## **1,1'-Linked Cyclopropane Derivatives: The Helical Conformation of Quinquecyclopropanol**\*\*

Takuya Kurahashi, Sergei I. Kozhushkov, Heiko Schill, Kathrin Meindl, Stephan Rühl, and Armin de Meijere\*

Dedicated to Professor Kenneth B. Wiberg on the occasion of his 80th birthday

Single-, double-, and even triple-helical structures play important roles for biological and synthetic macromolecules; however, for relatively small organic compounds helical arrangements are not common.<sup>[1]</sup> In most biological macromolecules such a helical structure is favored and maintained by hydrogen bonds. Helical conformations of saturated compounds without functional substituents is observed less frequently. Aliphatic perfluorocarbon chains are known to adopt a helical structure in the crystalline state and in solution as a result of electrostatic repulsion of the fluorine substituents in the 1- and 3-positions,<sup>[2]</sup> poly(ethyleneglycol) adopts a helical conformation in isobutyric acid solution,<sup>[3]</sup> and permethyldecasilane forms a helix in a helical schizophyllan matrix.<sup>[4]</sup> As formally saturated hydrocarbons have no driving forces to adopt helical conformations (apart from van der Waals interactions), their conformations range from "zig-zag" for linear hydrocarbons on one hand to helical for certain enantiomerically pure [n] triangulanes  $(1)^{[5,6]}$  on the other. Helicity of the latter, however, is predetermined by their rigid helical shape.



 $[1,1';2',1'';2'',1''';...;2^{n-2},1^{n-1}]$ Oligocyclopropanes (2), which have been discovered as substructures in two natural products from different sources,<sup>[7]</sup> exhibit quite interesting conformational properties depending on their substituents.

[\*] Dr. T. Kurahashi, Dr. S. I. Kozhushkov, Dr. H. Schill, Prof. Dr. A. de Meijere Institut für Organische und Biomolekulare Chemie Georg-August-Universität Göttingen Tammannstrasse 2, 37077 Göttingen (Germany) Fax: (+ 49) 551-399-475 E-mail: armin.demeijere@chemie.uni-goettingen.de K. Meindl, Dr. S. Rühl Institut für Anorganische Chemie Georg-August-Universität Göttingen Tammannstrasse 4, 37077 Göttingen (Germany)

- [\*\*] This work was supported by the State of Lower Saxony and the Fonds der Chemischen Industrie. T.K. is indebted to the Alexander von Humboldt Foundation for a research fellowship. The authors are grateful to Yasuhide Inokuma for the X-ray structure analysis of compound 18-DNB.
  - Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Thus, helical conformations were demonstrated for [1,1';2',1'']tercyclopropanedimethanol (**2**, n=3,  $R^1=R^2=$  CH<sub>2</sub>OH) and for [1,1';2',1'';2'',1''';2''',1'''']quinquecyclopropanedimethanol (**2**, n=5,  $R^1=R^2=$  CH<sub>2</sub>OH) in solution as well as in the solid state, while other compounds of this type adopted different conformations, at least in the crystals.<sup>[8]</sup>

Based on an earlier observation that bicyclopropyl (3) in the gaseous and the liquid state preferentially adopts a synclinal (gauche) conformation,<sup>[9]</sup> one is intuitively led to conceive that the higher 1,1'-linked oligocyclopropanes 4 (n >3) would prefer helical arrangements in which all bicyclopropyl subunits have either (+)- or (-)-gauche conformations. This notion is indeed supported by density functional theory (DFT) computations at the B3LYP/6-31G(d) level of theory. Since the only known higher 1,1'-linked oligocyclopropanes 4, the 1,1-dicyclopropylcyclopropane 4a (n=3, $R^1 = R^2 = H$ ,<sup>[10]</sup> its derivatives **4b-d** (n = 3,  $R^1 = R^2 = OH$ ,<sup>[11]</sup> OSiMe<sub>3</sub>,<sup>[11c,d]</sup> and OMs<sup>[11d]</sup>), and 1,1<sup>'''</sup>-dimethyl-[1,1';1',1'';1'',1''']quatercyclopropane **4e**  $(n=4, R^1=R^2=$ Me),<sup>[12]</sup> had not been structurally characterized at all, we set out to prepare such  $[1,1';1',1'';...;1^{n-2},1^{n-1}]$ oligocyclopropanes endowed with polar functionalities, in order to investigate their structural features.

The Matteson homologation methodology<sup>[13]</sup> was considered to be employable as the key step. In this, an organyl substituent migrates from the negatively charged boron to an adjacent carbon in a borate complex with inversion of configuration.<sup>[14]</sup> For example, intermediate 7, which is formed upon treatment of a lithium halocarbenoid like 6 (prepared from dibromocyclopropane (5) and n-butyllithium)with a borane, is converted into the corresponding 1organocyclopropylborane 8 (Scheme 1). The latter can then undergo the same transformation repeatedly upon treatment with the in situ generated carbenoid 6, eventually leading to 1,1<sup>n</sup>-disubstituted oligocyclopropanes 4 ( $n \ge 2$ ). Indeed, lithium halocyclopropylidenoids upon treatment with organoboronates have been found to produce cyclopropaneboronates in good yields.<sup>[13]</sup> Thus, when trimethylene methylboronate (9) was treated with a solution of dibromocyclopropane  $(5)^{[15]}$  in tetrahydrofuran, to which *n*-butyllithium had been



**Scheme 1.** Example of a Matteson-type homologation.

Angew. Chem. Int. Ed. 2007, 46, 6545-6548

© 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



added at -110 °C, and this treatment was iterated four more times, a mixture of cyclopropylcyclopropaneboronates was formed. Subsequent oxidation with hydrogen peroxide in the presence of sodium hydroxide gave a mixture of the cyclopropylcyclopropanols **10–12** in good overall yield (Scheme 2).



**Scheme 2.** Facile synthesis of bis-, ter-, and quatercyclopropane derivatives by a Matteson-type homologation of 1,1-dibromocyclopropane.

These products could be separated by column chromatography, and each cyclopropanol was individually transformed to the corresponding 3,5-dinitrobenzoate—**10**-DNB (81% yield), **11**-DNB (70%), and **12**-DNB (72%)—by reaction with 3,5-dinitrobenzoyl chloride (**13**). Crystals of all three dinitrobenzoates were grown and subjected to X-ray diffraction analysis.<sup>[16]</sup>

In order to obtain an even higher 1,1'-linked oligocyclopropanol than **12**, the same iterative homologation was performed with cyclopropaneboronates **14**<sup>[17]</sup> and **15** (Scheme 3).<sup>[18,19]</sup> Indeed, the [1,1';1',1'';1'',1''';1''',1'''']quinquecyclopropan-1-ol (**18**) was isolated in 32 % (from **14**) and 22 % yield (from **15**) along with tercyclopropanol **16** (22 % from **14**, 6 % from **15**) and quatercyclopropanol **17** (28 % from **14**, 14 % from **15**). The quinquecyclopropanol **18** was also converted to its dinitrobenzoate **18**-DNB, and the latter was analyzed by Xray diffraction.<sup>[16]</sup>

The DFT computations<sup>[20-25]</sup> for [1,1';1',1'';1'',1''';1''',1'''';1''',1'''';1''',1''''] sexicyclopropane (**19**) in the gas phase predicted dihedral angles of  $-55.0, +60.6, +62.5, +59.4, \text{ and } -52.5^{\circ}$  (see the Supporting Information) along the chain for the lowest energy conformer; in other words, the inner quatercy-clopropane fragment in this molecule has an all-(+)-gauche conformation, while the two outer cyclopropyl groups are (-)-gauche oriented. In the crystal, the quinquecyclopropane moiety of **18**-DNB, on going from the cyclopropanol to the



*Scheme 3.* Synthesis of quinquecyclopropanol **18** and computed conformation of sexicyclopropane **19**.

terminal cyclopropane moiety, has dihedral angles between each two neighboring cyclopropanes of 52.9, 64.5, 60.3, and  $-68.6^{\circ}$ , respectively (averages for the two independent molecules in the asymmetric unit); this orientation is completely analogous to that calculated for the inner section of the sexicyclopropane. In the crystals of the other three dinitrobenzoates **10**-DNB, **11**-DNB, and **12**-DNB the 1,1'linked cyclopropane moieties adopt analogous helical allgauche conformations.

The chemical behavior of the 1,1'-oligocyclopropylcyclopropanols 16-18 is also noteworthy as it differs from that commonly observed for 1-cyclopropyl-substituted cyclopropanols. Thus, an attempted conversion of the alcohols 17 and 18 to the corresponding bromides—which were desired for reduction to the unsubstituted quatercyclopropane 4 f (n = 4,  $\mathbf{R}^1 = \mathbf{R}^2 = \mathbf{H}$ ) and quinquecyclopropane **4g** (n = 5,  $\mathbf{R}^1 = \mathbf{R}^2 =$ H)-did neither occur with complete retention of their cyclopropane moieties (cf. Ref. [26]) nor with iterative ring enlargement by way of cascade rearrangements involving all their cyclopropane moieties.<sup>[11c,d,27]</sup> Instead, in each case only the cyclopropanol moiety itself underwent ring opening to a  $\beta$ -bromoketone fragment (cf. Ref. [28]) to give the 3-bromopropionyl-1,1'-oligocyclopropanes 20 and 21 in 64 and 92% yield, respectively, with retention of the other three-membered rings (Scheme 4).

$$H = 4 \qquad \begin{array}{c} Ph_{3}P \cdot Br_{2}, Py \\ \hline CH_{2}Cl_{2} \\ 17 \ n = 4 \\ 18 \ n = 5 \end{array} \qquad \begin{array}{c} Ph_{3}P \cdot Br_{2}, Py \\ \hline CH_{2}Cl_{2} \\ 20 \ n = 4 \ (64\%) \\ 21 \ n = 5 \ (92\%) \end{array}$$

**Scheme 4.** Ring opening of [1,1';1',1'';1'',1''']quatercyclopropan-1-ol (**17**) and [1,1';1',1'';1'',1''';1''',1''']quinquecyclopropan-1-ol (**18**) upon attempted conversion into the corresponding bromides.

Thus, both the 1,1-linkage and the 1,2-linkage of oligocyclopropanes lead to helical structures of relatively small molecules. The consequences of this preferred arrangement of  $[1,1';1',1'';...;1^{n-2},1^{n-1}]$ oligocyclopropane units are currently being studied.

## **Experimental Section**

Representative procedure: Synthesis of 18: n-Butyllithium in hexane (2.2 mmol, 0.91 mL of a 2.42 M solution in hexane) was added dropwise under argon to a solution of 1,1-dibromocyclopropane  $(5)^{[15]}$ (440 mg, 2.2 mmol) in anhydrous THF (20 mL) at -110 °C, and the mixture was stirred at -110°C for 5 min. The mixture was then treated with trimethylene cyclopropaneboronate (14) (252 mg, 2.0 mmol), and the resulting mixture was gradually warmed to room temperature within approximately 12 h. After that, dibromide 5 (440 mg, 2.2 mmol) was added at 25 °C, and the mixture was cooled to -110°C again. n-Butyllithium (2.2 mmol, 0.91 mL of a 2.42 м solution in hexane) was added at -110°C, and the mixture was gradually warmed to room temperature again. This procedure was repeated another three times. Finally, hydrogen peroxide (8 mmol, 908 mg, 820 µL of 30% aq. solution) and sodium hydroxide (5 mmol, 5 mL of 1N aq. solution) were added at 0°C, and the reaction mixture was stirred at 25°C for 6 h. The resulting mixture was extracted thoroughly with diethyl ether ( $6 \times 50$  mL), and the combined organic extracts were dried (MgSO<sub>4</sub>). The solution was concentrated under reduced pressure, and the residue was separated and purified by column chromatography (80 g of flash silica gel, 2×60 cm column, hexane/ether 10:1 $\rightarrow$ 4:1,  $R_{\rm f}$ =0.25 in hexane/ether 4:1) to yield quinquecyclopropan-1-ol 18 (139 mg, 32%) as a colorless oil. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 2.55$  (brs, 1H; OH), 1.66–1.57 (m, 1H; CH), 0.71-0.66 (m, 2H; CH<sub>2</sub>), 0.56-0.51 (m, 2H; CH<sub>2</sub>), 0.49-0.44 (m, 2H; CH<sub>2</sub>), 0.39–0.31 (m, 2H; CH<sub>2</sub>), 0.29–0.21 (m, 6H; CH<sub>2</sub>), 0.12– 0.06 (m, 4H; CH<sub>2</sub>), -0.02 to -0.09 ppm (m, 2H; CH<sub>2</sub>); <sup>13</sup>C NMR  $(62.9 \text{ MHz}, \text{CDCl}_3): \delta = 59.9 (C-OH), 25.7 (C), 25.2 (C), 23.6 (C), 14.8$ (CH), 12.4 (2CH<sub>2</sub>), 9.7 (2CH<sub>2</sub>), 8.0 (2CH<sub>2</sub>), 7.5 (2CH<sub>2</sub>), 1.9 ppm (2CH<sub>2</sub>). The structure of 18 was proved by X-ray crystal structure analysis of its 3,5-dinitrobenzoate 18-DNB.[16]

Received: May 7, 2007 Published online: July 24, 2007

**Keywords:** borates · cyclopropane · helical structures · lithiation · rearrangement

- For a highlight on this topic see: C. Schmuck, Angew. Chem. 2003, 115, 2552–2556; Angew. Chem. Int. Ed. 2003, 42, 2448– 2452.
- [2] K. Monde, N. Miura, M. Hashimoto, T. Taniguchi, T. Inabe, J. Am. Chem. Soc. 2006, 128, 6000-6001, and references [2,3] cited therein.
- [3] a) M. L. Alessi, A. I. Norman, S. E. Knowlton, D. L. Ho, S. C. Greer, *Macromolecules* 2005, *38*, 9333–9340; See also: b) L. Malysheva, A. Onipko, R. Valiokas, B. Liedberg, *J. Phys. Chem.* A 2005, *109*, 7788–7796.
- [4] S. Haraguchi, T. Hasegawa, M. Numata, M. Fujiki, K. Uezu, K. Sakurai, S. Shinkai, Org. Lett. 2005, 7, 5605-5608.
- [5] Reviews: a) A. de Meijere, S. I. Kozhushkov, H. Schill, *Chem. Rev.* 2006, *106*, 4926–4996; b) A. de Meijere, S. I. Kozhushkov, *Chem. Rev.* 2000, *100*, 93–142; c) A. de Meijere, S. I. Kozhushkov in *Advances in Strain in Organic Chemistry, Vol. 4* (Ed.: B. Halton), JAI, London, 1995, pp. 225–282.
- [6] a) A. de Meijere, A. F. Khlebnikov, R. R. Kostikov, S. I. Kozhushkov, P. R. Schreiner, A. Wittkopp, D. S. Yufit, Angew.

Chem. 1999, 111, 3682-3685; Angew. Chem. Int. Ed. 1999, 38, 3474-3477; b) A. de Meijere, A. F. Khlebnikov, S. I. Kozhushkov, R. R. Kostikov, P. R. Schreiner, A. Wittkopp, C. Rinderspacher, H. Menzel, D. S. Yufit, J. A. K. Howard, Chem. Eur. J. 2002, 8, 828-842; c) A. de Meijere, A. F. Khlebnikov, S. I. Kozhushkov, K. Miyazawa, D. Frank, P. R. Schreiner, B. C. Rinderspacher, D. S. Yufit, J. A. K. Howard, Angew. Chem. 2004, 116, 6715-6719; Angew. Chem. Int. Ed. 2004, 43, 6553-6557; d) A. de Meijere, A. F. Khlebnikov, S. I. Kozhushkov, D. S. Yufit, O. V. Chetina, J. A. K. Howard, T. Kurahashi, K. Miyazawa, D. Frank, P. R. Schreiner, B. C. Rinderspacher, M. Fujisawa, C. Yamamoto, Y. Okamoto, Chem. Eur. J. 2006, 12, 5697-5721.

- [7] Review: J. Pietruszka, Chem. Rev. 2003, 103, 1051-1070.
- [8] A. G. M. Barrett, R. A. James, G. E. Morton, P. A. Procopiou, C. Boehme, A. de Meijere, C. Griesinger, U. M. Reinscheid, *J. Org. Chem.* 2006, *71*, 2756–2759, and references [6,7] cited therein.
- [9] A. de Meijere, W. Lüttke, F. Heinrich, Justus Liebigs Ann. Chem. 1974, 306–327.
- [10] a) F. Effenberger, W. Podszun, Angew. Chem. 1969, 81, 1046–1047; Angew. Chem. Int. Ed. Engl. 1969, 8, 976; b) O. M. Nefedov, I. E. Dolgii, I. B. Shvedova, R. N. Shafran, Bull. Acad. Sci. USSR Div. Chem. Sci. 1972, 21, 1834–1836; Izv. Akad. Nauk SSSR Ser. Khim. 1972, 21, 1885–1887; c) W. Weber, U. Behrens, A. de Meijere, Chem. Ber. 1981, 114, 1196–1199.
- [11] a) T. Imamoto, Y. Kamiya, T. Hatajima, H. Takahashi, *Tetrahedron Lett.* 1989, *30*, 5149–5152; b) T. Imamoto, T. Hatajima, N. Takiyama, T. Takeyama, Y. Kamiya, T. Yoshizawa, *J. Chem. Soc. Perkin Trans. 1* 1991, 3127–3135; c) N. S. Zefirov, S. I. Kozhushkov, T. S. Kuznetsova, *Zh. Org. Khim.* 1988, *24*, 447–448; *J. Org. Chem. USSR* 1988, *24*, 395–396; d) N. S. Zefirov, K. A. Lukin, S. I. Kozhushkov, T. S. Kuznetsova, A. M. Domarev, I. M. Sosonkin, *Zh. Org. Khim.* 1989, *25*, 312–319; *J. Org. Chem. USSR* 1989, *25*, 278–284.
- [12] a) J. L. Ripoll, J. C. Limasset, J. M. Conia, *Tetrahedron* 1971, 27, 2431–2452. For cyclic analogues of compounds of type 4 see also a recent review (Ref. [5a]) and references therein.
- [13] Reviews: a) A. Pelter, K. Smith, H. C. Brown, *Borane Reagents*, Academic Press, New York, **1988**; b) D. S. Matteson in *Stereodirected Synthesis with Organoboranes, Vol. 32*, Springer, Berlin, **1995**. Recent applications: c) A. N. Thadani, R. A. Batey, *Tetrahedron Lett.* **2003**, *44*, 8051–8055; d) P. R. Blakemore, M. S. Burge, J. Am. Chem. Soc. **2007**, *129*, 3068–3069.
- [14] a) D. S. Matteson, D. Majumdar, J. Am. Chem. Soc. 1980, 102, 7588-7590; b) M. Duraisamy, H. M. Walborsky, J. Am. Chem. Soc. 1984, 106, 5035-5037; c) R. L. Danheiser, A. C. Savoca, J. Org. Chem. 1985, 50, 2401-2403; d) R. Inoue, H. Shinokubo, K. Oshima, Tetrahedron Lett. 1996, 37, 5377-5380.
- [15] C. Blankenship, L. A. Paquette, Synth. Commun. 1984, 14, 983– 987.
- [16] CCDC 642257 (10-DNB), CCDC 642256 (11-DNB), CCDC 642258 (12-DNB), and CCDC 642255 (18-DNB) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_ request/cif.
- [17] According to Beilstein X-fire, boronate 14 (chemical name: 2cyclopropyl-[1,3,2]dioxaborinane) is not known (see also the Supporting Information).
- [18] 1-Cyclopropylcyclopropaneboronate 15 [chemical name: 2-(bicyclopropyl-1-yl)-[1,3,2]dioxaborinane] was prepared from bicyclopropylidene<sup>[19]</sup> in 27% yield adopting a published protocol: K. Utimoto, M. Tamura, M. Tanouti, K. Sisido, *Tetrahedron* 1972, 28, 5697 – 5702. For details see the Supporting Information.
- [19] For reviews on bicyclopropylidenes see: a) A. de Meijere, S. I. Kozhushkov, A. F. Khlebnikov, *Zh. Org. Khim.* **1996**, *32*, 1607– 1626; *Russ. J. Org. Chem.* **1996**, *32*, 1555–1575; b) A. de Meijere,

© 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

## Communications

S. I. Kozhushkov, A. F. Khlebnikov, *Top. Curr. Chem.* 2000, 207, 89–147; c) A. de Meijere, S. I. Kozhushkov, *Eur. J. Org. Chem.* 2000, 3809–3822; d) A. de Meijere, S. I. Kozhushkov, T. Späth, M. von Seebach, S. Löhr, H. Nüske, T. Pohlmann, M. Es-Sayed, S. Bräse, *Pure Appl. Chem.* 2000, 72, 1745–1756.

- [20] Geometries were optimized by density functional theory (DFT) computations employing Becke's three-parameter functional with the Lee–Yang–Parr correlation functional (B3LYP)<sup>[21-24]</sup> utilizing the 6-31G(d) basis set<sup>[24]</sup> as implemented in Gaussian 03.<sup>[25]</sup>
- [21] A. D. Becke, Phys. Rev. A 1988, 38, 3098-3100.
- [22] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* 1988, 37, 785-789.
  [23] R. G. Parr, W. Yang, *Density Functional Theory of Atoms and*
- Molecules, Oxford University Press, New York, **1989**. [24] W. J. Hehre, L. Radom, P. v. R. Schleyer, J. A. Pople, *Ab Initio*
- [24] W. J. Freme, L. Kadom, F. V. K. Schleyer, J. A. Pople, Ab Initio Molecular Orbital Theory, Wiley-Interscience, New York, 1986.

- [25] Gaussian 03 (Revision C.02): M. J. Frisch et al., see the Supporting Information.
- [26] a) A. de Meijere, S. I. Kozhushkov, T. Späth, N. S. Zefirov, J. Org. Chem. 1993, 58, 502-505; b) A. de Meijere, S. I. Kozhushkov, T. Späth, Org. Synth. 2000, 78, 142-151.
- [27] L. Fitjer, D. Wehle, M. Noltemeyer, E. Egert, G. M. Sheldrick, *Chem. Ber.* 1984, 117, 203-221.
- [28] a) O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevskii, A. I. Savchenko, T. S. Pritytskaya, *Zh. Org. Khim.* 1991, *27*, 294–298; *J. Org. Chem. USSR* 1991, *27*, 250–253; b) M. V. Raiman, A. V. Pukin, V. I. Tyvorskii, N. De Kimpe, O. G. Kulinkovich, *Tetrahedron* 2003, *59*, 5265–5272; c) S. Baktharaman, S. Selvakumar, V. K. Singh, *Tetrahedron Lett.* 2005, *46*, 7527–7529; d) J. Jiao, L. X. Nguyen, D. R. Patterson, R. A. Flowers II, *Org. Lett.* 2007, *9*, 1323–1326.