Macromol. Symp. ***142**, 185–191 (1999)*

Highly Efficient Template-based Preparation of Shape-persistent Macrocyclics

S. Höger

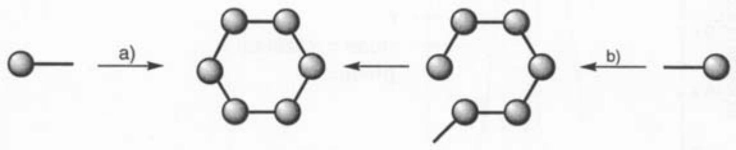
Max-Planck-Institute for Polymer Research, Ackermannweg 10, 55128 Mainz, Germany

SUMMARY: The synthesis of shape-persistent macrocycles via oxidative dimerization or trimerization of rigid bisacetylenes (via Glaser coupling) is described. To enhance the yield of the desired target structures, the precursors are temporarily covalently bound to a template resulting in an intramolecular coupling instead of an intermolecular coupling. As a result, product yields up to over 90 % are observed.

Introduction

Macrocyclic structures with a rigid, non-collapsible backbone and interior sizes of several nanometers are interesting objects in the field of Supramolecular Chemistry1). Besides interesting aggregation phenomena in solution2) and in the solid state3), especially their ability to act as host molecules for relatively large guest molecules has made them desirable target strtuctures4). However, only a limited number of reports on these molecules is available, probably because of the huge effort often required in their preparation.

Two extreme strategies for their synthesis can be distinguished. In the first startegy, the "shotgun synthesis", formation of the oligomeric precursor and its cyclization is performed in a one-pot procedure, leading to a wide variety of cyclic and non-cyclic oligomers and polymers (scheme 1a) 5).



Scheme 1: Different approaches to shape-persistent macrocycles

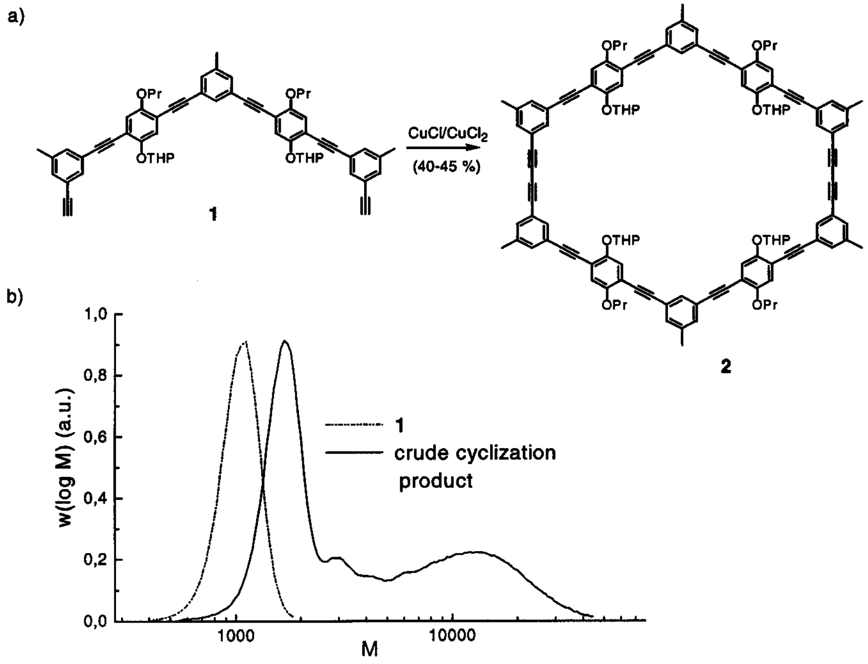
In contrast, if the precursor of the cyclization reaction is prepared repetitively in a seperate vessel prior to its cyclization, the intramolecular cyclization under (pseudo) high-dilution conditions generally gives high yields of the ring (scheme 1b). However, the synthesis of the precursor is often a time consuming multi-step procedure. Several examples exist in the

CCC 1022-1360/99/$ 17.50+.50/0

literature which allow comparisons between the effort needed to prepare the precursor and the cyclization yield⁶⁾. From these data it seems that macrocyclizations find themselves in a paradox: *either easily available starting materials are used for cyclizations resulting in a low product yield, or high yields and simplified purifications are obtained at the cost of a time-consuming precursor synthesis.*

Results and Discussion

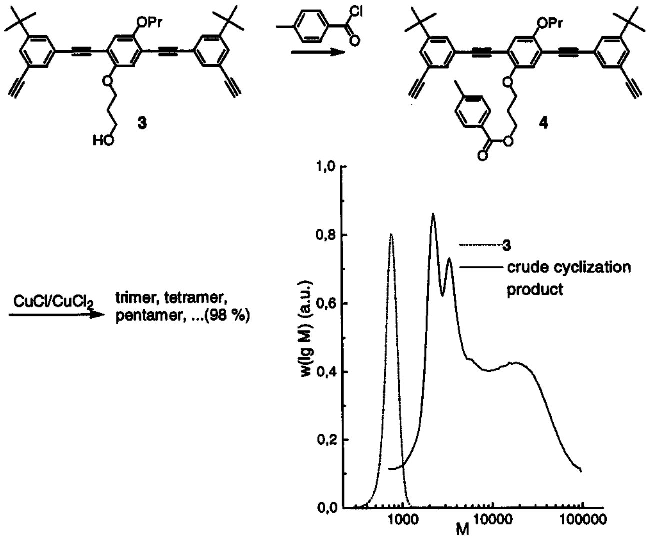
In our previous investigations of the synthesis and properties of shape-persistent macrocyclic amphiphiles with a switchable arrangement of the polar and non-polar functionalities, we used as cyclization step the intermolecular oxidative Glaser coupling of the rigid bisacetylenes **1** ("half-rings") under pseudo high-dilution conditions (scheme 2a)⁷⁾.



Scheme 2: Cyclization of rigid "half-rings" under pseudo high-dilution conditions

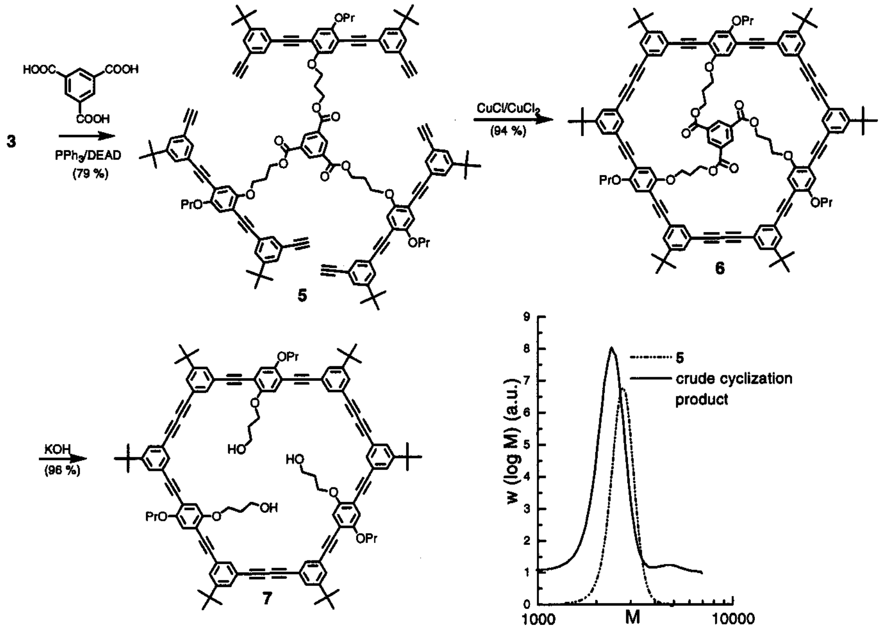
Gel permeation chromatography (GPC) has been proven to be a valuable tool for the investigation of the reaction products (the molecular weight is obtained from polystyrene calibration of the size exclusion chromatography (SEC) columns). Scheme 2b shows the elution diagrams of **1** and of the crude cyclization product which is usually obtained in more than 95 % yield. According to this data the cyclic dimer **2** is formed in 60 - 65 % yield along with cyclic trimer and cyclic or non-cyclic oligomers and polymers. **2** is obtained by simple recrystallization from dichloromethane in 40 - 45 % yield.

One approach to simplify precursor synthesis is the preparation of smaller building blocks such as **3** ("thirds of a ring") (scheme 3) in which prior to its oxidative cyclization the polar alcohol functionality must be protected, here as the benzoate **4**. Intermolecular cyclization under the same conditions as used for the cyclization of **1** forms a crude product (> 95 % yield) containing mostly polymeric material. The cyclic trimer is formed in only 20 - 25 % yield (according to GPC analysis) 8).



Scheme 3: Cyclization of rigid "thirds of a ring " under pseudo high-dilution conditions

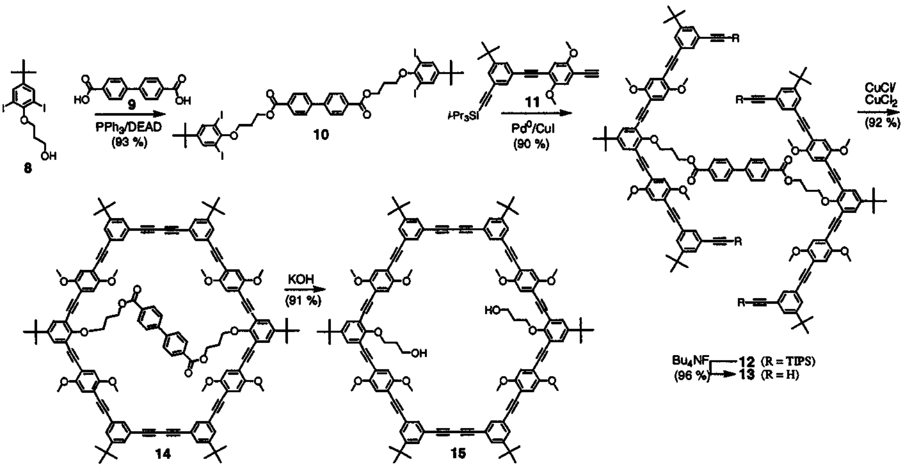
This relatively low yield is not surprising, since the joining of three building blocks in a cyclic compound is less probable than the joining of only two building blocks. However, if a different protective group for the alcohol functionality is chosen and the trimesinic acid ester **5** is prepared (under Mitsunobu conditions 9)) (scheme 10a), the cyclization of this template-bound hexaacetylene **5** under identical conditions yields a crude product which contains more than 95 % of the template-bound cyclic trimer **6** which is isolated in 94 % yield. Base catalysed cleavage of the ester bonds gives the desired macrocycle **7** in nearly quantitative yield [8].



Scheme 4: Template-directed synthesis of shape-persistent macrocycles

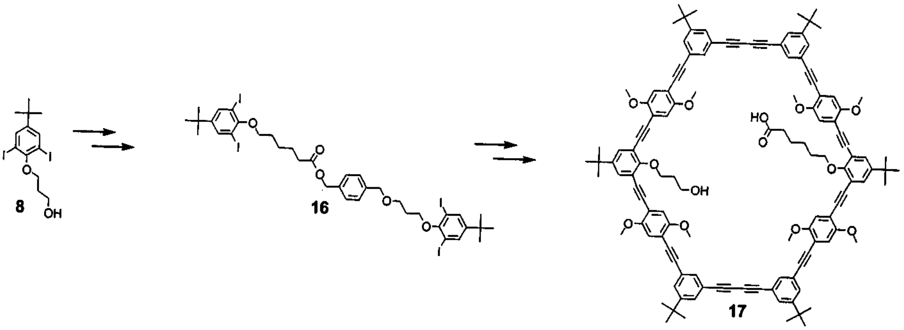
This was the first time that we were able to obtain a shape-persistent macrocycle with a switchable arrangement of the amphiphilic portions of the ring in high yield using relatively small and easily available starting materials. Moreover, it has been demonstrated by the successful cyclization of homologues of **5** with a dramatically enlarged distance between the template and the rigid acetylenic parts of the molecule that for a high product yield it is not necessary to arrange the bisacetylenes in a particular preorganised geometry. Rather, the high cyclization yield can be attributed to an overall low reactant concentration as a result of the high-dilution conditions together with a high local concentration of terminal acetylenes as a result of the intramolecular nature of the coupling reaction [10,11]. With the template strategy it is also possible to prepare macrocycles with polar groups pointing to the outside, valuable A_2-monomers[12].

Changing the succession of the steps in the synthesis of the templated precursors gives us even more opportunities to modify the functional groups within the ring (scheme 5)[13]. Instead of preparing the bisacetylenes first and attaching them to the template in a separate step, the complete synthesis of the templated tetraacetylenes is performed *at the template*. The corner pieces of the ring containing the functional groups (**8**) (which now points to the inside of the final structure leading to compounds with intraannular functional groups[14]) are first attached to the template (**9**) to give the templated tetraiodide **10**, the starting material for **15**, a nanometer-size shape-persistent structure with a convergent arrangement of functional groups.



Scheme 5: Template-directed synthesis of macrocycle containing intraannular substituents

There are several advantages to this strategy. First only a few steps are necessary to prepare the templated bisacetylenes. Second, all these steps give relatively high yields because the molecular weights and the physical properties of the reactants and products change so dramatically in every step that product purification is simplified. And last, but of perhaps highest significance, is the fact that macrocycles with two different functional groups can be prepared by the same methodology using the non-symmetrical tetraiodide **16** (scheme 6). The major advantage of this procedure is that all structural information necessary to obtain the non-symmetrical macrocycle **17** is introduced on the level of the low molecular weight precursors which are much easier to handle than high molecular weight ring precursors.



Scheme 6: Template-directed synthesis of macrocycle containing different intraannular substituents

References and notes

1) J.L. Atwood, J.E.D. Davies, D.D. Macnicol, F. Vögtle, (ed.), *Comprehensive Supramolecular Chemistry, vol. 3, Cyclodextrines*, Elsevier Science Ltd., Oxford, **1996**;

2) (a) J. Zhang, J.S. Moore, *J. Am. Chem. Soc.* **1992**, *114*, 9701; (b) A.S. Shetty, J. Zhang, J.S. Moore, *J. Am. Chem. Soc.* **1996**, *118*, 1019; (c) Y. Tobe, N. Utsumi, K. Kawabata, K. Naemura, *Tetrahedron Lett.* **1996**, *37*, 9325; (d) Y. Tobe, N. Utsumi, A. Nagano, K. Naemura, *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1285.

3) (a) J. Zhang, J.S. Moore, *J. Am. Chem. Soc.* **1994**, *116*, 2655; (b) S. Höger, C. Tschierske, K. Bonrad, V. Enkelmann, in preparation.

4) For macrocyclic host molecules based on the phenyl-ethynyl backbone see e.g. (a) H.L. Anderson, J.K.M. Sanders, *J. Chem. Soc. Chem. Commun.* **1989**, 1714; (b) L.G. Mackeay, H.L. Anderson, J.K.M. Sanders, *J. Chem. Soc. Chem. Commun.* **1992**, 43; (c) H.L. Anderson, J.K.M Sanders, *J. Chem. Soc. Chem. Commun.* **1992**, 946; (d) S.Anderson, U. Neidlein, V. Gramlich, F. Diederich, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1596; (e)D.L. Morrison, S. Höger, *J. Chem. Soc. Chem. Commun.* **1996**, 2313.

5) (a) L.T. Scott, M.J. Cooney, D. Johnels, *J. Am. Chem. Soc.* **1990**, *112*, 4054; (b) L.T. Scott, M.J. Cooney, in *Modern Acetylene Chemistry* (ed. P.J. Stang, F. Diederich), VCH, Weinheim, **1995**, pp. 321.

6) For example, see for a comparison: (a) H. A. Staab, K. Neunhoeffer, *Synthesis* **1974**, 424 and (b) J. S. Moore, J. Zhang, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 292, as well as (c) H.

Staab, F. Binning, *Chem. Ber.* **1967**, *100*, 293; and (d) V. Hensel, K. Lützow, J. Jakob, K. Gessler, W. Saenger, A.-D. Schlüter, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2654.

7) (a) S. Höger, V. Enkelmann, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2713; (b) S. Höger, A.-D. Meckenstock, S. Müller, *Chem. Eur. J.* **1998**, *4*, 2421.

8) S. Höger, A.-D. Meckenstock, H. Pellen, *J. Org. Chem.* **1997**, *62*, 4556.

9) (a) O. Mitsunobu, *Synthesis* **1981**, 1; (b) D.L. Hughes, *Org. React.* **1992**, *42*, 335.

10) For recent articles dealing with template reactions see e.g.: (a) B. Dietrich, P. Viout, J.-M. Lehn, *Macrocyclic Chemistry*, VCH, Weinheim, **1993**. (b) S. Anderson, H.L. Anderson, J.K.M. Sanders, *Acc. Chem. Res.* **1993**, *26*, 469; (c) R. Hoss, F. Vögtle, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 375; (d) J.L. Atwood, J.E.D. Davies, D.D. Macnicol, F. Vögtle, (ed.), *Comprehensive Supramolecular Chemistry, vol.* 9, Elsevier Science Ltd., Oxford, **1996**.

11) For some reviews and examples on the use of covalently attached templates in organic synthesis see e.g.: (a) R. Breslow, *Acc. Chem. Res.* **1980**, *13*, 170; (b) K.S. Feldman, Y.B. Lee, *J. Am. Chem. Soc.*, **1987**, *109*, 5850; (c) J.W. Gillard, R. Fortin, E.L. Grimm, M. Maillard, M. Tjepkema, M.A. Bernstein, R. Glaser, *Tetrahedron Lett.*, **1991**, *32*, 1145; (d) J.-I. Hong, S.K. Namgoong, A. Bernardi, W.C. Still, *J. Am. Chem. Soc.*, **1991**, *113*, 5111; (e) S. Valverde, A.M. Gómez, J.C. López, B. Herradón, *Tetrahedron Lett.* **1996**, *37*, 1105; (f) F. Cardullo, L. Isaacs, F. Diederich, J.-P. Gisselbrecht, C. Boudon, M. Gross, *J. Chem. Soc. Chem. Commun.* **1996**, 797; (g) H. Weizman, J. Libman, A. Shanzer, *J. Am. Chem. Soc.*, **1998**, *120*, 2188.

12) S. Höger, A.-D. Meckenstock, *Tetrahedron Lett.* **1998**, *39*, 1735.

13) S. Höger, A.-D. Meckenstock, *Chem. Eur. J.* **1999**, in press.

14) For early reports of the concept of intraannular functional groups see e.g.: (a) E. Weber, F. Vögtle, *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 149; (b) E. Weber, F. Vögtle, *Chem. Ber.* **1976**, *109*, 1803.

Acknowledgement: Financial support for a part of this work by the Fonds der Chemischen Industrie is gratefully acknowledged. The author thanks the German Chemical Society for Support by the Hermann Schnell-Stiftung.