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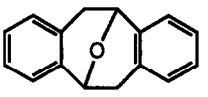
MOLECULAR CLEFTS 2. AN ANALOGUE OF KAGAN'S ETHER AS A MOLECULAR CLEFT: SYNTHESIS AND CLATHRATE FORMATION WITH ETHYL ACETATE

Michael Harmata* and Charles L. Barnes
Department of Chemistry University of Missouri-Columbia, Columbia, MO 65211

Summary: A convenient synthesis of 5α,8α,14α,17α–5,6,8,9,14,15,17,18–octahydro-5,17:8,14-diepoxy-dibenzo[e,e']benzo[1,2-a:4,5-a']dicyclooctene (**2**) is described. This molecular cleft represents the parent of a new class of chiral molecular tweezers. It forms a clathrate with ethyl acetate which is stable even after 12 hours at 0.1 Torr. The structure of **2** was established by spectral and X-ray data.

Recently, we reported the development of methodology for the synthesis of analogues of Kagan's ether, **1**.[1,2] In that paper, we cited 5α,8α,14α,17α–5,6,8,9,14,15,17,18–octahydro-5,17:8,14-diepoxydibenzo [e,e']benzo [1,2-a:4,5-a']dicyclooctene **2** as an appropriate target for the study of molecular clefts[3] related to **1**. Compound **2** represents the parent of a new class of molecular tweezers which we are in the course of



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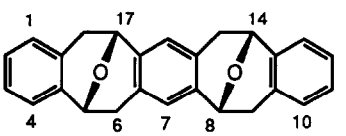
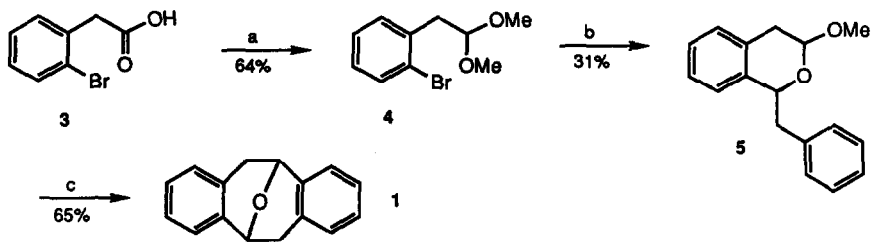


2

preparing and studying.[4] In this paper we report the synthesis of **2**, and its clathrate formation with ethyl acetate.

After much experimentation we discovered that the methodology which we had developed previously would not work well for the preparation of **2**. We thus reevaluated an approach developed for the synthesis of **1** as outlined in Scheme 1. Metalation of the readily available dimethyl acetal of ortho-bromophenylacetaldehyde,[5] alkylation with phenylacetaldehyde, and acid catalyzed ring closure afforded acetal **5** in fair yield. Cyclization of this compound as previously described gave **1** in good yield.[1] This methodology proved to be the key to the facile preparation of **2**.

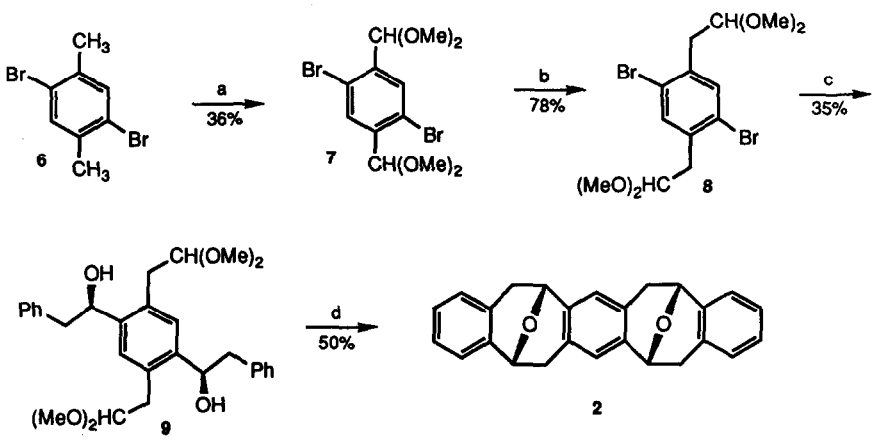
The synthesis of **2** is shown in Scheme 2. Commercially available 2, 5-dibromo-p-xylene **6** was oxidized with chromic acid and converted to the acetal **7** in 36% overall yield.[6] While this sequence proceeded in low yield, it was easy to perform. Conversion of **7** to **8** via a hydrolysis, homologation with methoxymethyl triphenyl phosphorane[7] and acetal formation proceeded in 78% overall yield after chromatography and recrystallization. Metal-halogen exchange with 4.3 equivalents of t-BuLi followed by alkylation with phenylacetaldehyde gave **9** in 35% yield after flash chromatographic purification.[8] Ring closure with tosic acid followed by treatment with $SnCl_4$ produced **2** in 50% after chromatography. No optimization has yet been attempted to improve this sequence.



(a) 1. BH_3.THF, 0^oC-25^oC, 8.5 h; 2. PCC (ref. 5); 3. MeOH, $(MeO)_3CH$, NH_4Cl, reflux, 3 h. (b) n-BuLi, THF, -78^oC, 25 min. then $PhCH_2CHO$; 2. TsOH, CH_2Cl_2, -20^oC, overnight. (c) $SnCl_4$, CH_2Cl_2, -78^oc, 1.25 h.

Scheme 1

The gross structure of **2** was easily established by its spectral characteristics. The 300 MHz ^1H NMR displayed a six proton multuplet at 7.14 - 7.03 ppm, a two proton doublet at 6.93 ppm (J = 7.3) and a 2 proton singlet at 6.70 ppm. Two two proton doublets at 5.25 ppm and 5.18 ppm (J = 6.1) were assigned to the protons at carbons 5, 8, 14, and 17 in accordance with assignments made for **1**.[9] Similarly, the exo and endo protons attached to carbons 6, 9, 15, 18 were observed at 3.49 ppm (dd, J = 6.2, 15.7) and 3.46 (dd J = 6.3, 16.3), respectively. Other data provided further confirmation of the structure of **2**.[10]



(a) 1. CrO_3, (ref. 6); 2. MeOH, H_2SO_4, reflux, 3.5h. (b) 1. 1N HCl, reflux, 2.5h; 2. $Ph_3PCHOMe$, THF, 25^oC; 3. MeOH, H_2SO_4, reflux, 12 h. (c) 4.3 eq. t-BuLi, THF, -78^oC, then $PhCH_2CHO$. (d) 1. cat. TsOH, CH_2Cl_2, -78^oC, 10 min., to 25^oC, 1 h; 2. $SnCl_4$, CH_2Cl_2, -78^oC, 30 min.

Scheme 2

Support for the structural assignment and confirmation of the relative stereochemical relationships in **2** were established by X-ray analysis.[11] The structure is shown in Figure 1.[12] Noteworthy is the hole created as two molecules of **2** pack nearly face to face in the lattice. The dimensions of this cavity appears to be large enough to contain a guest (ca. 10.7Å x 7.3Å x ∞).[13] Indeed, ethyl acetate was apparently occluded within the channels of the crystal lattice of **2**. NMR analysis indicated a stoichiometry of ca. 2.7:1 (**2**:ethyl acetate) for the clathrate.[14] This ratio remained constant even after 12 hours at .1 Torr.[13] The stability of the inclusion complex is

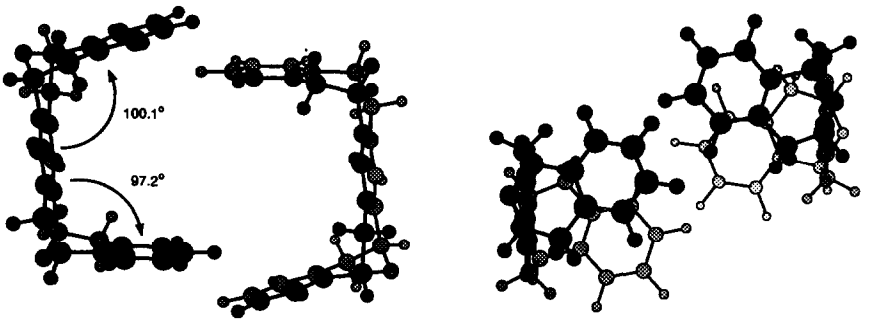


Figure 1. Crystal Structure of 2 (298° K). Side (left) and top (right) projections are shown.

noteworthy. At room temperature, disorder made it impossible to unambiguously define the orientation of the solvent molecule though it appeared to be located within the hole shown in Figure 1. X-ray data accumulated at a lower temperature (163°K) refined better and though still disordered, a reasonable location for the ethyl acetate could be formulated as shown in Figure 2.[11,15] The carbon-oxygen single bond of the solvent on the center of symmetry of the hole in the crystal lattice. This inclusion pattern suggests that symmetrical E-alkenes may be good candidates for clathrate formation and that this lattice structure may be useful for separating certain E/Z mixtures of alkenes; an idea we are currently trying to test.

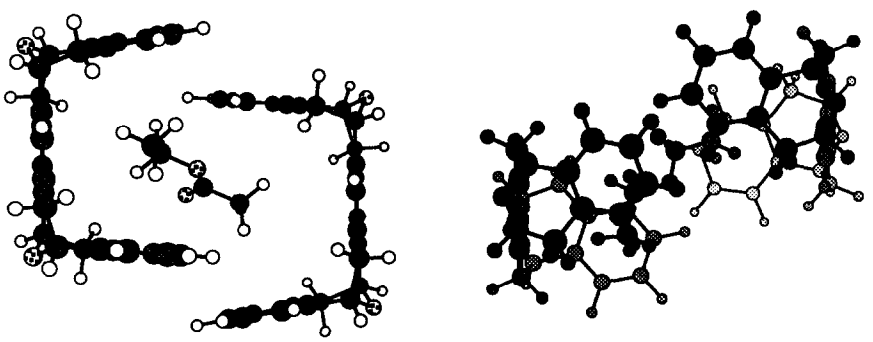


Figure 2. Crystal structure of 2-ethyl acetate clathrate (163° K). Side (left) and top (right) projections are shown. See reference 15.

As a hybrid of structural principles delineated by Toda,[16] Hart,[17] and Weber[18] for clathrate forming molecules, **2** and its congeners should provide further fascinating results in the area of solid state inclusion.[19] Further synthetic studies, clathrate preparations,[20] and solution phase binding experiments[21] are in progress and will be reported in due course.[22]

Acknowledgements: We are grateful to the National Science Foundation for partial support of the NMR (PCM-8115599) and MS (PCM-88117116) facilities at the University of Missouri-Columbia. Thanks to Dale Sanson for high field NMR data. Thanks to Joy E. Merritt for helping with naming **2**.

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(1) Harmata, M.; Murray, T. *J. Org. Chem.* **1989**, *54*, 3761.

(2) Wilcox and coworkers have made significant contributions in their studies of Troeger's base and its analogues. Troeger's is structurally very similar to **1**. See: (a) Adrian, J.C., Jr.; Wilcox, C.S. *J. Am. Chem Soc.* **1989**, *111*, 8055. (b) Sucholeiki, I.; Lynch, V.; Phan, L.; Wilcox, C.S. *J. Org. Chem.* **1988**, *53*, 98. (c) Wilcox, C.S.; Greer, L.M.; Lynch, V. *J. Am. Chem. Soc.* **1987**, *109*, 1865. (d) Larson, S.B.; Wilcox, C.S. *Acta Crystallogr., Sect. C. Cryst.-Struct. Commun.* **1986**, *C42*, 224. (e) Wilcox, C.S.; Cowart, M.D. *Tetrahedron Lett.* **1986**, 5563. (f) Wilcox, C.S. *Ibid.* **1985**, 5749.

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(8) The meso isomer of **9** was also formed in 35% yield. Its conversion to the "anticleft" meso isomer of **2** will be described elsewhere.

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(10) ^{13}C NMR ($CDCl_3$, 75 MHz) 137.9, 136.5, 131.8, 131.6, 129.3, 128.9, 126.7, 125.7, 125.1, 69.4, 69.2, 35.5 (slightly broadened). Anal Calcd for $C_{26}H_{22}O_2$: C, 85.22; H, 6.05. Found: C, 85.27; H, 6.07.

(11) X-ray data collected on an Enraf-Nonius CAD4 diffractometer, with a crystal of dimensions 0.15x0.25x0.40 mm. Space group $P2_1/c$ from systemic absences; Z=4. Cell dimensions at 298K, a=7.637(2), b=19.952(5), c=14.359(8) Å, β=90.09(3)°, V=2187(2) $Å^3$; at 163K, a=7.561(4), b=19.710(4), c=14.254(3) Å, β=90.19(3)°, V=2124(2) $Å^3$. At 298K, 2924 unique reflections were measured with MoKα radiation (λ=.71073Å) to $2\theta_{max}$=44°, with 2078 observed ($I \geq 3\sigma(I)$). The structure was solved by direct methods[23], and refined to R=0.055 and R_w=0.081. At 163K, 2954 unique reflections were measured, with 2002 observed. With the 298K structure as a starting model, refinement with this data gave R=0.052 and R_w=0.068. Refinements were performed with SDP.[24]

(12) The picture in the Figure was produced by CHEM-3D using the crystal coordinates of **2**. Hydrogens were added by CHEM-3D.

(13) This figure represents the distance between the least squares planes of the middle benzene rings and the distance between the inner terminal benzene rings of the two molecules of **2** shown in Figure 1.

(14) The crystal used in the X-ray and NMR study was grown from ethyl acetate by slow evaporation. Recrystallization of **2** from ethyl acetate gave crystals with a 2.7:1 ratio (**2**:ethyl acetate), a figure which also remained constant after 12 hours at 0.1 Torr. The disparity between the X-ray data, which suggests a 2:1 **2**:ethyl acetate ratio, and the NMR data may be rationalized both in terms of NMR integration error and particularly the simultaneous inclusion of other solvents, especially water. Indeed, the clathrate analyzed for 81.32% carbon and 6.24% hydrogen, too low in carbon for a 2:1 stoichiometry. In addition, volatile impurities are evident since desolvation (100°C, .1 Torr, overnight) of the clathrate gave the pure analytical sample mentioned in reference 10.

(15) The ethyl acetate in this Figure was constructed by joining 6 of 10 atom positions (generated from 5 unique atom positions about the inversion center) located in this region of the crystal by considering appropriate bond lengths and angles. This works reasonably but not perfectly. For example, the C=O bond length of the ethyl acetate constructed in this way is only .81Å.

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(19) For recent, comprehensive reviews of clathrate chemistry, see: (a) *Topp. Curr. Chem.* **1987**, *140*. (b) *Ibid.* **1988**, *149*.

(20) Compound **2** also forms a clathrate with iodine. Harmata, M.; Barnes, C.L. Unpublished results from these laboratories.

(21) ^1H NMR experiments ($CDCl_3$, 25°C) with picric acid and acryloyl chloride suggest no significant interaction between the would-be guests and **2**. This is not too surprising in view of the shallowness of the cleft in **2**.

(22) This work was presented at the 198th National Meeting of the American Chemical Society, Miami Beach, FL; ORGN 202.

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