ORGANIC LETTERS

2000
Vol. 2, No. 4
449−452

Macrocyclization and Molecular Interlocking via Mitsunobu Alkylation: Highlighting the Role of C–H···O Interactions in Templating

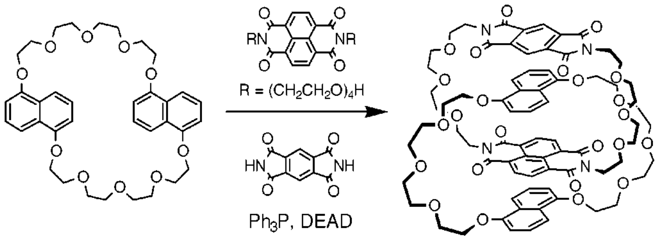
Jimmi G. Hansen,[†,‡] Neil Feeder,[†] Darren G. Hamilton,[†] Maxwell J. Gunter,[†,§] Jan Becher,[‡] and Jeremy K. M. Sanders*,[†]

University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K.

jkms@cam.ac.uk

Received November 30, 1999

ABSTRACT



A series of diimide-based macrocycles have been prepared using Mitsunobu-mediated alkylation as the macrocyclization step. These macrocycles could not be incorporated into [2]catenanes using previously established building blocks and coupling methodology. However, when one of the macrocycle syntheses was conducted in the presence of a dinaphtho crown ether, catenane formation was achieved. This result is discussed in terms of the ability of the components to establish intermolecular C–H···O hydrogen-bonding contacts.

In this Letter we describe the preparation of three macrocycles derived from aromatic diimides and poly(ethylene glycol) linkers and of a [2]catenane formed when the synthesis of one of the macrocycles is conducted in the presence of a complementary preformed dinaphtho crown ether. The achievement of macrocyclization and interlocking by means of Mitsunobu alkylation of aromatic diimides represents the third covalent means by which to prepare an interlocked system containing such components, in addition to Glaser−Hay coupling of terminal acetylenes and Grubbs' olefin metathesis;[1,2] a catenane of this type has also been assembled via zinc(II)−bipyridyl ligation.[3]

Our initial aim in preparing the diimide−polyether macrocycles described here was to attempt to reverse the roles of the linkers in our original [2]catenane **3**, assembled by coupling two units of acetylenic diimide **2** in the presence of dinaphtho crown **1** (Figure 1). The preformed diimide macrocycle **4** was intended to act as a template for cyclodimerization of acetylenic aromatic diether **5** to give [2]catenane **6**, a structural isomer of **3**. However, as we report below, such cyclizations failed to provide any interlocked products. In fact, the lack of evidence for any interaction between **4** and **5** led to a reconsideration of the molecular design, and ultimately to the selection of an alternative method for achieving molecular interlocking of diimide-derived macrocycles such as **4**.

Retrosynthetic analysis of **4** reveals several options. The route we selected acknowledges the fact that condensation

---

[†] University of Cambridge.

[‡] Department of Chemistry, Odense University, Campusvej 55, DK-5230 Odense M, Denmark.

[§] Department of Chemistry, University of New England, Armidale, New South Wales 2351, Australia.

(1) Hamilton, D. G.; Davies, J. E.; Prodi, L.; Sanders, J. K. M. *Chem. Eur. J.* **1998**, *4*, 608−620.

(2) Hamilton, D. G.; Feeder, N.; Teat, S. J.; Sanders, J. K. M. *New J. Chem.* **1998**, *22*, 1019−1021.

(3) Try, A. C.; Harding, M. M.; Hamilton, D. G.; Sanders, J. K. M. *Chem. Commun.* **1998**, 723−724.

10.1021/ol991289w CCC: $19.00

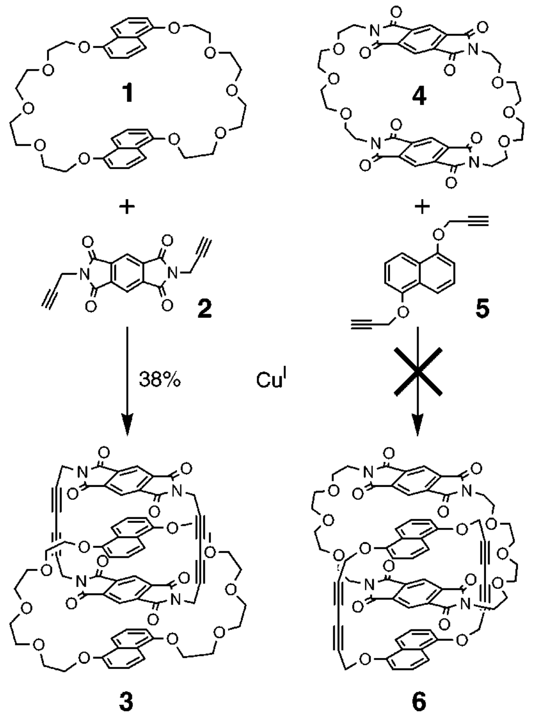
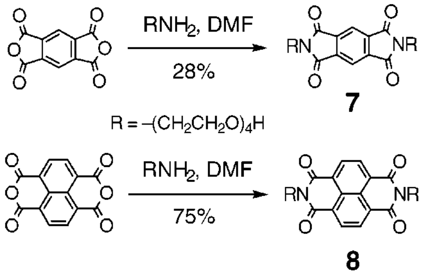


Figure 1. Successful and unsuccessful [2]catenane syntheses.

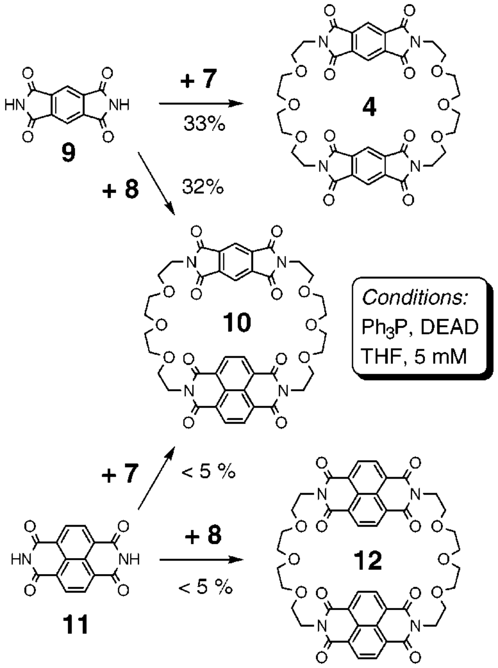
reactions of primary amines with aromatic dianhydrides proceed well. However, in our experience macrocyclization using amine−anhydride condensation is problematical[4] and we therefore targeted Mitsunobu alkylation of aromatic diimides with primary alcohols for the cyclization reaction since alkylation of aromatic diimides with simple terminal alcohols proceeds rapidly and efficiently.[2] Tetraethylene glycol-substituted pyromellitic and naphthalene diimide derivatives **7** and **8** were prepared in typical yields from the appropriate dianhydrides and 2-(2-(2-(2-aminoethoxy)ethoxy)-ethoxy)ethanol, itself available in three simple steps from tetraethylene glycol (Scheme 1).[5,6]

Scheme 1



Macrocyclizations were performed in dry THF containing 2.5 equiv of PPh_3, at 5 mM concentration of diol and diimide, by dropwise addition of DEAD (2.5 equiv). The aromatic diimides **9** and **11** are only very sparingly soluble in THF, an attribute that may indirectly favor macrocyclization by ensuring that only a very low concentration of diimide is maintained in solution. In the cases of preparation of macrocycles **4** and **10**, from the reaction of diimide **9** with diols **7** and **8**, respectively, reaction progress could be conveniently monitored by following the disappearance of the suspended diimide (Scheme 2).

Scheme 2



Preparation of bis-naphthalene diimide macrocycle **12** proved most problematical, a fact attributed to the extreme insolubility of diimide **11** in THF. During previous preparations of **11** we assayed its purity via derivatization by Mitsunobu alkylation.[2] The results indicated that the diimide was 80% pure, though it is possible that different batches of material may vary in their homogeneity. This may contribute to the extremely low isolated yields of **12**, though it should be noted that continuous sonication of the reaction mixture was necessary in order to obtain even this modest success. Likewise, only traces of the mixed diimide macrocycle **10** could be obtained from diol **7** and naphthalene diimide **11**; this latter route was not explored further since **10** could be obtained in comparable yield to **4** via the alternative route of cyclizing diol **8** with pyromellitic diimide **9**.

Using the coupling protocol previously employed in the synthesis of [2]catenane **3**, we attempted to achieve cyclodimerization and interlocking of bis-acetylene diether **5** with

---

(4) Hansen, J. G.; Bang, K. S.; Thorup, N.; Becher, J. *Eur. J. Org. Chem.*, in press.

(5) Ashton, P. R.; Huff, J.; Menzer, S.; Parsons, I. W.; Preece, J. A.; Stoddart, J. F.; Tolley, M. S.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **1996**, *2*, 31−44.

(6) Lebeau, L.; Oudet, P.; Mioskowski, C. *Helv. Chim. Acta* **1991**, *74*, 1697−1706.

diimide macrocycles **4** and **10**.[1] Notably, prior to addition of the copper salts used to promote coupling of the terminal acetylenes, the DMF solutions containing 1:2 molar ratios of macrocycle to bis-acetylene did not exhibit the strong solution colors that we have come to expect from mixtures of electron-rich and electron-deficient components of this type. Regardless, the copper salts were added and the reaction mixture treated and worked up as previously reported. No evidence for the formation of interlocked material was found. The reactions were repeated in chloroform using a modified protocol for the coupling reaction, but again no catenane formation was observed.[7]

While we cannot rule out some unfavorable interaction geometry that prevents cyclodimerization of **5** through the cavity of the diimide macrocycles, the lack of solution coloration—the signature of co-facial interaction in systems of this type—suggests that little or no binding occurs. Although strong solution coloration arising from donor–acceptor interactions is an indicator of association between aromatic diethers and acceptors, there is increasing suspicion that such interactions may not be the primary driving force for binding. Numerous weak C−H···O interactions have long been recognized as important structural control elements in the solid-state organization of charged catenanes based on electron-deficient bipyridinium systems and electron-rich aromatic diethers,[8,9] and recently relative weightings for the various noncovalent interactions operating within these systems have been suggested:[10] synthetic and computational study indicated that, for bipyridinium based catenanes, the C−H···O interactions between "acidic" bipyridinium protons and oxygen atoms in the polyether chains of the crown outweighed the contribution from stacking of the complementary π-systems by a factor of around 4 to 1.

Perhaps it is likely that our successful synthesis of [2]catenane **3** also has rather more to do with favorable C−H···O contacts than with establishing donor−acceptor interactions. The methylene group of the diimide component of this preparation is situated next to an electron-deficient imide nitrogen, satisfying the criterion of activation of a C−H bond by a neighboring "electronegative" group.[11] Notably, analysis of the solid-state structure of **3** reveals the presence of a relatively short and strong C−H···O hydrogen-bonding contact between a diimide methylene hydrogen and the central oxygen atom of the crown polyether chain (Figure 2).[12] Similar contacts are not present in the solid-state structures of related systems, but we are dealing with rather weak interactions which might readily be swamped by competing packing forces during crystal growth. However, a conclusion that arises as a consequence of acceptance of a potential role for C−H···O interactions is that a prerequisite for efficient binding would be to position "acidic" hydrogen atoms near suitable acceptors, such as the oxygen atoms of a polyether chain.[13] Our approach to [2]catenane **6** thus appears flawed: the methylene groups of acetylenic diether component **5** are adjacent to an electron-rich system not an electronegative one that might impart the requisite acidity on the hydrogen atoms and aid hydrogen bond formation and complexation.

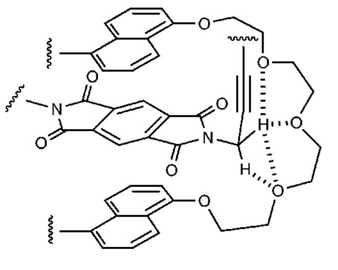
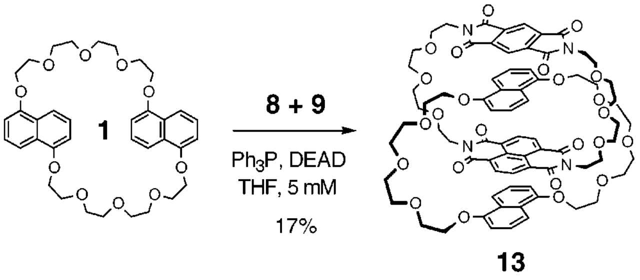


Figure 2. C−H···O contacts in the solid-state structure of **3**.

A logical conclusion to draw from the above discussion is that the benzene and naphthalene diimide diols **7** and **8**, which possess the requisite "acidic" methylene groups, may be viable catenane precursors: Mitsunobu macrocyclization of these materials with the appropriate aromatic diimides, **9** or **11**, in the presence of the dinaphtho crown **1** might lead to catenane formation. Promisingly, the formation of [2]catenanes could be detected by mass spectrometry from reactions of **7** with **9**, or **8** with **11**, in the presence of 1 equiv of crown **1**. However, the limited success of the latter reaction is doubtless hampered by the same solubility problems that plagued the synthesis of the free diimide macrocycle **12**; the lack of significant [2]catenane production from the former reaction is harder to explain other than by concluding that binding between these components is very weak. In stark contrast with these results is the isolation of a 17% yield of [2]catenane **13** as a deep red crystalline material from the reaction, under identical conditions, of diol **8** with diimide **9** in the presence of **1** (Scheme 3).

Scheme 3. A [2]Catenane via Mitsunobu Alkylation



Substantial, deep-red crystals of [2]catenane **13** could readily be grown from chloroform/methanol mixtures. For

---

[7] Anderson, H. L.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2223−2229.

[8] Ashton, P. R.; Goodnow, T. T.; Kaifer, A. E.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Vicent, C.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1396−1399.

[9] Anelli, P. L.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Delgado, M.; Gandolfi, M. T.; Goodnow, T. T.; Kaifer, A. E.; Philp, D.; Pietraszkiewicz, M.; Prodi, L.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Vicent, C.; Williams, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 193-218.

[10] Houk, K. N.; Menzer, S.; Newton, S. P.; Raymo, F. M.; Stoddart, J. F.; Williams, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1479−1487.

[11] Steiner, T. *Chem. Commun.* **1997**, 727−734.

the first time in our experience of catenanes the structural solution was obtained using a laboratory X-ray source and was refined to a final *R* value of 7.1% despite some disorder in one of the polyether links (see Supporting Information for details of the structural solution and refinement).

The [2]catenane structure contains only molecules in which the naphthalene diimide unit is located inside the crown macrocycle; the interaction of this diimide with the electron-rich aromatic diethers is known to be rather stronger than that with pyromellitic diimides.[14] Such a solid-state structural preference, presumably directed by comparative interaction energetics during the crystallization process, has been found in the solid-state structures of related systems. A familiar stacked array of complementary electron-rich and electron-deficient components is maintained (Figure 3), these units being essentially coplanar with only small (1−2.5°) angles between their mean planes. The naphthalene diether components are rigorously planar, and the first *O*-methylene bonds are only twisted from these planes by around 10°. In contrast, both diimide frameworks of **13** are substantially bowed. There are angles of around 5° between the mean planes of the imide rings within each diimide unit; the *N*-methylene bonds are bent by 5−10° away from coplanarity.

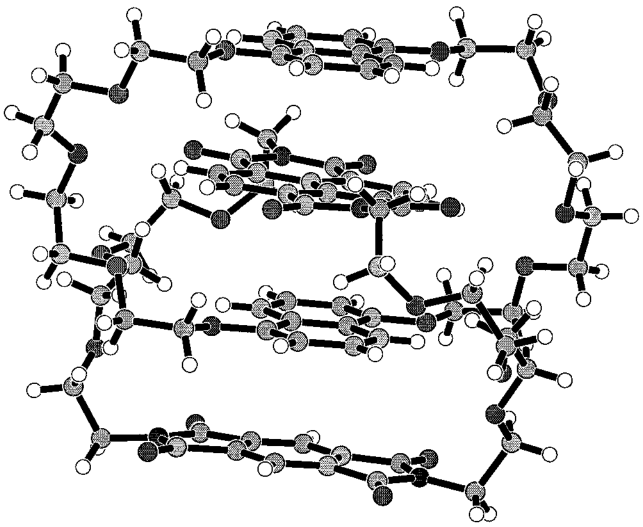


Figure 3. Solid-state structure of [2]catenane **13**.

Long axes drawn through the four stacked catenane components show that the two naphthalene diethers sit squarely one upon the other (twist angle 1°) while those of the diimides define an angle of 54°. However, examination of the relationship of each diimide to its neighboring naphthalene diethers reveals that each of the distinct diimides, pyromellitic and naphthalene, adopts its favored overlap arrangement. Pyromellitic diimides, in simple cocrystals and within interlocked systems, have been found to favor solid-state packing arrangements that place the long axes of the diimide close to perpendicular with those of electron-rich 1,5-dioxynaphthalene derivatives.[1,15] In the case of naphthalene diimides, a nearly parallel arrangement is observed.[16] The solid-state structure of [2]catenane **13** reveals the simultaneous satisfaction of these donor−acceptor structural preferences, which also extend to the packing of individual [2]catenanes in the crystal. In addition to a continuation of alternating donor and acceptor subunits within the crystal stacks, the perpendicular orientation of pyromellitic diimide and naphthalene diether is maintained, as is the preference for naphthalene diimides to be essentially parallel with this electron-rich group. The overall structural preferences are thus maintained both inter- and intramolecularly.

The work described in this Letter indicates that it could be misleading to expect the deployment of donor−acceptor interactions to be a sufficient primary design criterion for new catenane syntheses. In isolation, such interactions do not provide a sufficient driving force for successful molecular reaction. Only when the capacity to form C−H···O contacts is also present are successful assembly routes uncovered.[17]

Acknowledgment. We thank the U.K. EPSRC (J.K.M.S.) and the ESF SMARTON project of the European Union (J.G.H.) for financial support of this work.

Supporting Information Available: Synthetic procedures and analytical data for **7** and **8** and macrocycles **4**, **10**, **12**, and [2]catenane **13**; crystallographic data for [2]catenane **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991289W

---

[12] The shortest and strongest contacts (see ref 10) are those to the central oxygen atom of the polyether chain: H···O distance approximately 2.2 Å, C−H···O ∠ 148°. All other contacts are around 2.7 Å and C−H···O ∠ 100−120°. An additional, pertinent, example of a contact of this kind (H···O distance approximately 2.9 Å, C−H···O ∠ 128°) is to be found in the structure of a phthalimido-crown, a system that contains both a polyether chain and an imide-CH_2 grouping, see: Ashton, P. R.; Huff, J.; Menzer, S.; Parsons, I. W.; Preece, J. A.; Stoddart, J. F.; Tolley, M. S.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **1996**, *2*, 31−44.

[13] We had previously attempted to prepare more soluble analogues of [2]catenane **3** by equipping the diimide precursor with solubilizing ethyl groups in place of the methylene hydrogens, see: Hamilton, D. G.; Prodi, L.; Feeder, N.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1057−1065. No interlocked products were obtained from these reactions, and the product distribution from cyclizations of this modified diimide could not be influenced in any way with electron-rich template molecules. We attributed this failure to an inability of the soluble diimide to achieve a favorable donor−acceptor overlap geometry with electron-rich substrates as a result of the inclusion of bulky alkyl substituents. In light of the current results this failure may have as much, or rather more, to do with the absence of acidic methylene hydrogens occasioned by the inclusion of the additional alkyl groups.

[14] Hamilton, D. G.; Montalti, M.; Prodi, L.; Fontani, M.; Zanello, P.; Sanders, J. K. M. *Chem. Eur. J.* **2000**, *6*, 608−617.

[15] Hamilton, D. G.; Lynch, D. E.; Byriel, K. A.; Kennard, C. H. L. *Aust. J. Chem.* **1997**, *50*, 439−445.

[16] Lokey, R. S.; Iverson, B. L. *Nature* **1995**, *375*, 303−305.

[17] The capacity to form C−H···O contacts is partly a consequence of having "acidic" protons available, i.e. protons attached to electron-deficient systems. Accordingly, and rather by default, successful systems are likely to contain electron-deficient components (to provide the "acidic" protons) and electron-rich donor sites such as oxygen atoms.