Structure and Temperature Effects on the Cyclization of Rigid Bisacetylenes

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Since the report of Sondheimer et al.[1] on the use of Eglinton−Glaser coupling for the preparation of unsaturated macrocyclic compounds, the oxidative homocoupling reaction between the sp-carbon centers of terminal alkynes leading to butadiyne derivatives has become one of the most useful synthetic transformations for the preparation of medium- and large-ring systems,[2] as well as for the formation of boxlike molecules.[3] As with other cyclization reactions, the variety of different cyclization products decreases as the complexity of the precursor increases.[4] We recently reported the oxidative cyclization of the rather rigid kinked phenylene−ethynylene oligomer **1a** (Scheme 1) using a slurry of $CuCl/CuCl_2$ in pyridine as the catalyst/oxidant mixture.[3b] The reactions were performed at room temperature using pseudo-high-dilution conditions. According to the gel permeation chromatographic (GPC) analysis, the crude product contains the corresponding macrocycle **3a** at about 60−65%.[5,6] However, the results obtained by the oxidative cyclization of the oligomers **1b** and **1c** differ remarkably. Under identical conditions, the crude product of the oxidative coupling of **1b** contains **3b** at about 75−80%.

Table 1. Oxidative Cyclization of Rigid Bisacetylenes at Various Temperatures

	cyclization of			
	1a		**1c**	
T (°C)	**3a** in the crude product (GPC) (%)	**3a** (isolated) (%)	**3c** in the crude product (GPC) (%)	**3c** (isolated) (%)
20	60−65	40−45	40−45	30−35
60	80−85	65−70	70−75	45−50
90	75−80	25−30	75−80	35−40

On the contrary, the crude coupling product of **1c** contains **3c** only at about 40−45%.[7] These results clearly indicate that the arrangement of the functional groups (the tetrahydro-*2H*-pyranyl (THP) ethers) has a strong influence on the yield of cyclic dimer.

Although the exact mechanism of the oxidative acetylene dimerization remains unknown, a possible explanation for these results is that copper ion clusters or a copper salt surface act as a template in this reaction.[8] Coordination of the OTHP groups to the template would dramatically restrict the flexibility of the bisacetylic intermediate **2**, which is formed after the first oxidative coupling reaction. Although in every case the same number of coordination sites are connected to the copper salt, the steric restriction increases as the distance of the coordination side from the reacting free acetylenes decreases in the order **2b** < **2a** < **2c**. In other words, due to the aliphatic spacer, **2b** has the highest mobility, giving it the highest probability to react intramolecularly.

We also found a strong temperature dependence on the oxidative acetylene dimerization.[9] Addition of the bisacetylenes **1a** and **1c** to the catalyst suspension at elevated temperatures increased the amount of cyclic dimer in the crude product of the reaction (Table 1).[10] The optimum reaction temperature was found to be

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(1) (a) Leznoff, C. C.; Sondheimer, F. *J. Am. Chem. Soc.* **1968**, *90*, 731. (b) Haley, M. M.; Pak, J. J.; Brand, S. C. *Top. Curr. Chem.* **1999**, *201*, 81 and references therein.

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

(3) Examples for boxlike molecules prepared by the oxidative coupling of acetylenes: (a) Miller, S. P.; Whitlock, H. W. *J. Am. Chem. Soc.* **1984**, *106*, 1492. (b) O'Krongly, D.; Denmade, S. R.; Chiang, M. Y.; Breslow, R. *J. Am. Chem. Soc.* **1985**, *107*, 5544. (c) Berscheid, B.; Vögtle, F. *Synthesis* **1992**, 58.

(4) For direct comparison, see: (a) Staab, H. A.; Neunhoeffer, K. *Synthesis* **1974**, 424. (b) Moore, J. S.; Zhang, J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 292. (c) Staab, H.; Binning, F. *Chem. Ber.* **1967**, *100*, 293. (d) Hensel, V.; Lützow, K.; Jakob, J.; Gessler, K.; Saenger, W.; Schlüter, A.-D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2654.

(5) A solution of 0.2 mmol of **1** in 10 mL of dry pyridine was added to a suspension of 1.75 g of CuCl and 0.35 g of $CuCl_2$ in 40 mL of pyridine in 96 h (with the help of a syringe pump). After completion of the addition, the mixture was allowed to stir for an additional 4 days and then poured into CH_2Cl_2 and water. The organic phase was extracted with water, 25% NH_3 solution (in order to remove the copper salts), water, 10% acetic acid, water, 10% NaOH solution, and brine and dried over $MgSO_4$. After evaporation of the solvent to a small volume (about 5 mL), the coupling products were precipitated by the addition of methanol and collected by filtration to give the crude product in nearly quantitative yield. The GPC diagrams were measured in THF (flow rate 1 mL min^{-1}) at room temperature, using a combination of three styragel columns (porosity 10^3, 10^5, and 10^6 Å) and an UV detector operating at $\lambda = 254$ nm.

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

(7) Selected spectroscopic data: **3b**: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.55 (m, 4 H), 7.53 (s, 2 H), 7.39−7.38 (m, 2 H), 7.38−7.34 (m, 8 H), 7.06 (s, 4 H), 7.05 (s, 4 H), 4.53 (t, J = 6.8 Hz, 4 H), 4.09−4.01 (m, 16 H), 3.85−3.70 (m, 8 H), 3.47−3.36 (m, 8 H), 2.39 (s, 6 H), 2.37 (s, 12 H), 1.97−1.85 (m, 20 H), 1.70−1.58 (m, 22H), 1.55−1.42 (m, 22 H), 1.14 (t, J = 7.4 Hz); ^{13}C NMR (75.45 MHz, CD_2Cl_2) 154.31, 139.53, 139.32, 133.46, 133.14, 132.42, 124.41, 124.19, 122.41, 117.63, 114.66, 99.35, 94.68, 94.24, 87.21, 86.77, 81.49, 74.42, 71.77, 70.21, 67.92, 62.63, 31.42, 30.47, 29.95, 26.74, 26.61, 26.21, 23.34, 21.40, 20.29, 10.94. **3c**: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.49 (m, 2 H), 7.34 (m, 4 H), 7.32 (m, 4 H), 7.25 (m, 4 H), 7.22 (m, 4 H), 7.12 (s, 4 H), 7.11 (s, 4 H), 5.52 (m, 4 H), 4.04 (t, J = 6.2 Hz, 16 H), 3.83 (m, 4 H), 3.62 (m, 4 H), 2.37 (s, 6 H), 2.00−1.50 (m, 40 H), 1.14 (t, J = 7.5 Hz, 24 H). ^{13}C NMR (75.45 MHz, THF-d_8) δ 158.29, 154.89, 154.79, 139.46, 132.85, 132.37, 129.71, 126.18, 124.94, 123.64, 121.28, 120.80, 117.88, 115.28, 114.74, 97.40, 94.70, 94.06, 87.82, 87.28, 81.57, 74.49, 71.77, 62.37, 31.03, 26.10, 23.63, 21.05, 19.40, 10.93; MS (MALDI-TOF) m/z = 2052.4 [M + Ag^+].

(8) Reviews on template directed synthesis: (a) Dietrich, B.; Viout, P.; Lehn, J.-M. *Macrocyclic Chemistry*; VCH: Weinheim, 1993. (b) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *Acc. Chem. Res.* **1993**, *26*, 469. (c) Hoss, R.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 375. (d) Atwood, J. L., Davies, J. E. D., Macnicol, D. D., Vögtle, F., Ed. *Comprehensive Supramolecular Chemistry*; Elsevier Science Ltd., Oxford, 1996; Vol. 9. (e) Höger, S. *J. Polym. Sci. Pol. Chem.* **1999**, *37*, 2685. (f) That solvent molecules can act as templates in the oxidative acetylene coupling has also been proposed: Berscheid, R.; Vögtle, F. *Synthesis* **1992**, 58.

(9) An increase of the addition time from 4 to 7 days has within the experimental error no influence on the composition of the crude product. This is in accordance with theoretical predictions, which indicate that the yield of dimer *is not* a very sensitive function of the rate of addition, and a remarkable increase can only be observed if the rate of addition is changed by several orders of magnitude: Fastrez, J. *Tetrahedron Lett.* **1987**, *28*, 419.

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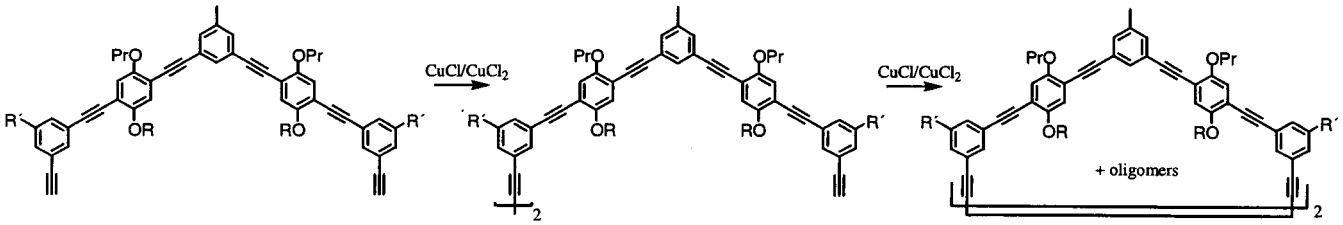
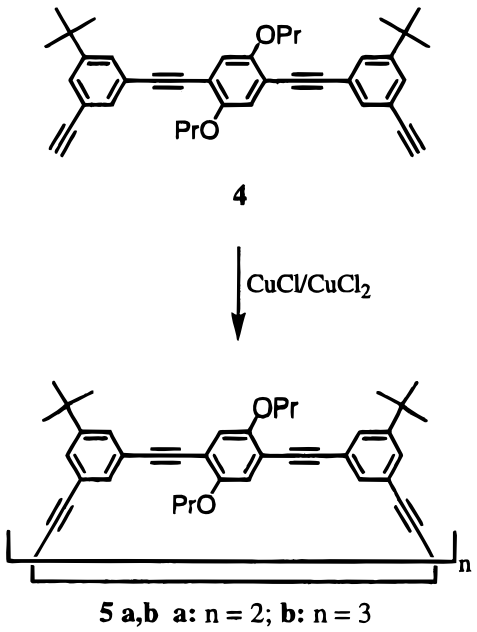
Scheme 1



Scheme 2



around 60 °C. Higher temperatures complicate the workup, which leads to a decreased amount of isolated crude product (about 60−80%), along with a diminished amount of isolated cyclic dimer (as low as 20−40%). For the same reason, it is necessary to stop heating the catalyst mixture immediately after the bisacetylene addition is complete. Workup is then performed after stirring overnight at room temperature. Using this procedure, we were able to isolate **3a** in up to 70% yield (from 1,2-dichloroethane) and **3c** in up to 50% yield (from pyridine) by recrystallization of the crude products.

We also investigated the oxidative cyclization of **4** at different temperatures (Scheme 2). The shape-persistent cyclic trimer **5b** is formed in about 35% yield regardless of whether the reaction was carried out at room temperature or 65 °C, along with higher oligomers and polymeric material.[11,12] However, at 65 °C, about 15−20% of the cyclic dimer **5a** is also formed, whereas its formation at room temperature is negligible.

The observations described here show that the intermolecular dimerization of functionalized bisacetylenes is strongly dependent on the arrangement of the functional groups, suggesting that the copper salts act as a template. In addition, the yield of cyclic dimer can be remarkably enhanced when the coupling is performed at higher temperatures, probably due to an increased mobility of the intermediate formed after the first coupling reaction.

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(10) For the effect of temperature on the product ratio of the cyclocondensation of A_2 and B_2 monomers, see, e.g.: Hammond, P. J.; Beer, P. D.; Hall, C. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1161.

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

(12) The cyclizations of **4** were performed under the same conditions as used for the cyclization of **1**. ^{1}H NMR analysis of the crude cyclization products showed no absorptions for residual acetylenic protons. The GPC trace of the crude room-temperature cyclization product contains resolved peaks of oligomers at 1840 (∼35%) and 2500 (∼15%) Da, as well as an unresolved hump of higher oligomers and polymers (∼50%) with no indication of the formation of cyclic dimers. Similarly, the GPC trace of the crude 60 °C cyclization product contains resolved peaks for oligomers at 1140 (15−20%), 1840 (∼35%), and 2510 (∼5−10%) Da, as well as an unresolved hump of higher oligomers and polymers (30−40%). The molecular weights are based on polystyrene calibration of the SEC columns. MALDI-TOF spectra (using 1,8,9-trihydroxyanthracene as the matrix in the presence of silver trifluoroacetate) shows for the crude room-temperature cyclization product signals at 1104.29 (cyclic dimer), 1656.67 (cyclic trimer), 1763.62 (cyclic trimer + Ag^+), 2316.04 (cyclic tetramer + Ag^+), 2870.5 (cyclic pentamer + Ag^+), 3423.89 (cyclic or noncyclic hexamer + Ag^+), and 3976.82 (cyclic or noncyclic heptamer + Ag^+) Da. However, it is worth mentioning that MALDI-TOF spectroscopy strongly overestimates the amount of small cycles compared to larger ones. Therefore, the MALDI-TOF spectra of the crude 60 °C cyclization product are dominated by signals at 1105.90 (cyclic dimer), 1656.55 (cyclic trimer), 1763.48 (cyclic trimer + Ag^+), and 2316.49 (cyclic tetramer + Ag^+) Da. As also observed previously (ref 11), we were not able to purify the reaction products, either by column chromatography or recrystallization.