Gaining Control over Molecular Threading: Benefits of Second Coordination Sites and Aqueous–Organic Interfaces in Rotaxane Synthesis

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Rotaxane synthesis is facilitated by the presence of two functional groups on the axle reagent; the yield of rotaxane is also substantially improved by reaction in a mixed aqueous–organic phase, compared to a homogeneous phase; the benefit may be associated with reaction at the interface.

High yield [2]rotaxane syntheses are usually performed *via* the intermediate formation of inclusion complexes, an approach that often requires the cyclic and/or linear components to have special structural features.[1] In contrast, polymeric rotaxanes can be prepared from simple polyglycols or similar molecules by the spontaneous sequential stringing of cyclic molecules onto a polymeric chain which contains many binding sites.[2] Here we report the formation of [2]rotaxanes from monofunctional and bifunctional 'axle' molecules including the isolation and X-ray structure of the rotaxane prepared from the bifunctional molecule. We also show that the yield of rotaxane is improved by synthesis in a biphasic system.

Rotaxane formation can be achieved by threading an axle reagent, bearing a bulky 'stopper' substituent on one end and a functional group on the other, through a molecular torus, followed by the reaction of the functional group with a blocking reagent. The functional group may serve two functions: coordination to the torus prior to reaction, and then as the site of reaction with the blocking group. Scheme 1 illustrates the system of principal interest in which amines **I** or **II** form amides **III** or **IV** by combination with blocking group **V**, and in the presence of crown ether **VI** produce rotaxanes **VII** or **VIII**. Several factors facilitate the threading process: (*a*) the switching of axle–torus coordination from the first (or terminal, **IX**) to the second (or internal, **X**) binding site of the difunctional axle molecule; (*b*) π–π stacking interactions between aromatic groups on the axle and torus components of the 'pre-rotaxane' complex (facilitating the switching of the coordination of the torus to the internal functional group); and (*c*) selective solvation of the hydrophilic terminal functional at the organic–aqueous interface (followed by blocking with a water soluble reagent).

For the components of the rotaxane system, dibenzo-[24]crown-8 **VI** was chosen as the torus molecule because it forms stable complexes with alkylammonium salts[3] and has a ring size big enough to accommodate the proposed molecular thread. The monofunctional axle is 4-anthracen-9-yl-butylamine (**I**), which was prepared in 72% yield from 9-(4-bromobutyl)-anthracene *via* the standard Gabriel method, followed by phthalimide hydrazinolysis. The bifunctional axle is *N*-1-anthracen-9-yl-methylethane-1,2-diamine **II**, prepared in 80% yield from 9-(chloromethyl)anthracene and an excess of ethylenediamine in dioxane.†

The water soluble acylating agent **V** was prepared by a route similar to that described[4] for 2-(benzoylthio)-1-methyl pyridinium chloride, from the reaction of 3,5-dimethylbenzoyl-chloride and 1-methyl-2(1*H*)-pyridothione in acetonitrile. The product **V**‡ is hydroscopic and was found to be stable in aqueous solution for at least 1 h. As **V** is also soluble in chloroform, the rotaxane-forming reaction can be performed in either a homogeneous organic solution or a biphasic (organic–aqueous) system; because the acylating agent **V** is concentrated significantly in the aqueous phase, reaction at the interface may contribute substantially to the overall process.

Isolable yields of rotaxane were only obtained from amine **II**. The products in the organic phase from the reaction in H_2O–$CHCl_3$ were, after drying, separated by column chromatography on silica gel with a $CHCl_3$–MeOH mixture. The rotaxane fraction **VIII** was obtained in approximately 20% yield as a viscous oil, containing rotaxane cation and a mixture of anions. The rotaxane was obtained in crystalline form as the ethylsulfate salt.§

The crystal structure (Fig. 1) clearly shows the axle–torus interactions, with H-bonds between the amine nitrogen and the oxygen atoms of the crown. Contact is also evident between the anthracene and one crown benzo group; in addition, the anion is H-bonded to the amide nitrogen. The mean plane of the anthracene moiety makes a 7.4(7)° angle with the mean plane of one benzo group, with the shortest carbon–benzo-centre distance of 3.67(1) Å.

Using the monofunctional axle, trace amounts of rotaxane **VII** were produced in homogeneous solution by mixing amine salt **I**·HSCN with an excess of crown **VI** in chloroform. Tributylamine was then added to trap the acid which forms during the acylation reaction. The acylating agent **V** was added last. The heterogeneous reaction was performed in an analogous

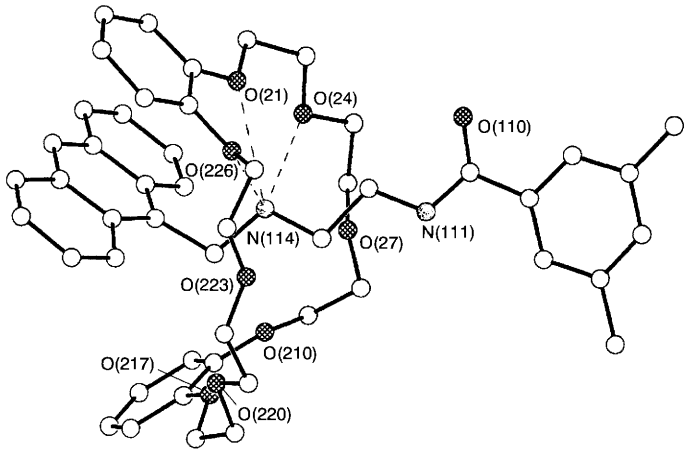

Fig. 1 View of the rotaxane cation **VIII** (H atoms omitted). The hydrogen bonds between the amine nitrogen and the crown ether oxygen atoms are shown as broken lines (lengths 2.87–2.99 Å).

manner except that the acylating agent was dissolved separately in water and the reaction mixture was shaken vigorously for 1 h. Formation of rotaxane in both cases was detected by FAB-MS. Peak 830 can be attributed either to the rotaxane or to a crown–amide adduct. In a separate experiment, however, amide **III** does not form a FAB-MS detectable adduct with **VI**. Moreover, peak 830 does not disappear in the mass spectrum after the addition of a large excess of another competing amide, *N*-ethylacetamide, which does form a FAB-detectable complex with **VI**. Although the rotaxane **VII** was detected by FAB-MS, it can only be produced in trace amounts since neither ^{1}H NMR nor TLC indicated the presence of substantial quantities.

With the bifunctional axle, strictly parallel homogeneous and heterogeneous reactions were conducted using the amine salt **II**·HSCN, crown **VI**, and acylating agent **V**; rotaxane **VIII** with m/z = 831 was detected by FAB-MS. In contrast to amide **III**, amide **IV** forms a FAB-MS detectable adduct with crown **VI**, whose mass spectral peak disappears completely upon the addition of KSCN. However, the rotaxane peaks from both the homogeneous and heterogeneous experiments remain intact under the same treatment. Its ^{1}H NMR spectrum also includes peaks from the crown ether component, which are readily distinguishable from those of the free crown ether (assigned by comparison with the spectrum of pure rotaxane). The yield and percentage conversion of starting material were estimated from relative integrals in NMR spectra. The yield from the interfacial experiment is approximately two times higher than that from the homogeneous experiment (22 and 12%, respectively, based on starting material). Overall conversion of starting material was 50 and 40%, respectively.

The increased yield of rotaxane in the interfacial experiment is primarily attributed to enhanced selectivity for rotaxane formation. We believe that complex **IX** (Scheme 1) has a tendency to accumulate at the interface owing to the surfactant properties of crown ethers and the dipolar structure of compound **II**·HSCN. Additional hydration energy could be gained through the threading of a primary amino-group through the macrocyclic ring followed by the transfer of this group into the aqueous phase. During this process, complex **IX**, which has the primary ammonium group coordinated, is transformed into complex **X**, which has the secondary ammonium group coordinated. Complex **X** is pre-organized for reaction with the acylating agent, and for the formation of the rotaxane **VIII** (Scheme 1).This strategy is related to previously described work on the formation of polyrotaxane or polycatenane mixtures *via* conventional interfacial or surface polycondensation reactions in which crown ethers, cyclodextrins, or cyclosiloxanes were added to reaction mixtures.[5]

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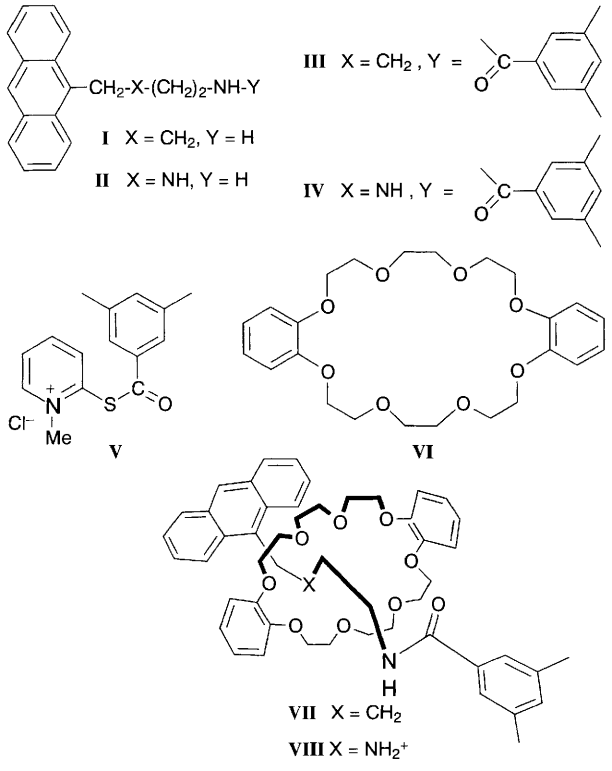
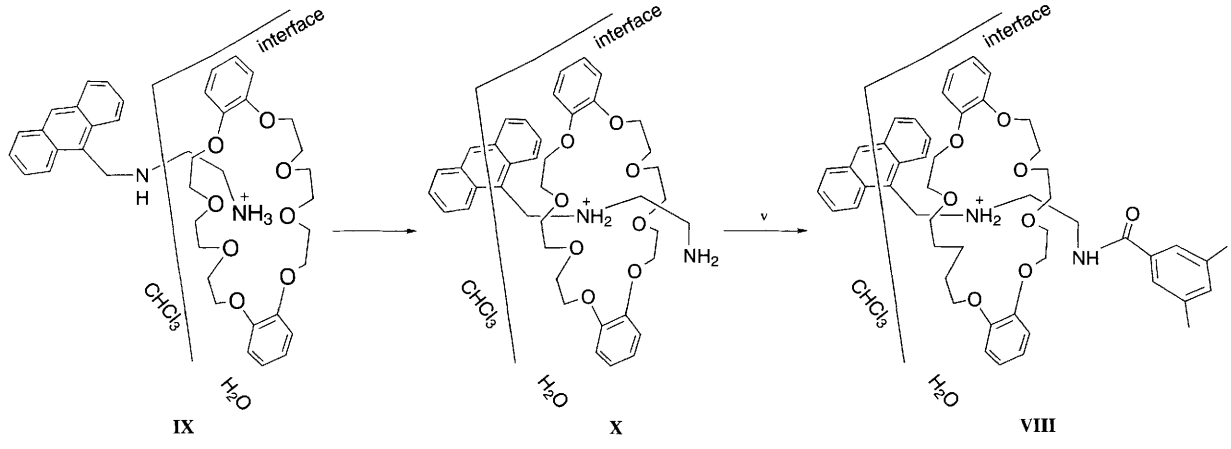


Footnotes

† Excess ethylenediamine was removed first by extraction into dilute sodium hydroxide solution. Any remaining ethylenediamine was removed by vacuum distillation. Monothiocyanate salts of **I** and **II** were prepared by the quantitative neutralization of the corresponding free base with 1 equiv. of an ethanolic solution of thiocyanic acid (prepared from potassium thiocyanate and perchloric acid).

Selected spectroscopic data: For **I**·HSCN: FAB-MS: m/z 250, 307, 499, corresponding to $[M - SCN]^+$, $[M - H]^+$, and $[2M - H - 2SCN]^+$, respectively; ^{1}H NMR [$(CD_3)_2SO$, 500 MHz, 20 °C] 1.75 (m, 4H), 2.83 (t, J 7 Hz, 2H), 3.63 (t, J 6.5 Hz, 2H), 7.49–7.76 (m, 7H), 8.08 (d, J 8.5 Hz, 2H), 8.33 (d, J 8.5 Hz, 2H), 8.48 (s, 1H). For **II**·HSCN: FAB-MS: m/z 191, 251 corresponding to $[M - NH(CH_2)_2SCN]^+$ and $[M - SCN]^+$; ^{1}H NMR [$(CD_3)_2SO$, 500 MHz, 20 °C]: 2.95 (m, 4H), 4.66 (s, 2H), 5.99 (br s, 4H), 7.52 (t, J 6.5 Hz, 2H), 7.58 (t, J 6.5 Hz, 2H), 8.08 (d, J 8.5 Hz, 2H), 8.43 (d, J 8.5 Hz, 2H), 8.55 (s, 1H).

‡ *Spectroscopic data* for **V**: FAB-MS: m/z 258 corresponding to $[M - Cl]^+$, ^{1}H NMR (D_2O, 500 MHz, fresh solution, 20 °C) 2.26 (s, 6H), 4.39 (s, 3H), 7.27 (s, 1H), 7.46 (s, 2H), 8.19 (m, 1H), 8.25 (d, J 8 Hz, 1H), 8.60 (m, 1H), 9.15 (d, J 6 Hz, 1H).



Scheme 1 Interfacial synthesis of rotaxane **VIII** from the bifunctional axle molecule **II**

§ *Spectroscopic data* for **VIII**·$SO_4C_2H_5$: FAB-MS: *m/z* 831 corresponding to [**VIII**]$^+$, ^{1}H NMR ($CDCl_3$, 500 MHz, 20 °C): 1.21 (t, *J* 7 Hz, 3H), 2.38 (s, 6H), 3.70 (m, 4H), 3.82 (m, 4H), 3.90 (m, 10 H), 4.07 (m, 4H), 4.19 (m, 8H), 5.57 (t, *J* 5.5 Hz, 2H), 6.21 (d, *J* 3.5 Hz, 4H), 6.56 (m, 4H), 7.10 (s, 1H), 7.26 (br s, 2H + $CHCl_3$), 7.38 (t, *J* 7 Hz, 2H), 7.49 (t, *J* 7 Hz, 2H), 7.70 (s, 2H), 7.73 (d, *J* 8.5 Hz, 2H), 7.98 (s, 1H), 8.57 (d, *J* 9 Hz, 2H), 8.89 (br s, 1H). X-Ray quality crystals (mp 186–189 °C) were obtained after recrystallization from a chloroform–ethyl acetate mixture.

Crystal data for $C_{52}H_{64}N_2O_{13}S$, M = 957.11, triclinic space group $P\bar{1}$, a = 12.374(6), b = 15.025(12), c = 15.075(8) Å, α = 109.67(6), β = 106.48(4), γ = 97.52(5)°, U = 2450(3) Å^3 (by least squares refinement on diffractometer angles for 16 reflections), T = 200(2) K, λ = 0.71073 A, Z = 2, D_{cal} = 1.297 Mg m^{-3}, $F(000)$ = 1010. Crystal dimensions 0.31 × 0.31 × 0.30 mm, μ(Mo-Kα) = 0.133 mm^{-1}. Siemens P3R3 four-circle diffractometer, ω–2θ mode. Maximum θ was 22.5°. 7504 reflections measured, 6430 unique. The structure was solved by direct methods using SHELXTL PLUS and refined using SHELXTL.[6] Anisotropic displacement parameters were used for all non-H atoms; H-atoms were given isotropic displacement parameters of U = 0.08 Å^2. The weighting scheme was $w = 1/[\sigma^2(F_o^2) + (0.1557P)^2 + 1.9851P]$ where $P = (F_o^2 + 2F_c^2)/3$. Goodness-of-fit on F^2 was 1.015, $R1$ [for 3593 reflections with $I > 2\sigma(I)$] = 0.0927, $wR2$ = 0.2826. Data/restraints/parameters 6427/0/616. The relatively large $R1$ is not unexpected in view of the weak scattering at high angles. Largest ΔF peak and hole 0.586 and −0.343 e Å^{-3}. Atomic coordinates, bond lengths and angles and thermal parameters, have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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