The Synthesis and Solubilization of Amide Macrocycles *via* Rotaxane Formation

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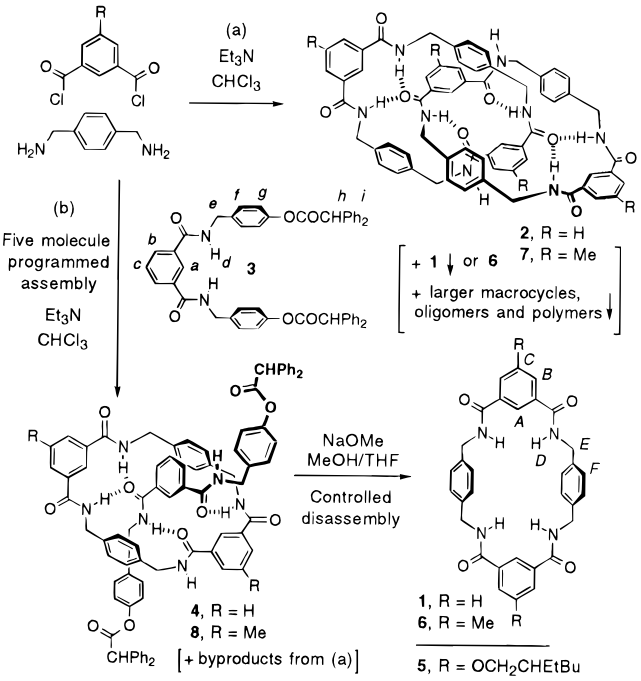
The application of supramolecular chemistry and noncovalent bond assembly processes to the preparation of difficult (or otherwise impossible) to obtain target molecules is an exciting emerging area of synthetic strategy and design.[1] Here we describe how the templated assembly of a macrocycle around a thread to form a [2]rotaxane,[2] followed by its quantitative disassembly into topologically simple components,[3] allows the facile preparation and chromatography-free purification of **1**, a molecule that had eluded isolation by conventional methodologies because of its inherent poor solubility characteristics. The mechanically interlocked intermediate circumvents the lack of solubility of the macrocycle by tying up its amide groups in intramolecular hydrogen bonding resulting in the [2]rotaxane being a remarkable 10^5 times more soluble in chloroform than its cyclic component. Disassembly of the rotaxane by transesterifcation of the bulky "stoppers" gives the target macrocycle in quantitative yield. Films of the liberated macrocycle bind rapidly and reversibly to CO_2.

We recently reported[4] that the [2]catenane **2** is the only product isolable from the condensation of *p*-xylylenediamine with isophthaloyl dichloride (Scheme 1a) with the tetraamido

Scheme 1



macrocycle **1**, intractable from a mixture of other precipitated cyclic oligomers and polymers. Molecules containing a high proportion of amide groups are frequently insoluble (*e.g.*, nylons, kevlar, *etc.*)[5] because of the high enthalpy of formation of intermolecular hydrogen bond networks formed in the solid state. Such problems can, however, be overcome through satisfying hydrogen-bonding requirements intramolecularly (*e.g.*, through protein folding),[6] and we therefore sought a synthetic route to **1** that involved an intermediate which could solubilize the macrocycle through internal hydrogen bonding thereby allowing its isolation and purification *via* standard laboratory techniques.

Equimolar quantities of isophthaloyl dichloride and *p*-xylylenediamine were slowly added to a chloroform solution of **3**,[7] an auxiliary designed to act as both a hydrogen-bonding template for the macrocycle and a "trap" by way of [2]rotaxane formation (Scheme 1b). After 5 equiv was added,[8] the reaction was filtered and washed with acid and base to leave only three components in the organic layer. These were separated by flash chromatography and identified as the unrotaxanated thread **3**, the [2]rotaxane **4** (28% yield), and the [2]catenane **2**. The isolated [2]rotaxane could then be disassembled *via* transesterification of the ester groups (NaOMe in MeOH/THF) to give the desired macrocycle **1**, which precipitated quantitatively and analytically pure from the reaction mixture. The practical utility of this synthetic strategy is further demonstrated by the fact that the purification of the [2]rotaxane is actually unnecessary for large-scale preparation of **1** or other benzylic amide macrocycles since the disassembly step works equally well on an unchromatographed mixture of the thread, [2]rotaxane, and [2]catenane.

The ^{1}H NMR spectra for **1**−**4** in [D_6]DMSO are shown in Figure 1. In the [2]rotaxane spectrum (Figure 1b) the resonances

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(1) A classic example is Cram's isolation of cyclobutadiene where a problematic property of the hydrocarbon (its high chemical reactivity) is overcome by insulating it from other reactive species inside a carcerand [Cram, D. J.; Tanner, M. E.; Thomas, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1024−1027]. Examples involving topologically nontrivial compounds include the Stoddart synthesis of a [3]catenane which is more efficient than that of its central ring component on its own because stabilizing interactions during catenation overcome the kinetic barrier to macrocyclization [Amabilino, D. B.; Ashton, P. R.; Brown, C. L.; Córdova, E.; Godinez, L. A.; Goodnow, T. T.; Kaifer, A. E.; Newton, S. P.; Pietraszkiewicz, M.; Philp, D.; Raymo, F. M.; Reder, A. S.; Rutland, M. T.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Williams, D. J. *J. Am. Chem. Soc.* **1995**, *117*, 1271−1293]. Catenanes are also intermediates in some DNA replication processes [Bates, A. D.; Maxwell, A. *DNA Topology*; Oxford University Press: New York, 1993].

(2) The only other examples of rotaxane syntheses where the macrocycle is cyclized around the thread are based upon the π-electron rich/π-electron deficient system developed by Stoddart [Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725−2828], although Sauvage has applied similar "clipping" strategies extensively in catenane synthesis [Dietrich-Buchecker, C. O.; Sauvage, J. P. *Chem. Rev.* **1987**, *87*, 795−810 and Sauvage, J. P. *Acc. Chem. Res.* **1990**, *23*, 319−327]. Vögtle has recently reported the synthesis of amide-based rotaxanes *via* a "threading" strategy. See: Vögtle, F.; Händel, M.; Meier, S.; Ottens-Hildebrandt, S.; Ott, F.; Schmidt, T. *Liebigs Ann. Chem.* **1995**, 739−743. Vögtle, F.; Jäger, R.; Händel, M.; Ottens-Hildebrandt, S.; Schmidt, W. *Synthesis* **1996**, 353−356. Vögtle, F.; Jäger, R.; Händel, M.; Ottens-Hildebrandt, S. *Pure Appl. Chem.* **1996**, *68*, 225−232. Vögtle, F.; Händel, M.; Jäger, R.; Meier, S.; Harder, G. *Chem. Eur. J.* **1996**, *2*, 640−643. Jäger, R.; Händel, M.; Harren, J.; Rissanen, K.; Vögtle, F. *Liebigs Ann. Chem.* **1996**, 1201−1207.

(3) Degradable catenanes and rotaxanes date back to some of the earliest examples of catenane and rotaxane synthesis [Wasserman, E. *J. Am. Chem. Soc.* **1960**, *82*, 4433−4434 and Harrison, I. T.; Harrison, S. *J. Am. Chem. Soc.* **1967**, *89*, 5723−5724]. The Birmingham group has recently described their utility in the templated synthesis of a "molecular square", see: Raymo, F. M.; Stoddart, J. F. *Pure Appl. Chem.* **1996**, *68*, 313−322. Asakawa, M.; Ashton, P. R.; Menzer, S.; Raymo, F. M.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **1996**, *2*, 877−893.

(4) Johnston, A. G.; Leigh, D. A.; Pritchard, R. J.; Deegan, M. D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1209−1212.

(5) Yang, H. H. *Aromatic High-Strength Fibers*; John Wiley & Sons: New York, 1989.

(6) *Protein Folding;* Creighton, T. E., Ed.; Freeman: New York, 1992.

(7) The thread (**3**) was synthesised in three chromatography-free steps from 4-hydroxybenzonitrile: (i) Raney Ni, NH_3, MeOH; (ii) isophthaloyl dichloride, Et_3N, THF; (iii) $Ph_2CHCOCl$, Et_3N, THF; 56% overall yield.

(8) The reaction reaches a virtual end point after several equivalents of acid chloride and bisamine are added, probably because of the buildup of the concentration of amide, amine, and ammonium species which can compete for and disrupt the hydrogen bonding necessary for the rotaxane assembly mechanism. Filtration and washing of the reaction mixture can be used to increase the yield of [2]rotaxane if necessary.

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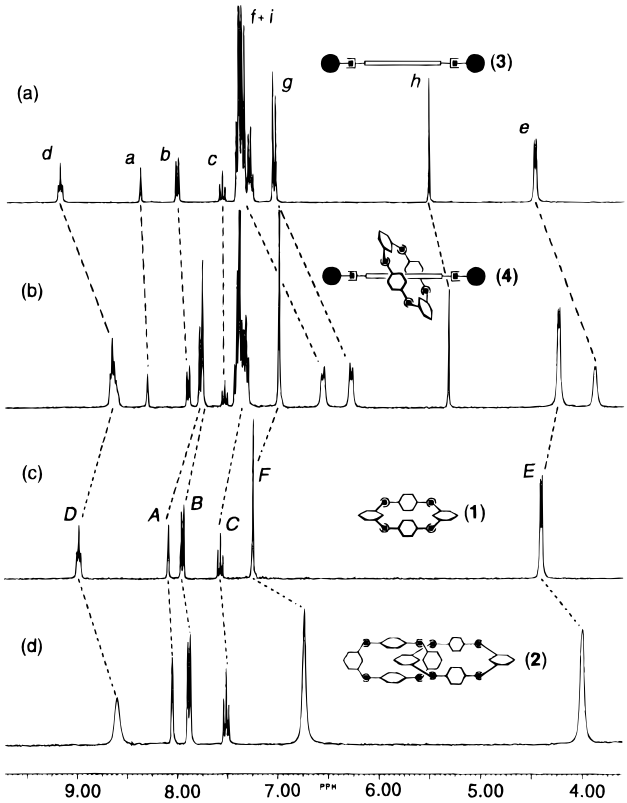

Figure 1. ^{1}H NMR spectra (300 MHz) in [D_6]DMSO of (a) the thread (**3**), (b) the [2]rotaxane (**4**), (c) the macrocycle (**1**), and (d) the [2]-catenane (**2**).[4] The key to the assignments of the resonances of **1**−**4** are shown on the individual components in Scheme 1.

for the benzylic region of the thread (H_{e-h}) are shifted significantly upfield with respect to the analogous protons in the unrotaxanated thread (**3**, Figure 1a) by the xylylene rings of the macrocyclic sheath. In contrast, the protons (H_{a-c}) of the isophthaloyl unit of the thread appear at virtually the same chemical shifts in both rotaxane and unrotaxanated thread, indicating that the preferred relative positions of the two components of the rotaxane in DMSO has the macrocycle located around the polarphobic ends of the thread. The proton resonances in the free macrocycle (**1**, Figure 1c) are shifted downfield with respect to the analogous protons in the [2]-rotaxane (**4**, Figure 1b) and the [2]catenane[4] (**2**, Figure 1d). The broadening of several of the resonances in both interlocked compounds is caused by dynamic processes (*e.g.*, spinning of rings) that are not fully resolved at room temperature.

Comparison of the ^{1}H NMR spectra of the thread and rotaxane in $CDCl_3$ (Supporting Information) shows that in this solvent the macrocycle is hydrogen bonded to the central unit of the thread (one such hydrogen-bonding network is shown in Scheme 1).[9,10] The involvement of five or all six amide groups of the rotaxane in intramolecular hydrogen bonds is doubtless responsible for the high solubility (100 g L^{-1}) of **4** in chloroform compared to that of its component macrocycle (<1 mg L^{-1}). The use of rotaxanation to enhance the solubility of benzylic amide macrocycles in nonpolar solvents compares favorably to the conventional methods of covalent derivatization. The bis-((2-ethylhexyl)oxy) derivative **5** has the highest chloroform solubility (8 g L^{-1}) we have determined to date for any noninterlocked derivative of **1**.

Changing the bisacid chloride from isophthaloyl to 5-methylisophthaloyl also produces a chloroform-soluble (2 + 2) macrocycle (**6**)[11] and was used to assess the templating effect in the rotaxanation reaction by considering the "overall yield" of the (2 + 2) macrocycle through summation of the yields of the macrocycle on its own together with those species where it is also a component, namely the (2 + 2) + (2 + 2) [2]catenane **7** and (2 + 2) + 1 [2]rotaxane **8**. In the absence of the thread the yields of **6** and **7** are 22% and 20%, respectively,[11] an "overall macrocycle yield" of 42%. In the presence of the thread **3**, 2 equiv of acid chloride and 2 equiv of xylylenediamine give the [2]rotaxane **8** (13%), the macrocycle **6** (20%), and the catenane **7** (19%), an overall macrocycle yield of 52% indicating that the thread does actively direct the formation of the macrocycle rather than simply trap it.

Macrocycle **1** was designed as a potential receptor for CO_2.[4,12] Although **1** is insufficiently soluble in nonpolar solvents to assess any hydrogen bond-mediated complexation properties in solution, solid thin films could be assessed for their CO_2 binding affinity by measuring the change in frequency of oscillation between two 5 MHz 60 mm^2 piezoelectric crystals (one coated with 10 μg of **1** deposited from evaporation of a saturated solution of the macrocycle in DMF) that occurs when they are exposed to the analyte gas.[13] Exposure of the two crystals to an atmosphere of CO_2 resulted in a rapid frequency change greater than 300 Hz. A control experiment using a similar crystal coated with the [2]rotaxane **2**, gave a response of <5 Hz upon changing gases.[14] A detailed investigation of the binding properties of films of **1** and related macrocycles is ongoing.

The use of noncovalent bond assembly processes such as rotaxanation[15] and catenation[10a] to alter molecular properties, or to select and/or isolate target structures and intermediates, promises to be a powerful tool with potential for exploitation in many areas. The simple route to **1** employed here demonstrates again the *practicality* of utilizing these strategies in the laboratory.

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Supporting Information Available: Experimental details (5 pages). See any current masthead page for ordering and Internet access instructions.

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(9) Low-temperature ^{1}H NMR spectra of **4** in $CDCl_3$ show that pirouetting of the macrocycle occurs more quickly (890 s^{-1} at 298 K) than shuttling of the macrocycle along the thread (560 s^{-1} at 298 K) reflecting an increased degree of molecular rearrangement that must happen in order for shuttling to occur.

(10) Solvent-dependent translational isomerism has been observed in (a) amphiphilic benzylic amide catenanes [Leigh, D. A.; Moody, K.; Smart, J. P.; Watson, K. J.; Slawin, A. M. Z. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 306−310] and (b) some of the Stoddart catenanes [Ashton, P. R.; Blower, M.; Philp, D.; Spencer, N.; Stoddart, J. F.; Tolley, M. S.; Ballardini, R.; Ciano, M.; Balzani, V.; Gandolfi, M. T.; Prodi, L.; McLean, C. H. *New J. Chem.* **1993**, *17*, 689−695].

(11) Johnston, A. G.; Leigh, D. A.; Nezhat, L.; Smart, J. P.; Deegan, M. D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1212−1216. The ($n + n$) notation indicates the number of reactant molecules used to form each interlocked component of the product.

(12) The convergent amide hydrogen bonding groups at either end of **1** are not required to be orthogonal to each other to bind to the lone pairs of the CO_2 oxygen atoms, as one might assume by analogy to the orientation of C═C═C allene substituents. The $D_{\infty h}$ symmetry of CO_2 confers a symmetrical electron density around the O═C═O axis.

(13) The gas sensing system used was similar to that described by Lu et al. [Lu, C.-J.; Shih, J. S. *Anal. Chim. Acta* **1995**, *306*, 129−137]. Chloroform-soluble analogues of **1**, such as **5** and **6**, bind weakly and reversibly to CO_2 in nonpolar solvents as well as thin films.

(14) This does not prove that the mode of CO_2 binding is primarily within the cavity of **1**, however, since "nondesigned" exocyclic binding which is not normally a significant process in solution can play an important role in gas−solid interface host−guest systems [Grate, J. W.; Patrash, S. J.; Abraham, M. H.; Du, C. M. *Anal. Chem.* **1996**, *68*, 913−917].

(15) Gibson, H. W.; Liu, S.; Lecavalier, P.; Wu, C.; Shen, Y. X. *J. Am. Chem. Soc.* **1995**, *117*, 852−874 and references therein.