ORGANIC LETTERS

2009
Vol. 11, No. 15
3450−3452

Chiral Crystallization: Freezing a Rapid Cope Rearrangement in the Solid State

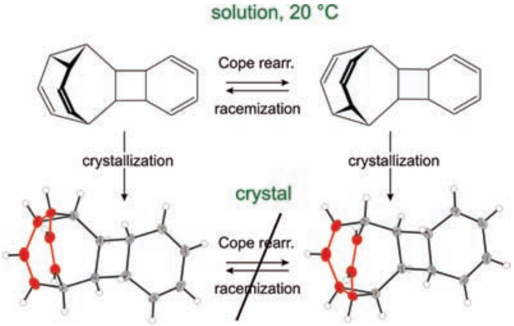
Jan Siegwarth, Jan Bornhöft, Christian Näther, and Rainer Herges*

Otto-Diels-Institut für Organische Chemie, Christian-Albrechts-Universität Kiel, Otto-Hahn-Platz 4, 24098 Kiel, Germany

rherges@oc.uni-kiel.de

Received June 12, 2009

ABSTRACT



Homotropylidene and its derivatives undergo a fast Cope rearrangement. A homotropylidene system (cyclooctatetraene dimer) is reported that racemizes rapidly by such a valence isomerization in solution at room temperature. In the solid state, however, this rearrangement is frozen, and the single crystals precipitating from the racemic solution contain only one enantiomer. Since very large crystals can be grown, the racemic solution in principle can be converted into a single enantiomer by crystallization.

About 10% of the known chiral organic compounds crystallize as conglomerates.[1] Pasteur manually separated the two oppositely handed crystal types of a tartrate salt and obtained enantiopure compounds.[2] While this procedure might be tedious on a large scale, enantioselective seeding of racemic solutions is an industrial process for enantioseparation.[3] As one of the two enantiomers preferentially crystallizes, the solution is enriched by the other enantiomer. In principle, a complete conversion of the racemate into one enantiomer in the solid state can be achieved if a rapid racemization refurnishes the 1:1 equilibrium of both enantiomers in the solution or melt during crystallization. Several examples of such spontaneous asymmetric crystallizations have been observed.[4] One of the first systematic investigations was performed by Pincock et al. in 1971 on the crystallization of 1,1′-binaphthyl from its racemic melt.[5] Crystallization of 200 samples and determination of the optical rotation resulted in a Gaussian distribution of enantiomeric excess. Averged over all experiments, the specific rotation, as expected, was close to zero. Another very well investigated example of spontaneous generation of optical activity is the crystallization of sodium chlorate upon stirring. $NaClO_3$ is an achiral salt in solution, but it crystallizes in *dextrorotatory* and *levorotatory* crystals.[6] The chiral symmetry breaking was explained by secondary nucleation. A randomly generated “mother crystal” splits into a large number of secondary crystals of the same handedness. Later, Viedma demonstrated that a slight enantiomeric excess (5%) in a suspension of

---

[1] Eliel, E.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

[2] Pasteur, L. *C. R. Hebd. Seance Acad. Sci. Paris* **1848**, *26*, 535.

[3] (a) Wang, Y; Chen, A. M. *Org. Proc. Res. Dev.* **2008**, *12*, 282. (b) Wood, W. M. L. *Chirality Ind. II* **1997**, 119.

[4] For reviews, see: (a) McBride, J. M.; Carter, R. L. *Angew. Chem.* **1991**, *103*, 298. (b) Crusats, J.; Veintemillas-Verdaguer, S.; Ribo, J. M. *Chem.*—*Eur. J.* **2006**, *12*, 7776.

[5] Pincock, R. E.; Perkins, R. R.; Ma, A. S.; Wilson, K. R. *Science* **1971**, *174*, 1018.

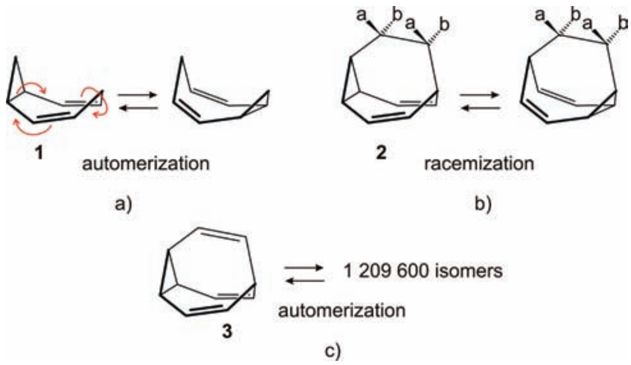
[6] (a) Kondepundi, D. K.; Kaufmann, R. J.; Singh, N. *Science* **1990**, *250*, 975. (b) Kondepudi, D. K.; Bullock, K. L.; Digits, J. A.; Hall, J. K.; Miller, J. M. *J. Am. Chem. Soc.* **1993**, *115*, 10211.

10.1021/ol901326p CCC: $40.75

dextrorotatory and *levorotatory* NaClO$_3$ crystals in water was amplified to complete chiral purity by simple abrasive grinding. He replaced the hypothesis of an initial single chiral mother crystal by a nonlinear autocatalysis and recycling process.[7] The underlying thermodynamic concept was discussed in detail.[4b,8] Ethylenediammonium sulfate is another example for directed chiral symmetry breaking.[9] Recently, interesting applications of the deracemization of amino acid derivatives by abrasive grinding were reported.[10−12]

We now report on the formation of chiral crystals from a nonrotatory solution of a homotropylidene derivative (cyclooctatetraene dimer) which is racemizing via a rapid Cope rearrangement. Furthermore, we present the first X-ray structures of the two cyclooctatetraene dimers and the tetramer. 3,4-Homotropylidene **1** undergoes a rapid Cope rearrangement between two identical structures at temperatures >100 °C (Scheme 1a).[13] Doering et al. coined the term molecules with "fluctual structure" for compounds undergoing fast automerizations.[14] Bridging of homotropylidene **1** with an ethylene unit in positions 4 and 8 substantially lowers the activation barrier of the Cope rearrangement. The automerization reaction in the parent system tricyclo-[3.3.2.04.6]decadiene-(2.7) **2** ($a = b =$ H, Scheme 1b) is fast at room temperature.[15] Further substitution at positions 9 and 10 (a ≠ b, Scheme 1 b) breaks the C_s symmetry of **2**. The molecules now are chiral, and the Cope rearrangement interconverts the two enantiomers. Such a chiral homotropylidene derivative is easily accessible by dimerization of cyclooctatetraene.

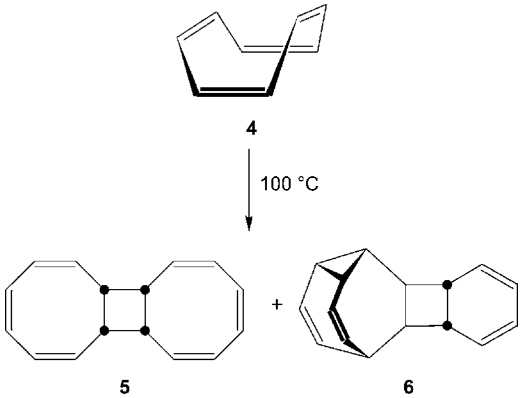
Scheme 1[a]



[a] Cope rearrangements in polycyclic systems: (a) automerization of homotropylidene; (b) racemization of symmetrically substituted tricyclo-[3.3.2.0^{4,6}]decadienes-(2.7) **2**; (c) bullvalene **3** undergoes a degenerate Cope rearrangement yielding 10!/3 symmetry equivalent isomers.

Cyclooctatetraene **4** dimerizes upon heating to 100 °C yielding two valence isomers, a cyclobutane dimer **5** (melting point 52 °C) and a homotropylidene derivative **6** (melting point 72 °C), respectively (Scheme 2).[16] The latter exhibits a rapid valence isomerization via Cope rearrangement in solution (Scheme 2).[15,17,18] The rate of this interconversion was determined by Schröder et al. to be 187800 s^{-1} (determined at 0 °C).[19] The rate of this rearrangement exceeds the one of bullvalene **3** by a factor of 350. Upon UV irradiation, the homotropylidene derivative **6** can be converted to bullvalene **3** and benzene via cycloreversion in 80% yield.[20]

Scheme 2



The structure of the cyclooctatetraene dimer **5** was discussed controversially. We now confirm the *syn* configuration of **5** proposed by Schröder et al. unambiguously by X-ray diffraction (cf. Figure 1).

Figure 1. ORTEP drawing of the crystal structure of cyclooctatetraene dimer **5** (determined at 170 K); thermal ellipsoids shown with 50% probability. The assymmetric unit contains two crystallographic independent molecules.

Figure 2 shows the ORTEP drawing of the X-ray structure of the cyclooctatetraene dimer **6** (melting point 72 °C). As

---

(7) Viedma, C. *Phys. Rev. Lett.* **2005**, *94*, 065504.

(8) (a) Blackmond, D. G. *Chem.—Eur. J.* **2007**, *13*, 3290. (b) Crusats, J.; Veintemillas-Verdaguer, J. M. R. *Chem.—Eur. J.* **2007**, *13*, 10303. (c) Blackmond, D. G. *Chem.—Eur. J.* **2007**, *13*, 10306.

(9) (a) Cheung, P. S. M.; Gagnon, J.; Surprenant, J.; Tao, Y.; Xu, H.; Cuccia, L. A. *Chem. Commun.* **2008**, 987. (b) Cheung, P. S. M.; Cuccia, L. A. *Chem. Commun.* **2009**, 1337.

(10) Kaptein, B.; Noorduin, W. L.; Meekes, H.; van Enckevort, W. J. P.; Kellog, R. M.; Vlieg, E. *Angew. Chem.* **2008***120*7336; *Angew. Int. Ed.* **2008**, *47*, 7226.

(11) Noorduin, W. L.; Meekes, H.; Enckevort, W. J. P.; Millemaggi, A.; Leeman, M.; Kaptein, B.; Kellog, R. M.; Vlieg, E. *Angew. Chem.* **2008***120*6545; *Angew. Chem., Int. Ed.* **2008**, *47*, 6445.

(12) Viedma, C.; Ortiz, J. E; de Torres, T.; Izumi, T.; Blackmond, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 15274.

(13) Doering, W., v. E.; Roth, W. R. *Tetrahedron* **1963**, *19*, 715.

(14) Doering, W. v. E.; Roth, W. R. *Angew. Chem.* **1963***75*27; *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 115.

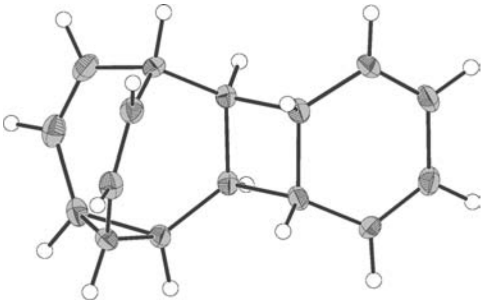


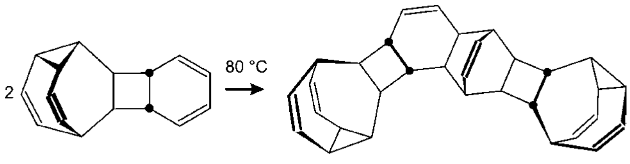
Figure 2. ORTEP drawing of the crystal structure of homotropylidene derivative **6** (determined at 170 K); thermal ellipsoids shown with 50% probability.

in the case of dimer **5**, the structure assigned by Schröder et al. could be confirmed. Surprisingly, in the crystal phase the degenerate Cope system is frozen. The X-ray structure determination at 170 K as well as at 298 K exhibit almost the same bond lengths (1.556 Å vs 1.555 Å for the C−C bond which is broken during the Cope rearrangement and 2.456 Å vs 2.448 Å for the C−C bond which is formed). Therefore, an isomerization in the crystal state can be excluded. Our findings are in agreement with ^{13}C MAS NMR spectra recorded by Poupko et al.[18] No line broadening and no magnetization transfer effects and no cross peaks in 2D exchange spectra were observed on heating to 55 °C. This indicates that no rearrangement took place on the time scale of the experiment (∼20 s).

Even though homotropylidene derivative **6** is chiral and rapidly racemizing in solution, only one of the enantiomers was found in the unit cell of the crystal. The corresponding space group is $P2_12_12_1$, which is chiral and noncentrosymmetric. Hence, the crystals are chiral. Large single crystals weighing several grams were obtained by slow evaporation of the solvent. Unfortunately, determination of the absolute structure of the crystals was not possible due to the lack of heavy atoms. Nevertheless, since no abrasive/grinding method was used for crystalliziation, one can assume that a conglomerate of corresponding *dextro*- and *levo*-crystals was obtained.

Besides dimers **5** and **6**, Schröder et al. isolated a corresponding cyclooctatetraene tetramer **7**.[16c] Hoesch et al. obtained the cyclooctatetraene tetramer **7** in 30% yield by heating the dimer **6** to 80 °C.[21] Formation of the tetramer **7** via Diels−Alder reaction was assumed (cf. Scheme 3). We were able to grow crystals of the tetramer **7** that were suitable for X-ray analysis. The data (ORTEP drawing, Figure 3) unequivocally confirm the structure proposed previously.

Scheme 3



6 **7**

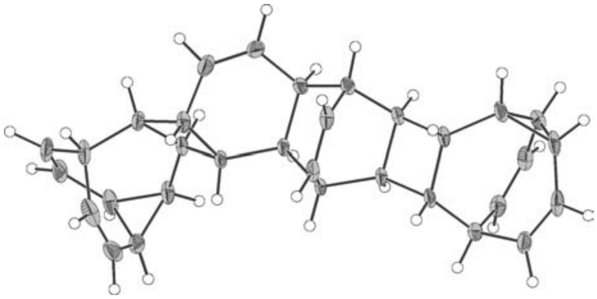


Figure 3. ORTEP drawing of the crystal structure of the cyclooctatetraene tetramer **7**; thermal ellipsoids shown with 50% probability.

The tetramer **7** contains two homotropylidene subunits. In contrast to the cyclooctatetraene dimer **6** that crystallized in the chiral space group $P2_12_12_1$, tetramer **7** was found to crystallize in space group *P*-1. Since the latter is centrosymmetric and achiral, both enantiomers of the tetramer **7** crystallize as a racemate. For both compounds, the rapid valence isomerization observed in solution is frozen in the solid state.

Supporting Information Available: Experimental procedures and characterization of compounds **5**−**7**; NMR spectra of compounds **5**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901326P

---

(15) Merenyi, R.; Oth, J. F. M.; Schröder, G. *Chem. Ber.* **1964**, *97*, 3150.

(16) (a) Reppe, W.; Schlichtign, O.; Klager, K.; Toepel, T. *Liebigs Ann. Chem.* **1948**, *560*, 1. (b) Schröder, G.; Martin, W. *Angew. Chem.* **1966**, *78*, 117; *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 130. (c) Schröder, G. *Chem. Ber.* **1964**, *97*, 3131.

(17) Nakanishi, H.; Yamamoto, O. *Chem. Lett.* **1973**, 1273.

(18) Poupko, R.; Müller, K.; Krieger, C.; Zimmermann, H.; Luz, Z. *J. Am. Chem. Soc.* **1996**, *118*, 8015.

(19) Schröder, G.; Oth, J. F. M.; Merényi, R. *Angew. Chem.* **1965**, *77*, 774; *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 752.

(20) Schröder, G. *Chem. Ber.* **1964**, *97*, 3140.

(21) Hoesch, L.; Dreiding, A. S.; Oth, J. F. M. *Isr. J. Chem.* **1972**, *10*, 439.