Letter

Reversible synthesis of π-associated [2]catenanes by ring-closing metathesis: towards dynamic combinatorial libraries of catenanes

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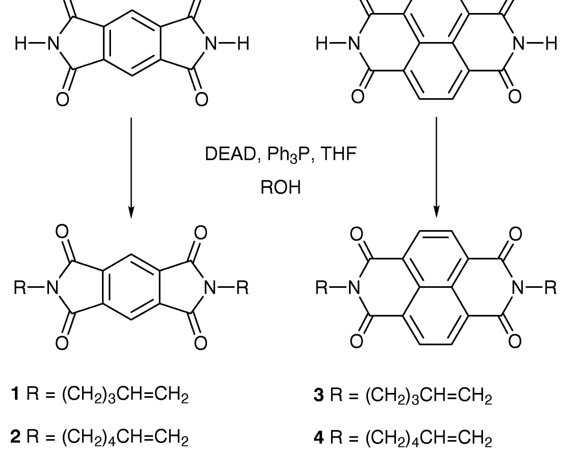
Ring-closing metathesis of aromatic diimides substituted with olefin-terminated alkyl chains in the presence of a dinaphtho crown ether affords neutral [2]catenanes. Templating π-donor/π-acceptor interactions are exploited to drive mechanical interlocking and favour production of the more thermodynamically stable catenane products. Structure proof was provided by single-crystal X-ray synchrotron diffraction of a representative catenane.

In this letter we describe how catalytic ring-closing metathesis (RCM) may be used to prepare neutral π-associated [2]catenanes under thermodynamic control.[1] The approach employs our well-established kinetically controlled catenane assembly process based on the electronic complementarity of π-deficient aromatic diimides and π-rich aromatic diethers.[2] We,[3] and others,[4] have highlighted the need to engineer reversibility into syntheses of complex molecular systems in order that 'incorrect' bond formation can be proof-read and repaired. This capability may be programmed into a molecular system in the form of non-covalent interactions favouring a particular supramolecular geometry; for example, interactions between the component rings of a catenane may be exploited to favour production of the interlocked ring compound over the free macrocycles. This approach has been demonstrated with two 'magic ring' catenane syntheses, that is, the mutual interlocking of two *preformed* rings, directed and driven by hydrophobic and hydrogen-bonding interactions, respectively.[5,6]

The concept of product selection *via* the expression of a thermodynamic preference has appeared in various contexts in recent years. Lehn and coworkers have demonstrated various modes of self-sorting and selection in a variety of linear and circular inorganic helicates.[7–9] Progression to self-sorting at the covalent level has been achieved for mixtures of building blocks where a thermodynamic driving force is provided by the conformational stability of particular macrocyclic products.[10] Thermodynamic templating has been demonstrated for an equilibrating mixture of cyclocholate receptors where the addition of alkali metals is observed to alter the distribution of cyclic oligomers,[11] and, very recently, Hioki and Still have reported the substrate-promoted chemical amplification of a macrocyclic receptor containing reversible covalent linkages.[12] Finally, we have shown that reversible [2]catenane formation may be quantitatively driven by donor–acceptor interactions in a system utilizing reversible zinc(II)-bipyridyl ligation.[13]

To progress to wholly covalent systems we required a reversible bond-forming process compatible with the rather weak nature of donor-acceptor interactions. Catalytic RCM operates in chlorinated organic solvents at room temperature and has previously been applied to many complex macrocycle syntheses, including catenanes[14] and knots.[15] Accordingly, we equipped the electron deficient diimide components of our system with olefin-terminated alkyl substituents. Mitsunobu alkylation[16] of the parent diimides proved an efficient and versatile procedure and provided diolefins **1**–**4** in good yield from the corresponding unsaturated alcohols (Scheme 1).†

Addition of two molar equivalents of diimide derivatives **2** or **4** to a 5 mM solution of crown ether **5** in chloroform established familiar orange- and purple-coloured solutions respectively, the result of formation of donor–acceptor complexes. Subsequent addition of Grubbs' catalyst **6** (0.05–0.10 equiv.) led to smooth formation of [2]catenanes **7** and **9**; periodic LC-MS analyses of the reaction mixtures revealed the presence of the catenanes at *m*/*z* 1358 and 1458 ($[M + NH_4]^+$), respectively; little change in the product distributions was



Scheme 1 Preparation of olefinic aromatic diimides *via* Mitsonobu alkylation

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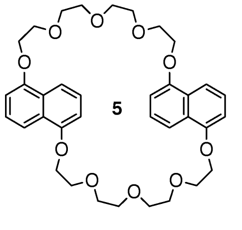
† Example diolefin synthesis, **2**: Pyromellitic diimide (200 mg, 0.93 mmol) was suspended in 15 mL of dry THF containing 5-hexen-1-ol (185 mg, 222 μL, 1.9 mmol) and Ph_3P (485 mg, 1.9 mmol). Diethylazodicarboxylate (322 mg, 291 μL, 1.9 mmol) was added dropwise *via* syringe under argon and the clear yellow solution was stirred for 15 min. Flash column chromatography (SiO_2; $CHCl_3$) gave **2** ($R_f \approx 0.6$) as a pale yellow solid (232 mg, 66%): ^1H NMR (250 MHz, $CDCl_3$) δ 8.25 (s, 2H), 5.84–5.68 (m, 1H), 5.04–4.92 (m, 2H), 3.74 (t, $J = 7$ Hz, 2H), 2.10 (q, $J = 7$ Hz, 2H), 1.73 (quintet, $J = 7$ Hz, 2H), 1.45 (quintet, $J = 7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.28, 138.04, 137.26, 118.15, 115.08, 38.56, 33.14, 27.85, 26.05.

observed after 3 days. Preparative TLC gave around 20% yields of [2]catenane **7** as a mixture of three finely separated alkene isomers (*cis*/*cis*, *cis*/*trans*, *trans*/*trans*). Hydrogenation of the mixture (H_2, Pd–C) gave a single saturated interlocked product **8** in near quantitative yield.‡§ Isolated yields of around 50% (post-hydrogenation) were obtained for [2]catenane **11**, consistent with the stronger electron-accepting nature of naphthalene diimides; this increase parallels the results of kinetic syntheses of related systems.[2]

As with related catenanes in this series only very tiny crystals could be obtained (from DMSO-d_6). However, the solid-state structure of a representative example has been obtained from one such crystal using X-ray synchrotron diffraction. The structure of **11** reveals a familiar arrangement of mutually interlocked complementary macrocycles with the planes of the electron-rich and electron-deficient subunits adopting an alternating parallel stacked arrangement with interplanar spacings of around 3.5 Å. These intramolecular donor–acceptor stacking interactions are perpetuated intermolecularly, individual [2]catenanes stacking one upon another to continue the alternating pattern (Fig. 1). However, whilst the aromatic subunits within individual catenanes are essentially parallel individual catenanes are tilted by 6–7° with respect to each other, producing a pronounced 'wave' in the extended donor–acceptor stack. The overlap orientation of the sandwiched naphthalene diimide unit is similar to that previously observed in a donor-acceptor co-crystal comprised of the components of **11**, the long axes being disposed in a parallel fashion.[17] The external diimide is twisted relative to the included subunit, presumably as a consequence of the structural organization needed to accommodate the lengthy tetraethylene glycol and decyl linker chains. The substantial twist angle (≈40°) between the long axes of the diimide components renders this macrocycle, and hence individual [2]catenane molecules, chiral. The extended donor–acceptor stacks of chiral [2]catenanes in crystals of **11** are built of alternating enantiomers (Fig. 1), in contrast to our earliest system where individual columns of catenanes are comprised of a single enantiomer.[2]

Omitting the crown from the initial RCM reaction of **4** prompted the formation of a white precipitate, presumably comprised of a variety of linear and cyclic oligomeric species.¶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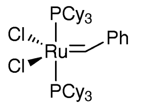
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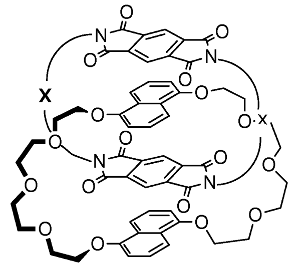
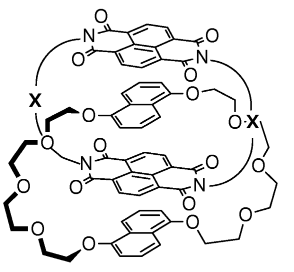

7 X = $-(CH_2)_4CH{=}CH(CH_2)_4-$
8 X = $-(CH_2)_{10}-$


9 X = $-(CH_2)_4CH{=}CH(CH_2)_4-$
10 X = $-(CH_2)_3CH{=}CH(CH_2)_4-$
11 X = $-(CH_2)_{10}-$
12 X = $-(CH_2)_9-$

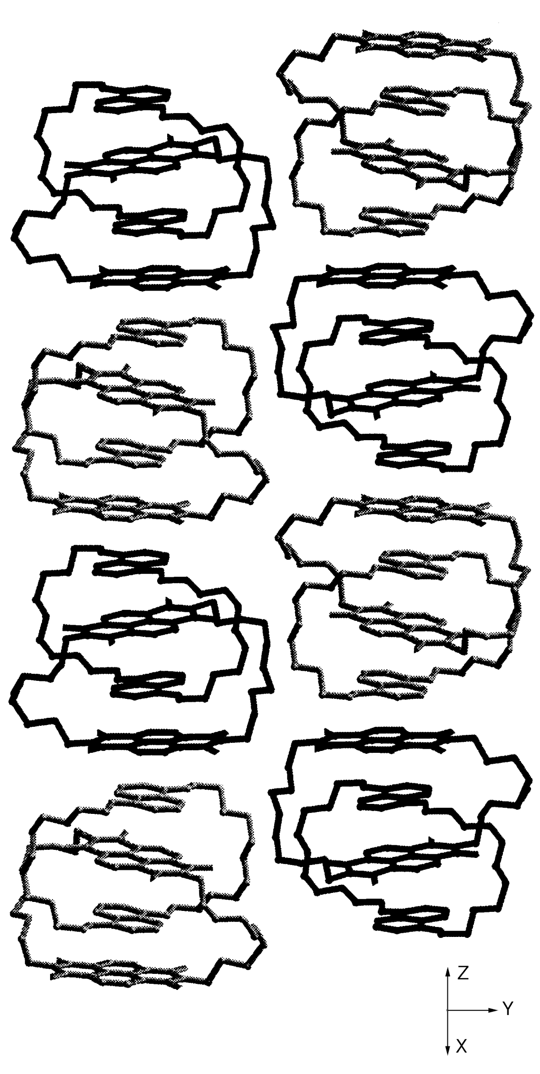


Fig. 1 Solid-state structure of **11** displayed using Cerius Molecular Simulations software (alternating enantiomers in the stacks have different shading)

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‡ Example catenane synthesis, **8**: Grubbs' catalyst (1 mg, 1.25 μmol; Strem Chemicals, Royston, UK) was added to a solution of diolefin **2** (19 mg, 50 μmol) and crown **5** (16 mg, 25 μmol) in dry $CHCl_3$ (5 mL, ≈5 mM) under argon. After three days stirring at room temperature LC-MS analysis revealed the presence of catenane **7** at *m*/*z* 1358 $[M + NH_4]^+$; for competition experiments this material could be isolated by repeated preparative TLC (SiO_2; MeOH–$CHCl_3$, 1:99) to afford pure **7** as a mixture of three isomers (7 mg, 21%). Alternatively, the metathesis mixture could be hydrogenated ($CHCl_3$; H_2, Pd–C) to afford **8** as the single saturated interlocked product (LC-MS; *m*/*z* 1362, $[M + NH_4]^+$) after preparative TLC separation (SiO_2; MeOH–$CHCl_3$, 0.5:99.5).

§ Crystal data for **11**: $C_{84}H_{92}N_4O_{18}$, $M_r = 1445.6$, monoclinic, $a = 12.741(2)$, $b = 28.768(4)$, $c = 21.035(3)$ Å, $b = 106.620(10)°$, $U = 7387.9(19)$ Å^3, space group $P2_1/n$, $Z = 4$, $\rho_{calcd} = 1.30$ g cm^{-3}. Crystal size 0.17 × 0.06 × 0.01 mm. Bruker SMART CCD diffractometer on the single-crystal diffraction station 9.8 at the Daresbury Laboratory Synchrotron Radiation Source (UK): 150 K, $\lambda = 0.6883$ Å. θ range for data collection 3.46 to 25.00°; corrections were applied for incident beam decay. The structure was solved by direct methods and refined by full-matrix least-squares analysis on F^2; 38373 reflections measured of which 14127 were observed as unique ($R_{int} = 0.08$). Despite substantial disorder in one of the C_{10} chains the structure refined to $R = 0.075$, $R_w = 0.145$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this material should quote the full literature citation and the reference number 102181.

¶ The composition of the precipitate has proved difficult to ascertain, though FAB-MS analysis does reveal the presence of a cyclic dimer: *m*/*z* 805, $[M + H]^+$.

After three days of stirring, half a molar equivalent of crown **5** and additional catalyst were added. The production of [2]catenane product could be monitored by periodic LC-MS analysis; after three further days stirring hydrogenation and separation as described before afforded similar isolated yields of **11** as obtained from direct RCM of **4** in the presence of **5**. The reversible nature of the olefin bond-forming reaction endows the system with the ability to recover from an energetically unfavourable state and drive molecular interlocking. This experiment is identical in concept to Grubbs and coworkers' alkali metal-templated conversion of an olefinic ethylene–glycol polymer to discrete unsaturated crown macrocycles.[18]

For an unambiguous demonstration of reversibility in these reactions we performed competition experiments wherein a preformed [2]catenane is challenged with the addition of an alternative diimide derivative. Catalytic RCM of catenane **7** with an excess of diolefin **4** yielded some of the predicted more thermodynamically stable interlocked product **9**, but only after protracted reaction. Similarly, addition of an excess of the shorter five-carbon chain naphthalene diimide derivative **3** to [2]catenane **9** also indicated slow incorporation of the new diolefin to afford small amounts of [2]catenane **10**. It is clear that, at these solubility-limited concentrations, slow reaction kinetics militate against attainment of ideal statistical distributions. It is also likely that the current systems lack sufficient thermodynamic gradients between closely related derivatives for chemical evolution to be observed on a reasonable time scale. Perhaps an additional problem lies in attempting to maintain several competing species simultaneously in solution. Nevertheless, a 1 : 2 : 2 ratio of crown **5** to diolefins **3** and **4** at 5 mM crown concentration gave around 70% isolated yield of C_{10}- and C_9-linked interlocked products **11** and **12** after hydrogenation; no C_8-linked catenane was observed. The C_{10}- and C_9-linked products were isolated in an approximate ratio of 1 : 5, perhaps indicating a thermodynamic preference for the shorter linked derivative **10** (at least prior to hydrogenation) arising from a tighter mutual fit of the component macrocycles.

These results show that it is possible to create a range of catenanes under reversible conditions and that hydrogenation provides a simple method to lock irreversibly the resulting rings in place. They also bring closer the creation of dynamic combinatorial libraries[19] of catenanes from mixtures of π-rich and π-poor components, especially when coupled with a method for reversibly controlling the ability of these components to interact.[20]

Acknowledgements

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References

1 For a comprehensive account of catenane chemistry see: D. B. Amabilino and J. F. Stoddart, *Chem. Rev.*, 1995, **95**, 2725.
2 D. G. Hamilton, J. E. Davies, L. Prodi and J. K. M. Sanders, *Chem. Eur. J.*, 1998, **4**, 608.
3 D. G. Hamilton, N. Feeder, L. Prodi, S. J. Teat, W. Clegg and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1998, **120**, 1096.
4 D. B. Amabilino, P. R. Ashton, L. Pérez-García and J. F. Stoddart, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2378.
5 M. Fujita, F. Ibukuro, H. Hagihara and K. Ogura, *Nature* (*London*), 1994, **367**, 720.
6 D. A. Leigh, personal communication.
7 J.-M. Lehn, A. Rigault, J. Siegel, J. Harrowfield, B. Chevrier and D. Moras, *Proc. Natl. Acad. Sci. USA*, 1987, **84**, 2565.
8 B. Hasenknopf, J. M. Lehn, B. O. Kneisel, G. Baum and D. Fenske, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1838.
9 B. Hasenknopf, J.-M. Lehn, N. Boumediene, A. Dupont-Gervais, A. Van Dorsselaer, B. Kneisel and D. Fenske, *J. Am. Chem. Soc.*, 1997, **119**, 10956.
10 S. J. Rowan, D. G. Hamilton, P. A. Brady and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1997, **119**, 2578.
11 P. A. Brady and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3237.
12 H. Hioki and W. C. Still, *J. Org. Chem.*, 1998, **63**, 904.
13 A. C. Try, M. M. Harding, D. G. Hamilton and J. K. M. Sanders, *Chem. Commun.*, 1998, 723.
14 B. Mohr, M. Weck, J.-P. Sauvage and R. H. Grubbs, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1308.
15 C. Dietrich-Buchecker, G. N. Rapenne and J.-P. Sauvage, *Chem. Commun.*, 1997, 2053.
16 O. Mitsunobu, W. Makato and T. Sano, *J. Am. Chem. Soc.*, 1972, **94**, 679.
17 R. S. Lokey and B. L. Iverson, *Nature* (*London*), 1995, **375**, 303.
18 M. J. Marsella, H. D. Maynard and R. H. Grubbs, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1101.
19 S. J. Rowan, P. S. Lukeman, D. J. Reynolds, J. K. M. Sanders, *New J. Chem.*, 1998, **22**, 1015.
20 D. G. Hamilton and J. K. M. Sanders, *Chem. Commun.*, 1998, 1749.

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