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Stereoselective Cyclotetramerization of a 3-(Hydroxymethyl)salicylaldehyde

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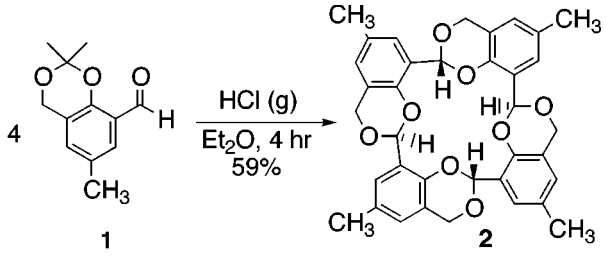
ABSTRACT



Both 3-(hydroxymethyl)-5-methylsalicylaldehyde and its acetonide condense in the presence of hydrogen chloride in ether to form macrocyclic S_4-symmetric tetraacetal 2. The reaction is completely oligo- and stereoselective, forming only the tetramer and only the achiral (*R*,*S*,*R*,*S*)-stereoisomer. Acid-catalyzed equilibration studies and molecular mechanics calculations indicate that the stereoselectivity is thermodynamic in origin. In the crystal the saddle-shaped molecules of 2 form coaxial stacks reminiscent of the packing of Pringles potato chips.

Macrocycles are prominent in both natural products and synthetic molecules designed to bind metal ions or other targets of molecular recognition.[1] The repetitive substructures typical of synthetic macrocycles such as crown ethers[2] or calixarenes[3] allow a simple synthetic strategy based on cyclooligomerization of a suitable monomer unit. However, these cyclooligomerizations are often unselective in the ring sizes that are formed, necessitating careful optimizations, tedious separations, or template-based syntheses. Here we describe the facile cyclization of a 3-(hydroxymethyl)-salicylaldehyde under acidic conditions, where acetal formation leads specifically and in good yield to a cyclic tetramer containing an inner 16-membered ring. Remarkably, the reaction is completely stereospecific, with only one of four possible stereoisomers being formed.

Acetonide-protected 3-(hydroxymethyl)-5-methylsalicylaldehyde (**1**), prepared in two steps from commercially available 2,6-bis(hydroxymethyl)-4-methylphenol,[4] reacts when treated in ether solution with a brisk stream of hydrogen chloride gas to form ether-insoluble macrocycle **2** in 59% yield (eq 1). The unprotected 3-(hydroxymethyl)-5-methylsalicylaldehyde (**3**)[5] reacts similarly to give **2** in 53% yield. The macrocyclic acetal isolated by filtration from these reactions is pure by ^{1}H NMR but is usually slightly pink in color; it may be decolorized by crystallization from dichloromethane/ether. Vigorous bubbling of HCl is essential, as adding HCl slowly or using other acids leads primarily to hydrolysis of acetonide **1** (or macrocyclic acetal **2**) to form aldehyde **3**. The formation of **2** from **3** under rapid flushing

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(2) Bradshaw, J. S.; Izatt, R. M.; Bordunov, A. V.; Zhu, C. Y.; Hathaway, J. K. Crown Ethers. In Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F.; Lehn, J.-M., Eds. *Comprehensive Supramolecular Chemistry*; Elsevier Science Ltd.: Exeter, UK, 1996; Vol. 1, pp 35−95.

(3) Gutsche, C. D. *Calixarenes*. In *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1989.

(4) (a) Fraser, C.; Johnston, L.; Rheingold, A. L.; Haggerty, B. S.; Williams, G. K.; Whelan, J.; Bosnich, B. *Inorg. Chem.* **1992**, *31*, 1835−1844. (b) Chirakul, P.; Hampton, P. D.; Bencze, Z. *Abstr. Pap. Am. Chem. Soc.* **1998**, *216*, ORGN-118.

(5) Xie, R. G.; Zhang, Z. J.; Yan, J. M.; Yuan, D. Q. *Synth. Commun.* **1994**, *24*, 53−58.

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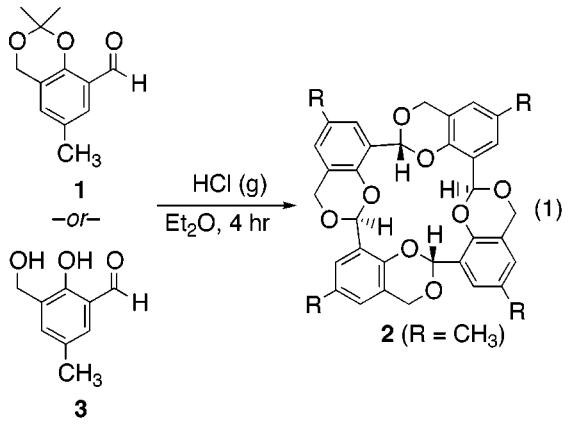
with hydrogen chloride suggests that HCl may shift the equilibrium in favor of dehydration by protonating or hydrogen bonding to the water produced on cyclization.



The spectral characteristics of macrocycle **2**,[6] especially its very simple ^{1}H and ^{13}C NMR spectra, indicate that it is formed as a single molecular species without any sign of rings of other sizes. Mass spectral data identify its nuclearity as a tetramer, corresponding to an inner 16-membered ring. The asymmetry of the acetal carbon gives rise to four possible diastereomers of **2**, of which only one is observed in amounts detectable by ^{1}H NMR (>98% pure). The observation of only one type of monomer unit by ^{1}H and ^{13}C NMR indicates that the stereoisomer must be either *RRRR* (maximally C_4-symmetric) or *RSRS* (S_4-symmetric). The alternative isomers with *RRSS* or *RRRS* configurations, possessing maximal C_i and C_1 symmetries, respectively, would be expected to give doubling or quadrupling of NMR resonances.

The identity of **2** as the *RSRS* diastereomer was established by X-ray crystallography (Figure 1).[7] The compound crystallizes without solvent in the tetragonal space group $I\bar{4}$, with the 4-fold rotary inversion axis passing through the center of the molecule. The molecule therefore possesses crystallographically required S_4 symmetry and is a rare example of a species that is achiral despite lacking a mirror plane or center of symmetry.[8] Alignment of the molecular S_4 axes along the crystallographic *c* axis results in a crystal packing pattern where the molecules form parallel stacks (Figure 2)

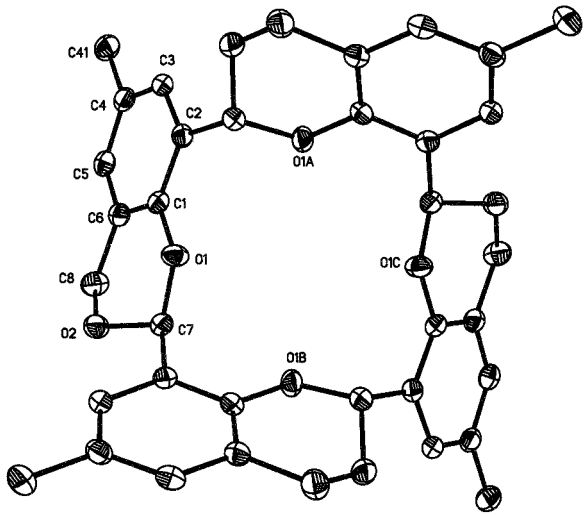


Figure 1. Thermal ellipsoid plot of **2**, with thermal ellipsoids shown at the 30% level. Selected bond lengths (Å) and angles (deg): C1−O1, 1.376(3); C7−O1, 1.446(3); C7−O2, 1.393(3); C8−O2, 1.428(3); O1−C7−O2, 110.4(2).

of saddle-shaped molecules resting snugly one atop the next (Figure 3), much like the packing of Pringles potato chips inside their cylindrical cans.

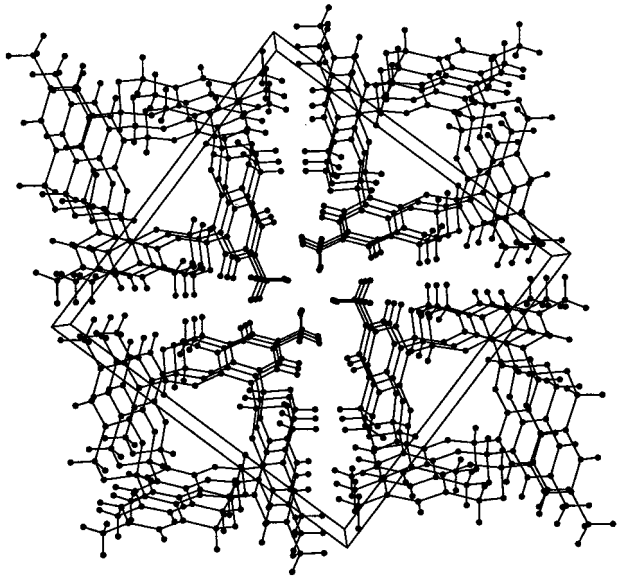


Figure 2. Unit cell diagram of **2** (viewed down the *c* axis), showing the relative arrangement of the stacks in the crystal.

The oligo- and stereoselectivity of the reactions that form **2** could be due, in principle, either to enhanced thermodynamic stability of (*RSRS*)-**2** over other isomers and oligomers, to its selective crystallization from the reaction mixture, or to kinetic preferences in its formation. Computational and chemical studies both strongly suggest that the

(6) Spectroscopic and analytical data for **2**. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, Ar−C*H*$_3$), 5.00, 5.13 (d, 14.7 Hz, 1H ea., Ar−C*HH*′−O), 6.26 (s, 1H, ArC*H*(OR)(OR′)), 6.86, 7.39 (d, 1.5 Hz, 1 H ea., 3,5-Ar−*H*). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 20.70 (−*C*H$_3$), 67.12 (Ar−*C*H$_2$), 93.57 (Ar−*C*H), 120.60 (4-*C*), 124.40 (6-*C*), 125.48, 126.41 (3, 5-*C*), 130.48 (2-*C*), 149.29 (1-*C*). IR (evapd film, cm^{-1}): 2914, 2857 (m, ν_{C-H}), 1616 (m, $\nu_{C=C}$), 1488 (s), 1403 (s), 1362 (w), 1332 (m), 1237, 1219 (s, ν_{C-O}), 1158 (m), 1095 (m), 1026 (w), 966 (s), 906 (m), 864 (m), 834 (w), 788 (w), 762 (w), 732 (m). FABMS: m/z = 593 (M + H). Anal. Calcd for $C_{36}H_{32}O_8$: C, 72.96; H, 5.44. Found: C, 73.00; H, 5.52.

(7) Crystals of **2** were grown as colorless blocks by slow diffusion of ether into chloroform. Crystal data for **2**: $C_{36}H_{32}O_8$, M = 592.62, T = 293 K, tetragonal, space group $I\bar{4}$, a = 15.7903(9) Å, c = 5.8038(6) Å, V = 1447.1(2) Å^3, Z = 2, ρ_c = 1.360 g cm^{-3}, μ (Mo Kα) = 0.096 mm^{-1}, F(000) = 624, crystal size 0.40 × 0.08 × 0.05 mm. A total of 1269 unique reflections with θ = 1.82−24.99° were collected. For 1075 reflections with $I > 4\sigma(I)$, R = 0.0377, GOF(F^2) = 1.040.

(8) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994.

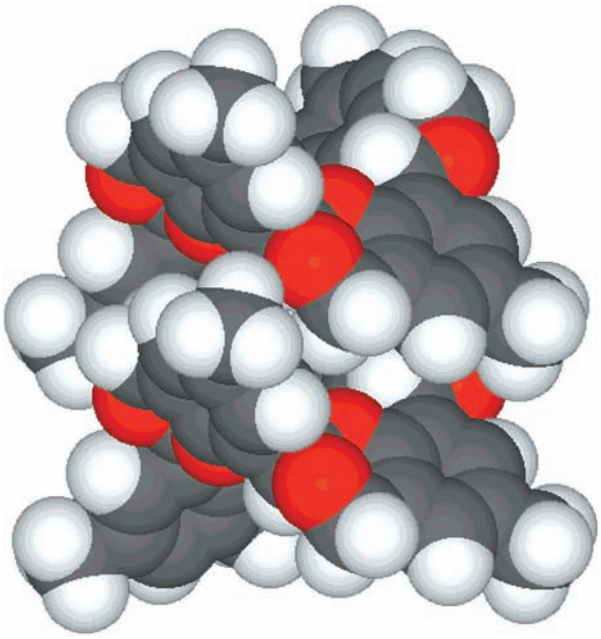


Figure 3. Space-filling diagram of two adjacent molecules of **2** in the crystal (viewed perpendicular to the *c* axis).

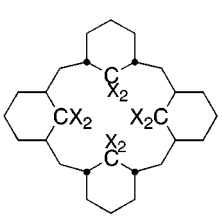
thermodynamic stability of **2** is responsible for its selective formation. Molecular mechanics studies of the four stereoisomers of the parent (R = H) macrocycle **2a** were performed using the MM3 force field[9] as implemented in the program MACROMODEL.[10] The potential suitability of this force field for modeling these compounds[11] is suggested by the excellent agreement between the crystallographically observed structure of **2** and the calculated minimum-energy conformation of (*RSRS*)-**2a**, with an rms deviation for the 40 nonhydrogen atoms in **2a** of only 0.17 Å. The MM3 calculations predict that the *RSRS* isomer is significantly more stable than any of the other isomers (Table 1), with its minimum-energy conformation 2.4 kcal/mol more stable than the minimum-energy conformation of the next most stable *RRRR*-isomer. Experimentally, no other isomers of **2** are observed even under conditions that allow the epimerization of the acetal stereocenters. After a solution of **2** in CD_2Cl_2 was allowed to stand in a sealed tube in the presence of camphorsulfonic acid for 2 months, the only species detectable by ^{1}H NMR were **2** and a small amount of the aldehyde **3** (due to hydrolysis by traces of water). The >98% isomeric purity of **2** under these conditions corresponds to a $\Delta G° >$ 2.3 kcal/mol for isomerization of **2** to its stereoisomers, in good agreement with the molecular mechanics calculations.

Table 1. Relative Conformational Energies of the Diastereomers of **2a**[a]

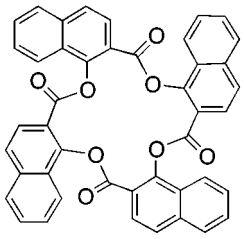
stereoisomer	maximal symmetry[b]	actual symmetry[b]	relative energy of most stable conformation (kcal/mol)
RSRS	S_4	S_4	0.00
RRRR	C_4	C_2	+2.39
RRRS	C_1	C_1	+3.18
RRSS	C_i	C_1	+6.64

[a] Conformational energies were calculated using the MM3 force field[9] as implemented in the program MACROMODEL 5.5.[10] [b] Maximal symmetry refers to the most symmetrical structure permitted by the stereocenters; actual symmetry is that found in the computed minimum-energy conformation.

The thermodynamic preference for the *RSRS* isomer of **2** is reminiscent of recent observations of Biali and co-workers, who obtained the annelated 16-membered macrocycles **4a** and **4b** as single D_{2d}-symmetric stereoisomers via hydrogenation of calix[4]arene.[12] In the case of calixketone **4b**, this preference is undoubtedly thermodynamic, since it was produced by base-catalyzed epimerization of a mixture of stereoisomers.[12b] Interestingly, both **4a** and **4b**, as well as saddle-shaped tetra-1-naphthoide **5**,[13] also form stacks in their crystals. It is intuitively appealing that saddle-shaped molecules should form stacks based on purely steric considerations,[14] and this motif may find future use as a design element in crystal engineering. The geometric features of the molecules appear to translate into their supramolecular structures in a straightforward manner. For example, the rather gently curving structure of **2** permits a 5.80 Å centroid-to-centroid approach within a stack, much smaller than is observed in the more strongly curved **4**−**5** (all with ∼10 Å centroid-to-centroid separations).



4a (X = H)
4b (X$_2$ = O)



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In summary, acid-catalyzed cyclization of 3-(hydroxymethyl)-5-methylsalicylaldehyde **3** or its acetonide **1** produces the macrocyclic tetraacetal **2** as a single stereoisomer in good yield. This route therefore provides an extremely efficient and simple entry into a macrocycle with a rigid,

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(10) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.
(11) Previous acetal-containing molecules have been modeled with MM3 with mixed success: (a) Rychnovsky, S. D.; Yang, G.; Powers, J. P. *J. Org. Chem.* **1993**, *58*, 5251−5255. (b) Tvaroska, I.; Carver, J. P. *J. Phys. Chem.* **1994**, *98*, 9477−9485. (c) Kneisler, J. R.; Allinger, N. L. *J. Comput. Chem.* **1996**, *17*, 757−766. (d) Ma, B. Y.; Schaefer, H. F.; Allinger, N. L. *J. Am. Chem. Soc.* **1998**, *120*, 3411−3422.
(12) (a) Columbus, I.; Biali, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 3060−3067. (b) Columbus, I.; Haj-Zaroula, M.; Biali, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 11806−11807.
(13) Gerdil, R.; Bernardinelli, G. *Acta Crystallogr. C* **1985**, *41*, 1523−1525.
(14) For another example of an S_4-symmetric 16-membered macrocycle where a similar crystal packing is enforced by intermolecular hydrogen−bonding, see: Seebach, D.; Matthews, J. L.; Meden, A.; Wessels, T.; Baerlocher, C.; McCusker, L. B. *Helv. Chim. Acta* **1997**, *80*, 173−182.

well-defined molecular structure and with an apparent propensity to adopt a stacked structure in crystalline form. Because the reaction is under thermodynamic control, this route should be compatible with a wide range of substituents at the 5-position of the hydroxymethylsalicylaldehyde. Given the intense current interest in molecular squares,[15] compounds such as **2** may find use as easily assembled scaffolds for holding four functional groups in a well-defined nanomolecular array.[16]

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Supporting Information Available: Tables of crystallographic parameters, atomic coordinates, bond lengths and angles, anisotropic thermal parameters, and hydrogen coordinates for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006630N

(15) Stang, P. J.; Olenyuk, B. *Acc. Chem. Res.* **1997**, *30*, 502−518.

(16) The methyl groups in **2** form a four-sided figure roughly intermediate between a square and a tetrahedron, with an "edge" distance of 10.5 Å and a "diagonal" distance of 12.2 Å (calculated for a square, 14.9 Å).