Organic "Magic Rings": The Hydrogen Bond-Directed Assembly of Catenanes under Thermodynamic Control

Timothy J. Kidd,† David A. Leigh,*,† and Andrew J. Wilson†

Department of Chemistry
University of Manchester Institute of Science and Technology
Sackville Street, Manchester M60 1QD, United Kingdom

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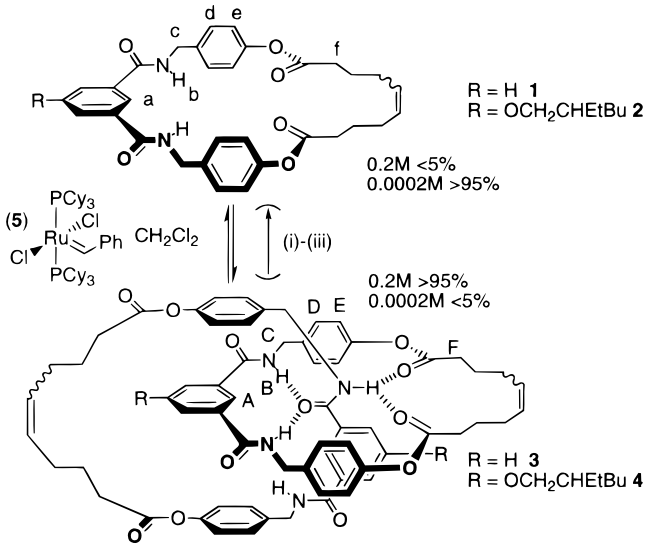
A common feature of most current strategies used to prepare mechanically interlocked rings (catenanes) is that the final macrocyclization reaction is generally carried out under *kinetic* control.[1,2] As a result, if ring closure does not proceed via an already threaded precursor, "mistakes"—noninterlocked macrocycles—are produced that cannot be "corrected". Catenane formation under *thermodynamic* control ("strict self-assembly"[2]) has previously been achieved with use of weak, reversibly formed, metal−ligand bonds[3] with the result that the strong intercomponent interactions normally employed to direct mechanical interlocking can be exploited to bring about very high yields of catenanes.[3b−g] In several celebrated examples,[3b−e] Fujita et al. have described systems where metallomacrocycles can be converted almost exclusively into [2]catenanes through hydrophobic binding—a feat noted as being reminiscent of the conjurors trick of interlocking seemingly "magic" rings. Here we report that a similar approach can be applied to wholly organic ring systems by exploiting the hydrogen bond-mediated assembly of self-complementary macrocycles and the current generation of highly versatile olefin metathesis catalysts[4] in reversible ring opening and closing (RORCM) reactions.[5−7] Under appropriate RORCM conditions (in which, possibly uniquely for a chemical transformation requiring external reagents, there is virtually[8] no net change in the number, type, stereochemistry, or sequence of covalent

Scheme 1. Thermodynamically Controlled Self-Assembly/Disassembly of Benzylic Amide Macrocycles and [2]Catenanes under RORCM[a]



[a] Disassembly of the [2]catenanes into their component rings can also be achieved by switching off the intercomponent hydrogen bonding prior to RORCM: (i) $(CF_3CO)_2O$, Δ, 100%; (ii) **5**, CH_2Cl_2; (iii) MeOH, Δ, 100%.

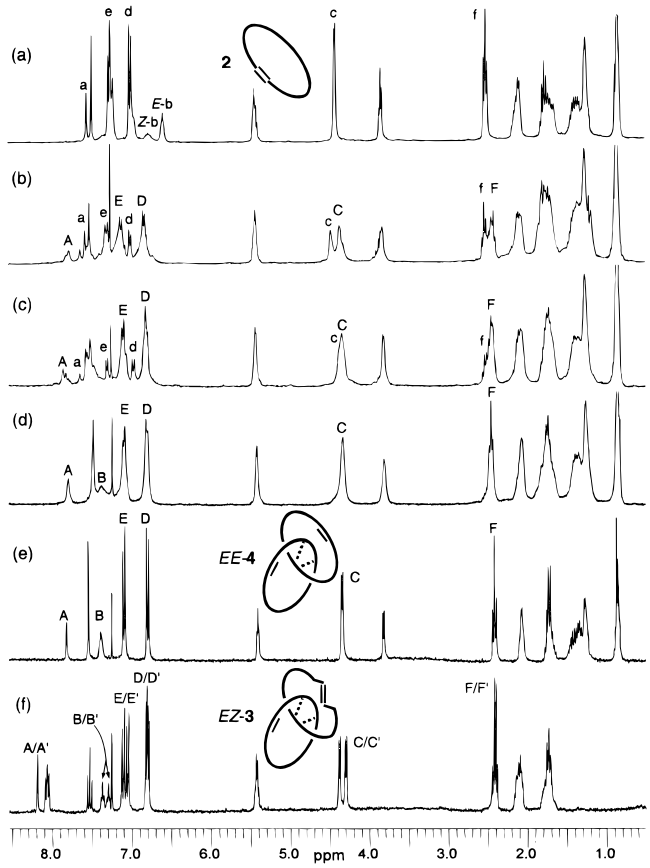


Figure 1. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of (a) the product mixture at equilibrium from RORCM from initial concentrations of **2**/**4** of 0.0002 M, (b) 0.002 M, (c) 0.02 M, and (d) 0.2 M; (e) homocircuit [2]catenane *EE*-**4**; and (f) heterocircuit [2]catenane *EZ*-**3**. Small case letters denote resonances from the noninterlocked macrocycle; upper case letters denote the equivalent resonances in the [2]catenanes.

† Current Address: Department of Chemistry, University of Warwick, Coventry CV4 7AL, United Kingdom.

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(2) Processes which utilize noncovalent forces to assemble an interlocked complex that is subsequently "captured" by irreversible covalent bond formation ("self-assembly with covalent modification") only operate under thermodynamic control *before* the final cyclization step [Amabilino, D. B.; Ashton, P. R.; Pérez-García, L.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2378−2380]. "Strict self-assembly" pathways spontaneously and reversibly convert components into products at thermodynamic equilibrium [Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154−1196].

(3) (a) Gruter, G.-J. M.; de Kanter, F. J. J.; Markies, P. R.; Nomoto, T.; Akkerman, O. S.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1993**, *115*, 12179−12180. (b) Fujita, M.; Ibukuro, F.; Hagihara, H.; Ogura, K. *Nature* **1994**, *367*, 720−723. (c) Fujita, M.; Ibukuro, F.; Yamaguchi, K.; Ogura, K. *J. Am. Chem. Soc.* **1995**, *117*, 4175−4176. (d) Fujita, M.; Ibukuro, F.; Seki, H.; Kamo, O.; Imanari, M.; Ogura, K. *J. Am. Chem. Soc.* **1996**, *118*, 899−900. (e) Fujita, M.; Aoyagi, M.; Ibukuro, F.; Ogura, K.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 611−612. (f) Whang, D.; Park, K.-M.; Heo, J.; Ashton, P.; Kim, K. *J. Am. Chem. Soc.* **1998**, *120*, 4899−4900. (g) Try, A. C.; Harding, M. M.; Hamilton, D. G.; Sanders, J. K. M. *Chem. Commun.* **1998**, 723−724.

(4) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450.

(5) For tandem RORCM reactions which covert one ring system into a *different* ring system see: Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634−6640.

(6) For a highly efficient catenane synthesis by ring closing metathesis (RCM) see: Mohr, B.; Weck, M.; Sauvage, J.-P.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1308−1310.[13,14] For the synthesis of a molecular knot by RCM see: Dietrich-Buchecker, C.; Rapenne, G.; Sauvage, J.-P. *Chem. Commun.* **1997**, 2053−2054.

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bonds), isophthaloyl benzylic amide macrocycles possessing an internal olefin spontaneously self-assemble via interlocking to give [2]catenanes in >95% yield. Since carbon−carbon double bonds are fundamentally robust, catenanes produced in this way are kinetically stable when separated from the metathesis catalyst. Alternatively, they can be quantitatively converted back to their unlocked component macrocycles simply by diluting the RORCM reaction mixture or by "switching off" (by reversible trifluoroacetylation of the amides) the inter-macrocycle hydrogen bonding interactions prior to RORCM.

Benzylic amide macrocycles **1** and **2** were prepared according to methods given in the Supporting Information. The macrocycles were each isolated as mixtures of *E*- and *Z*-diastereomers and used as such in the metathesis experiments. RORCM was carried out in CH_2Cl_2 (the noncompeting solvent maximizes the strength of the inter-ring hydrogen bonding interactions) with use of the commercially available benzylidene version[4a] of Grubbs' catalyst, **5**.[9] At different concentrations the reactions yielded different product distributions, as evidenced by HPLC and ^{1}H NMR spectroscopy (e.g. Figure 1a−d). At concentrations of 0.0002 M or less only simple macrocycle could be detected.[10] By using higher reaction concentrations, progressively more and more catenane (**3** or **4**) is produced until at equilibrium at 0.2 M >95% is a mixture of the three catenane diolefin isomers (*EE*, *EZ*, *ZZ*). Taking the product mixture from one metathesis reaction and reexposing it to catalyst at a different concentration converts the product distribution to that obtained if only the macrocycle (or catenane) is metathesized at that concentration, demonstrating that the reactions are truly under thermodynamic control. At concentrations higher than 0.2M mass spectrometry and analytical HPLC show that higher cyclic oligomers become increasingly abundant and the yield of catenane falls.

Saturated analogues of these amphiphilic benzylic amide catenanes have previously[11] been prepared in up to 18% yield by condensation of alkyl bis-acid chlorides and (masked) phenols and their interlocked nature confirmed by X-ray crystallography and a range of spectroscopic and spectrometric measurements. The saturated catenanes are easily distinguished from both their uninterlocked components and higher macrocycles by characteristic shifts in their ^{1}H NMR spectra in $CDCl_3$ arising from the co-conformation adopted by the interlocked macrocycles to maximize intercomponent hydrogen bonding interactions.[11] The isomeric mixture of **3** and **4** produced in each olefin metathesis experiment was catalytically hydrogenated (H_2, Pd/C, 100%) and the resulting products shown to be identical to the saturated [2]-catenanes prepared unambiguously from the corresponding bisphenol and sebacoyl chloride.

In two cases (*EZ* isomer of **3**, *EE* isomer of **4**)[12] single catenane olefin isomers could actually be separated from the RORCM reaction mixture by preparative HPLC. The ^{1}H NMR spectra of these individual diolefin isomers are shown in Figures 1e and 1f, respectively. Comparison of these spectra with those of **1** and **2** (e.g. Figure 1a) shows exactly the same shielding and deshielding trends observed for the saturated catenanes. For example, H_A is held in the deshielding zone of an amide carbonyl group by inter-macrocycle hydrogen bonding and so is shifted *downfield* compared to the analogous proton, H_a, in the noninterlocked macrocycle; H_B is also deshielded (with respect to H_b) by hydrogen bonding, but H_{C-F} all appear *upfield* with respect to H_{c-f} due to shielding from the aromatic rings of the other component macrocycle.

Just as the development of protecting groups for sensitive functional groups has gone hand-in-hand with advances in complex natural product synthesis, the introduction of methodology for the reversible modulation of noncovalent interactions is going to become increasingly important in the design, assembly, disassembly, and interconversion of sophisticated nanoscale superstructures.[13] Trifluoroacetylation of **3** or **4** ($(CF_3CO)_2O$, Δ) provides a mild and efficient method for switching off the inter-macrocycle hydrogen bonding interactions utilized for catenane formation. In the absence of the Grubbs catalyst the trifluoroacetylated catenanes are stable, but under RORCM conditions the rings smoothly dissociate to produce, after quantitative detrifluoroactylation (MeOH, Δ), the original component macrocycles **1** or **2**.

The combination of directed hydrogen bonding interactions and RORCM provides a powerful method for the assembly (or disassembly) of interlocked compounds through the built in recycling of nonpreferred byproducts, a key requirement in developing "engineering up" approaches to large functional supermolecules.[2] Significantly, since the reversible ring opening reaction involves breaking a strong C═C bond and only occurs in the presence of a specific catalyst, molecules assembled by this strategy are not inherently labile. The result is the best of both worlds: thermodynamically controlled "error-checking" during synthesis combined with a kinetically robust final superstructure.[14]

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Supporting Information Available: Experimental details for the synthesis of **1** and **2**; ^{1}H NMR data for the saturated derivatives of **2** and **4** prepared from the phenols and sebacoyl chloride (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) For evidence of some catenane formation during RORCM of macrocycles without recognition sites see: Wolovsky, R. *J. Am. Chem. Soc.* **1970**, *92*, 2132−2133; Wasserman, E.; Ben-Efraim, D. A.; Wolovsky, R. *J. Am. Chem. Soc.* **1970**, *92*, 2133−2135. For a recent discussion of the mechanism involved in those reactions see: Gruter, G.-J. M.; Akkerman, O. S.; Bickelhaupt, F. *Tetrahedron* **1996**, *52*, 2565−2572.

(8) The metathesis "catalyst" is actually a precatalyst or reaction initiator, so a small amount of macrocycle/catenane is lost through cross metathesis with the benzylidene ligand of **5**.

(9) General experimental procedure for RORCM: An anhydrous 0.0002−0.2 M solution of the olefin (0.35 mmol, **1** is not completely soluble in CH_2Cl_2 at 0.2 M and was used as a saturated suspension at that concentration) in freshly distilled dichloromethane was successively degassed and re-saturated with argon for at least 10 min before being injected directly into a flame-dried Schlenk tube containing the ruthenium carbene **5** (3−15 mg, 1−5 mol %) under a constant stream of argon with a gastight syringe. The reaction mixture was left stirring under a steady stream of argon for between 1 and 5 days until an unchanging product distribution was evidenced by analytical HPLC, then filtered through silica gel ($CHCl_3$/MeOH as eluent) to remove residual catalyst and leave catenane (using 0.2 M reaction concentration), macrocycle (0.0002 M), or mixtures thereof (0.02 and 0.002 M). Further purification with a Gilson 712 HPLC on a preparative column packed with Spherisorb S5W ($ClCH_2CH_2Cl$/*i*PrOH) allowed the separation of individual catenane diolefin isomers *EE*-**4** and *EZ*-**3**.

(10) The product distribution produced at equilibrium is independent of whether the starting material used is macrocycle, catenane, higher cyclooligomers, etc. or a mixture of these from another RORCM reaction. However, unstrained internal olefin metathesis is much slower than terminal olefin metathesis and the reactions normally require at least 24 h (and sometimes as long as 5 days with small catalyst loadings at dilute reaction concentrations) to undergo enough ring opening−ring closing cycles to allow the product distribution to reach a steady state. For such long reaction times decomposition of the catalyst by O_2 can be problematical and therefore the RORCM reactions require rigorous degassing before and during the experiment.

(11) Leigh, D. A.; Moody, K.; Smart, J. P.; Watson, K. J.; Slawin, A. M. Z. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 306−310.

(12) Olefin stereochemistry was determined from ^{13}C NMR chemical shifts of allylic carbons and characteristic IR bands [Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*, 4th ed., revised; McGraw-Hill: London, 1989].

(13) **Note Added in Proof.** For a recent example involving the temporary blocking of a cyclophane cavity in another catenane synthesis employing RCM see: Hamilton, D. G.; Sanders, J. K. M. *Chem. Commun.* **1998**, 1749−1750.

(14) **Note Added in Proof.** A π-electron rich/π-electron poor heterocircuit catenane synthesis by RORCM has recently been reported [Hamilton, D. G.; Feeder, N.; Teat, S. J.; Sanders, J. K. M. *New J. Chem.* **1998**, 1019−1021], although solubility-limited concentrations and slow reaction kinetics [see footnote 10] make the system only *quasi*-reversible thus far and consequently the product distribution is not under strict thermodynamic control.