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Preparation of Cyclophanes by Room-Temperature Ring-Closing Alkyne Metathesis with Imidazolin-2-iminato Tungsten Alkylidyne Complexes

Stephan Beer,[†] Kai Brandhorst,[†,‡] Jörg Grunenberg,[‡] Cristian G. Hrib,[†] Peter G. Jones,[†] and Matthias Tamm*[,†]

Institut für Anorganische und Analytische Chemie and Institut für Organische Chemie, Technische Universität Carolo-Wilhelmina, Hagenring 30, D-38106 Braunschweig, Germany

m.tamm@tu-bs.de

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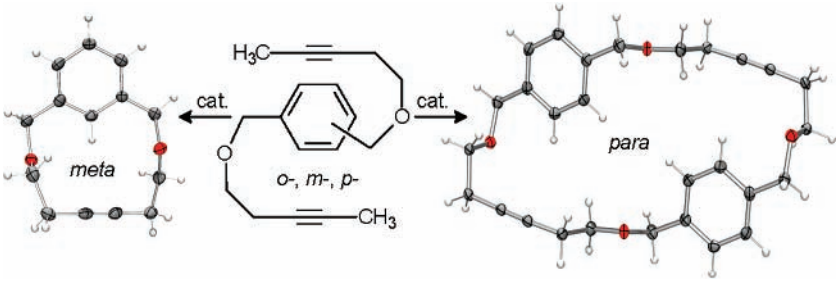
ABSTRACT



Room-temperature ring-closing alkyne metathesis of 1,2-, 1,3-, and 1,4-bis(3-pentynyloxymethyl)benzenes has been investigated in the presence of catalytic amounts of an imidazolin-2-iminato tungsten alkylidyne complex. The *m*- and *p*-diynes selectively form the respective [10]metacyclophane or [10.10]paracyclophane, respectively, whereas a mixture of monomeric and dimeric cycloalkynes is obtained in the case of the *o*-diyne. DFT calculations reveal that the different selectivities can be attributed to the relative thermodynamic stability of the emerging cyclophanes.

Alkene metathesis has revolutionized both organic chemistry and material science in an extraordinary fashion.[1] In particular, ring-closing metathesis (RCM) of dienes has emerged during the past decade as an excellent tool for the synthesis of complex natural products, although the lack of stereocontrol of the newly formed double bond is still a shortcoming.[2] This drawback can be avoided by the application of ring-closing alkyne metathesis (RCAM) of diynes, which allows a subsequent semireduction of the C−C triple bond in the cycloalkyne either by Lindlar reduction or by hy-

[†] Institut für Anorganische und Analytische Chemie.
[‡] Institüt für Organische Chemie.

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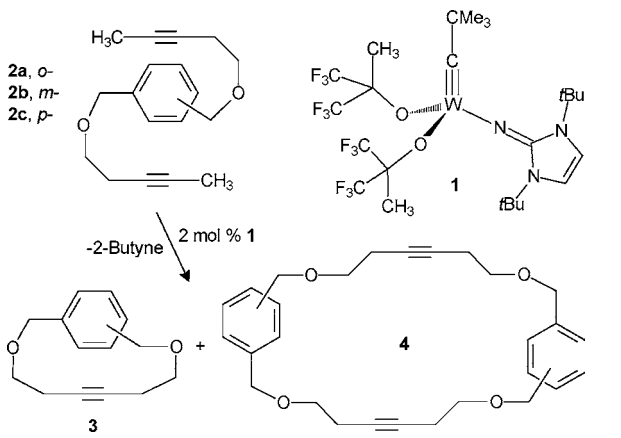
drosilylation/protodesilylation to obtain selectively the respective *Z*- or *E*-alkenes.[3] However, only a limited number of well-defined alkylidyne complexes are known to date that fulfill the expectations for an alkyne metathesis catalyst with regard to its activity, substrate compatibility, and required reaction temperature.[4] Among these, the neopentylidyne complex [$Me_3CC{\equiv}W(OCMe_3)_3$] represents the most widely used tungsten-based species.[5] In addition, several catalytically active systems have been established that are based on $Mo(CO)_6$ and phenol additives[6] or that rely on the activation of molybdenum(III)triamido complexes of the general type [$Mo\{N(tBu)Ar\}_3$].[7] Recently, we have introduced well-defined imidazolin-2-iminato tungsten alkylidyne complexes such as **1** (Scheme 1), which exhibit unprecedented catalytic

Scheme 1



activity in alkyne cross-metathesis (ACM) of 1-phenylpropynes at ambient temperature.[8] Efficient RCAM to afford a dioxacycloalkyne was also achieved and, in continuation of this work, we present a comparative study of the impact of the substitution pattern on the cyclization of *o*-, *m*- and *p*-bis-(3-pentynyloxymethyl)benzenes, **2**. Successful ring-closure by alkyne metathesis would allow convenient access to unsaturated derivatives of [10]cyclophanes, a class of compounds originally established more than 50 years ago by Cram and co-workers.[9,10]

The diynes **2** were prepared by Williamson etherification of 3-pentyn-1-ol with the appropriate 1,2-, 1,3-, or 1,4-dibromoxylenes, respectively. In a typical experiment, RCAM was achieved by stirring a 4.5 mM solution of **2a**−**c** and the catalyst **1** (2 mol %) in hexane at room temperature under reduced pressure (350 mbar) to remove 2-butyne continuously. After 2 h, the reaction mixture was filtered through alumina to remove the catalyst, and evaporation of the solvent afforded white crystalline solids, which were analyzed by NMR and GC/MS techniques. In the case of **2b**, exclusive formation of a single product was observed, which exhibits a characteristic ^{1}H NMR resonance at 8.30 ppm in $CDCl_3$ assignable to the arylic proton in the 2-position. This significant downfield shift can be attributed to the penetration of this hydrogen atom into the deshielding area of the C−C triple bond, an observation that clearly suggested the formation of the [10]metacyclophane **3b** in an exceptionally selective manner.[11] This assumption was unequivocally confirmed by an X-ray diffraction analysis of single crystals obtained in 93% yield by cooling of a hexane solution to 4 °C. The molecular structure of **3b** is shown in Figure 1, revealing the existence of an unstrained 13-membered ring with C−H distances of 3.02 Å between the hydrogen atom H7 and the alkyne carbon atoms C1 and C2. It should be noted, however, that significantly shorter intermolecular contacts are observed, e.g., C1···H11 = 2.86 Å and C2···H11 = 2.83 Å.

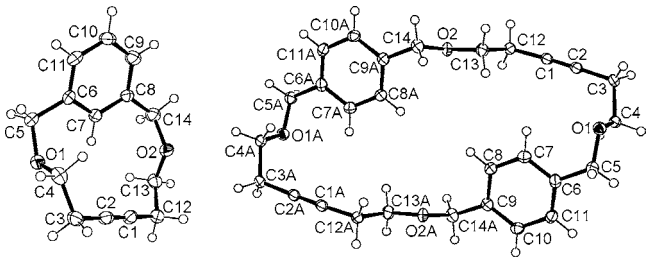


Figure 1. ORTEP diagrams of **3b** (left) and **4c** (right) with thermal displacement parameters drawn at 50% probability. Selected bond lengths [Å] and angles [deg] in **3b**/**4c**: C1−C2 1.189(5)/1.188(5), C1−C2−C3 178.1(4)/177.9(4), C2−C1−C12 177.9(4)/177.2(4).

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Employing **2c** also resulted in the clean formation of a single product, which precipitated from hexane solution in the course of the RCAM reaction. Recrystallization from $CHCl_3$ afforded a single-crystalline material in 68% yield, which proved to be the [10.10]paracyclophane **4c** by X-ray diffraction analysis.[12] The molecule resides on a crystallographic inversion center, generating a highly symmetric 28-membered ring with coplanar aromatic rings and alkyne moieties (Figure 1). At first, the absence of any detectable amounts of monomeric **3c** is somewhat surprising in view of the large number of [10]paracyclophanes, including the cycloalkyne 5-[10]paracyclophyne,[9a] which have been synthesized by acyloin ring closure.[9] However, this observation is in agreement with a previous report on the cyclization of xylylene-bridged bis(oxyphenylpropynes), which failed to give the 14-membered tolane derivative in case of a para-substituted diyne substrate.[13] Furthermore, it should be emphasized that the synthesis of the [10.10]paracyclophane **4c** by alkyne metathesis resembles the method for the preparation of naturally occurring [*n*,*n*]paracyclophanes (cylindrocyclophanes) by olefin metathesis dimerization.[14]

In contrast to the selective RCAM reactions of **2b** and **2c**, the use of the ortho-substituted isomer **2a** produced a mixture of **3a** and **4a** in a 24:76 ratio, determined by integration of the well-resolved ^{1}H NMR resonances of the benzylic and aliphatic CH_2O hydrogen atoms. Both isomers could be separated by fractional crystallization, and single crystals of the [10]orthocyclophane **3a** could be obtained from the supernatant hexane solution after removal of dimeric **4a**. An X-ray diffraction analysis confirmed the formation of a 12-membered ring; however, the structure could not be adequately refined because of modulation and twinning effects. Attempts to interpret the data in a more satisfactory manner are ongoing.

To rationalize the striking differences in the selectivity of the RCAM reactions with **2a**, **2b**, and **2c**, we carried out a series of DFT calculations on all six cyclophanes **3** and **4**.[15] In analogy to the reversible nature of the olefin metathesis reaction,[14a,b,16] it is reasonable to propose that the catalyst **1**, which is active at room temperature, is able to establish an equilibrium between **3** and **4** by reversible ring-opening and ring-closing metathesis (RORCM)[17] reactions (eq 1)

$$\mathbf{3} + \mathbf{3} \rightleftharpoons \mathbf{4} \qquad (1)$$

and that the associated standard Gibbs free energies $\Delta G°$ dictate the respective product ratios. Table 1 summarizes the $\Delta G°$ values and the corresponding equilibrium constants K_c together with the calculated and experimental ratios. The calculations fully confirm our experimental observations, since the equilibrium should lie almost completely on the

Table 1. Gibbs Free Energies $\Delta G°$ and Equilibrium Constants K_c for the Reaction of Two Molecules **3** to Form Dimeric **4**

isomers	$\Delta G°$ (kcal mol^{-1})[a]	$K_c = [\mathbf{4}]/[\mathbf{3}]^2$ (M^{-1})	calcd ratio[b]	exp. ratio[c]
o- (**3a**, **4a**)	−2,78	1.1×10^2	77:23	24:76
m- (**3b**, **4b**)	+4.00	1.1×10^{-3}	100:0	100:0
p- (**3c**, **4c**)	−9.66	1.2×10^7	1:99	0:100

[a] $\Delta G° = -RT \ln K_c$ (T = 298 K). [b] Calculated molar ratio for c_0(monomer) = 4.5 mM. [c] Experimental molar ratio for c_0(monomer) = 4.5 mM.

(10) For books on cyclophanes, see: (a) Gleiter, R., Hopf, H., Eds. *Modern Cyclophane Chemistry*; Wiley-VCH: Weinheim, 2004. (b) Diederich, F., Ed. *Cyclophanes*; The Royal Society of Chemistry: Cambridge, 1991. (c) Vögtle, F. *Cyclophane Chemistry*; John Wiley & Sons: New York, 1993.

(11) For instance, the corresponding saturated all-carbon [10]metacyclophane could be obtained in 9% and 22% yield by using Suzuki−Miyaura coupling or nickel-catalyzed Grignard cyclocoupling, respectively: (a) Smith, B. B.; Hill, D. E.; Cropp, T. A.; Walsh, R. D.; Cartrette, D.; Hipps, S.; Shachter, A. M.; Pennington, W. T.; Kwochka, W. R. *J. Org. Chem.* **2002**, *67*, 5333−5337. (b) Tamao, K.; Kodarna, S.-i.; Nakatsuka, T.; Kiso, Y.; Kumada, M. *J. Am. Chem. Soc.* **1975**, *97*, 4405−4406.

(12) For the synthesis of the corresponding saturated all-carbon [10.10]-paracyclophane in 12% yield by acyloin condensation followed by Clemmensen reduction, see: Maseal, M.; Kerdelhub, J.-L.; Batsanov, A. S.; Begley, M. J. *J. Chem. Soc., Perkin Trans. I* **1996**, 1141−1151.

(13) Brizius, G.; Billingsley, K.; Smith, M. D.; Bunz, U. H. F. *Org. Lett.* **2003**, *5*, 3951−3954. The authors state explicitly that "repeated attempts to close **10** to **14** under different conditions failed with a variety of catalytic in situ systems". This is in conflict with an erroneous illustration in Scheme 1 of their report, which indicates a yield of 18% for the 14-membered cyclic monomer.

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(15) The gas-phase global minima were obtained by full conformational analysis using the MMFF94 force field (Halgren, T. A *J. Comp. Chem.* **1996**, *17*, 490−519) together with a Monte Carlo torsional sampling as implemented in the Macromodel 9.5 program (*MacroModel*, version 9.5; Schrödinger, LLC: New York, 2007). The respective lowest-energy conformation was optimized by applying density functional theory. The B3LYP hybrid functional (Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652) was employed, and all atoms were described by the 6-311G(d,p) basis set. Enthalphic and entropic contributions were calculated by statistical thermodynamics as implemented in the Gaussian03 set of programs (Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian03*, Revision D.02; Gaussian, Inc.: Wallingford CT, 2004).

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monomer side in case of **3b**/**4b** and on the dimer side in case of **3c**/**4c**. In contrast, the calculations for the ortho system reveal that both **3a** and **4a** should be present in detectable amounts for an initial monomer concentration of $c_0 = 4.5$ mM.

Figure 2 shows the calculated ratios **3**:**4** against the initial monomer concentration in the range $10^{-7}-10^{4}$ M. As expected, variation of the concentration most strongly affects the monomer-to-dimer ratio for the ortho system **3a**/**4a**. In contrast, the meta monomer remains the only detectable species at relevant concentrations (up to one mol L^{-1}), whereas significant amounts of the experimentally elusive para monomer should only form under very high dilution conditions. We emphasize that consideration of only monomers and dimers represents an oversimplification, since a more detailed description must also take into account the formation of larger oligomeric species, in particular at higher concentration. Furthermore, kinetic effects should also be contemplated in the future, but we assume that the differences in energy between relevant transition states are in a similar order of magnitude as the energy differences between the monomeric and dimeric cycloalkynes **3** and **4**, so that their relative thermodynamic stability is a good measure for predicting the outcome of reversible ring-closing reactions.

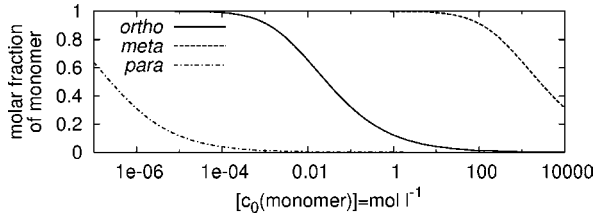

Figure 2. Molar fraction of [10]cyclophanes **3** as a function of the initial monomer concentration c_0.

Supporting Information Available: Full synthetic, characterization, theoretical calculation, and X-ray structural details. This material is available free of charge via the Internet at http://pubs.acs.org.

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