translational isomerism in catenanes.[6b,c] It therefore seemed feasible that combining two (or more) hydrogen bonding peptide units with additional lipophilic regions (to provide distinct polarphobic stations) in a thread could provide a simple route to multistationed, hydrogen bond-assembled molecular shuttles whose structure and dynamics are governable by judicial choice of their operating environment (Figure 1).

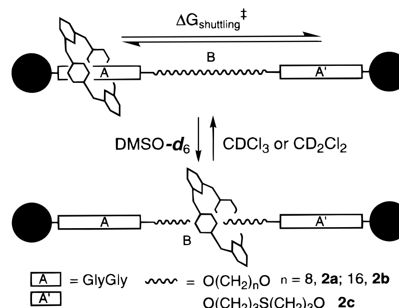

Figure 1. Controlling the *position* of the macrocycle in multistationed peptide-based molecular shuttles. In $CDCl_3$ or CD_2Cl_2 the macrocycle shuttles between degenerate hydrogen-bonding stations A and A′. In DMSO-d_6 the macrocycle is located at polarphobic station B.

Compounds **1a**−**c** were synthesized in two steps (Scheme 1) from a commercially available glycylglycine ethyl ester salt to give threads containing two identical (*i.e.* degenerate) peptide stations A and A′ separated by a third, lipophilic, station B, which in the case of **1c** contained a sulfur atom to allow further derivatization. Treatment of each thread with 4 equiv of isophthaloyl dichloride and *p*-xylylenediamine (Et_3N, $CHCl_3$) gave a mixture of unconsumed thread, the corresponding [2]-rotaxane (**2a**−**c**, produced in 30, 28, and 36% yields, respectively), small amounts of the [3]rotaxanes (3, 2, and 4%), and the octaamide [2]catenane,[7] all of which could be conveniently separated by column chromatography.

The solvent dependent translational isomerism of the [2]-rotaxanes is apparent from comparison of the ^1H NMR spectra of the rotaxanes and threads in DMSO-d_6 and $CDCl_3$ (*e.g.*, **1a** and **2a**, Figure 2). In $CDCl_3$ the macrocycle shuttles between the two degenerate hydrogen bonding (peptide) stations A and A′. The occupied A/A′ station protons (H_{a-e}, Figure 2b) are shielded by the xylylene rings of the macrocycle and experience significant shifts consistent with the four-point intercomponent hydrogen bonding motif shown in Scheme 1, but reduced in magnitude compared to those found[4i] for simple glycylglycine rotaxanes as a result of the shuttle spending only half its time at each station. Protons on the lipophilic station B (H_{f-i}) experience little shielding in $CDCl_3$ compared to the analogous protons on the thread, indicating that the macrocycle spends no appreciable time on station B but just passes through on its way between A and A′. The simplicity of the rotaxane spectrum (one set of resonances for the station A and A′ protons and H_E appearing as a doublet rather than the ABX system observed in unsymmetrical peptide rotaxanes) shows that both spinning of the macrocycle about the thread and shuttling of the macrocycle between stations A and A′ is rapid on the NMR time scale at room temperature. However, cooling below the coalescence temperature for the shuttling process (Figure 2c) freezes the macrocycle at a single peptide station (A or A′) and allows observation of discrete resonances for both occupied and unoccupied stations (unprimed and primed labels, respectively).

Calculations[8] based on variable-temperature ^1H NMR data give a $\Delta G^{\ddagger}$ for shuttling in halogenated solvents ($CDCl_3$ or CD_2-

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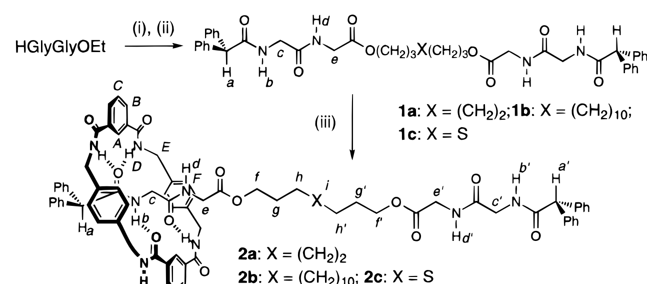
Scheme 1[a]



[a] (i) $Ph_2CHCOCl$, Et_3N, $CHCl_3$, 97%. (ii) diol, $(Bu_2ClSn)_2O$, Δ, PhMe, 86% **1a**, 74% **1b**, 80% **1c**. (iii) Isophthaloyl dichloride, *p*-xylylenediamine, Et_3N, $CHCl_3$, 30% **2a**, 28% **2b**, 36% **2c**.

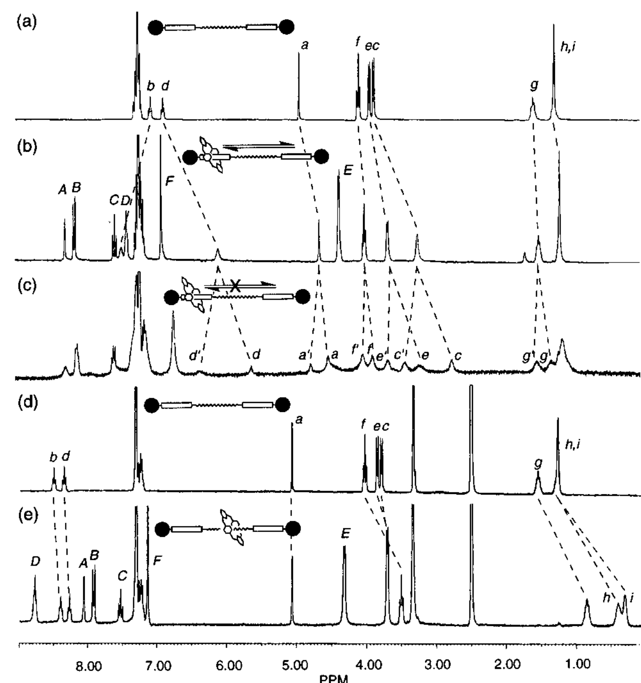


Figure 2. 300-MHz ^{1}H NMR spectra of thread and shuttle (0.02 mmol dm^{-3}): (a) **1a** $CDCl_3$, 298 K; (b) **2a** $CDCl_3$, 298 K; (c) **2a** $CDCl_3$, 234 K; (d) **1a** DMSO-d_6, 298 K; (e) **2a** DMSO-d_6, 298 K.

Cl_2) of 11.2 ± 0.3 kcal mol^{-1} for **2a**, 12.4 ± 0.3 kcal mol^{-1} for **2b**, and 10.9 ± 0.3 kcal mol^{-1} for **2c**, which correspond to shuttling rates of 37000, 5200, and 62000 s^{-1}, respectively, at 298 K. The degeneracy of A and A′ means that once the intercomponent hydrogen bonding is broken shuttling of the macrocycle between them is essentially a one-dimensional diffusion process along the vector of the thread. Thus the increased activation energy cost (1.2 kcal mol^{-1}) for **2b** over **2a** actually reflects the increased distance that the shuttle must travel between the peptide stations!

In response to a major change in the polarity of the environment of the shuttles (changing from halogenated solvents to DMSO-d_6),[9] the macrocycle stops shuttling between stations A and A′ and instead spends nearly all of its time on the lipophilic station B (Figure 1). This is evident from comparison of the ^{1}H NMR spectra of the thread **1a** and rotaxane **2a** in DMSO-d_6 (Figure 2, parts d and e). The protons associated with the peptide units (H_{a-e}) undergo negligible shielding while H_{f-i} on the lipophilic station B are shielded by as much as 0.85 ppm with respect to the thread, with those in the center of the station experiencing the greatest shifts. This, of course, contrasts to the behavior of simple peptide rotaxanes where no specific polarphobic station is present when addition of DMSO leads to nonspecific location of the macrocycle along the thread.

In addition to being able to control the *position* of the macrocycle in peptide-based molecular shuttles, the sensitivity of the intercomponent hydrogen bond strengths can be exploited to control the *rates* of shuttling in nonpolar solvents (Figure 3). Addition of small quantities (0.1−5% by volume) of CD_3-OD to solutions of **2a**−**c** in $CDCl_3$ or CD_2Cl_2 reduces the strengths of the intramolecular hydrogen bonds, decreasing $\Delta G_{shuttling}^{\ddagger}$ and speeding up the shuttling of the macrocycle between the two peptide stations. Increases in shuttling rate occur after addition of as little as 0.1% CD_3OD (which doubles the rate of shuttling of **2c** in CD_2Cl_2 from 8 s^{-1} to 16 s^{-1} at 203 K) and continue up to 5% CD_3OD, which reduces $\Delta G_{shuttling}^{\ddagger}$ of **2c** in CD_2Cl_2 by 2.3 kcal mol^{-1}, equivalent to an increase in the rate of shuttling from 8 s^{-1} to 2300 s^{-1} at 203 K (62000 s^{-1} to >3 million s^{-1} at 298 K).[9]

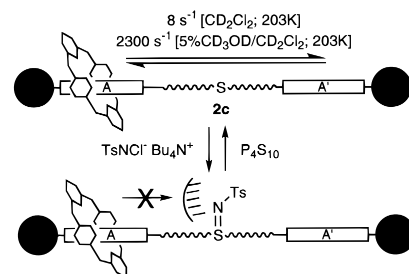


Figure 3. Controlling the *dynamics* of macrocycle translation in multistationed peptide-based molecular shuttles. Addition of CD_3OD to a solution of **2c** in CD_2Cl_2 decreases $\Delta G_{shuttling}^{\ddagger}$ by up to 2.3 kcal mol^{-1}. Tosyl imination of **2c** provides a chemically-reversible steric barrier to shuttling.

Chemical derivatization was also investigated as a means of governing the dynamics of these molecular shuttles (Figure 3). Somewhat surprisingly, oxidation (MCPBA, CH_2Cl_2) of **2c** to the corresponding sulfoxide (0 °C, 1 h, 81%) or sulfone (room temperature, 6 h, 92%) has no effect on the rate of shuttling. Clearly, once the hydrogen bonding of the macrocycle to an individual station is broken, the distance it must travel to the next station is much more influential on the rate of shuttling than steric barriers that are not quite large enough to completely prevent passage of the macrocycle. The shuttling process in **2c** can be stopped, however, by introduction (TsNCl, Bu_4NOH, CH_2Cl_2, 2 h, 93%)[10] of a bulky tosyl group orthogonal to the vector of the thread. Shuttling between the peptide stations can subsequently be reestablished by reduction (P_4S_{10}, CH_2Cl_2, 4 h, 100%)[11] of the imine back to the sulfide, **2c**.[12]

Acknowledgment. This work was supported by the EPSRC IPS managed program.

Supporting Information Available: Experimental details for the synthesis of **2a**, **2b**, and **2c**; NMR data for solvent dependent translational isomerism of **2b** and stopping of shuttling by imination of **2c** (8 pages). See any current masthead page for ordering and Internet access instructions.

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(8) The rates of shuttling were calculated at the coalescence temperature (T_c) by the standard NMR method [Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982] and at temperatures lower than T_c by selective inversion recovery (SIR) experiments where an 180° pulse is given to a resonance and the rate of transfer to the signal it is in slow exchange with (*i.e.* the rate of macrocycle shuttling) is determined directly. The Eyring equation was used to estimate $\Delta G^{\ddagger}$ and extrapolate the rate of shuttling to other temperatures [Sutherland, I. O. *Annu. Rep. NMR Spectrosc.* **1971**, *4*, 71−235].

(9) Similar decreases in $\Delta G^{\ddagger}$ (up to 2.1 and 2.3 kcal mol^{-1}, respectively) were found for addition of 0.1−5% CD_3OD to **2a** and **2b**. Addition of more than 5% CD_3OD begins to decrease the integrity of the positioning of the macrocycle at just the peptide stations. In addition to DMSO-d_6, the macrocycle is positioned primarily at the polarphobic station in tetramethylurea, tetramethylene sulfone, and dimethylformamide.

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(12) For the first example of a *polymeric* hydrogen bond-assembled molecular shuttle see: Gong, C.; Gibson, H. W. *Angew. Chem.* In press.