to be 112°. Molecular mechanics calculations yield a COC bond angle of 111.78°, more in agreement with experimental data.[49] In-phase ring stretching vibrational frequencies resulting from Raman spectroscopy for cycloalkanes and cyclic aliphatic ethers have been found to be roughly proportional to the bond angle.[47,50] A study on the correlation of planarity of rings with the substitution pattern in chlorinated dibenzodioxin was conducted by Chen, using IR data.[44]

The infrared vapor phase spectrum for 2,3,7,8-tetrachlorodibenzodioxin was recorded, and its COC bond angle (α) was calculated from IR data by using mass approximations for the terminal atom in a nonlinear XY_2 model and by neglect of the valence force field equations of the symmetric stretch-bending term. Details of these calculations, describing the molecular geometries using IR data for 2,3,7,8-tetrachloro- and other chlorinated dibenzodioxins and the limiting approximations, are reported elsewhere by Grainger, Reddy, and Patterson.[45] The COC bond angle (α) derived for 2,3,7,8-tetrachlordibenzodioxin was 115.1° compared with 115.6° determined from X-ray diffraction data.[43] In addition, for furan we calculate a COC bond angle of 110.8°, which is in agreement with the experimental value of 110.7 (2)°.[51]

With the new parameter set, we find that a near planar structure is favored for 2,3,7,8-tetrachlorodibenzodioxin. Our calculations indicate that an extreme "butterfly" conformation is not a minimum energy conformation. MM2 gives a COC angle of 116.9°, with one of the phenyl rings bent out of the plane, defined by the other phenyl group, by approximately 5°.

(48) Blukis, U.; Kasai, P. H.; Myers, R. J. *J. Chem. Phys.* **1963**, *38*, 2753.
(49) Allinger, N. L.; Chung, D. Y. *J. Am. Chem. Soc.* **1976**, *98*, 6798.
(50) Colthup, N.; Daly, L.; Wiberly, S. *Introduction to Infrared and Raman Spectroscopy*; Academic: New York, 1975.
(51) Bak, B.; Christensen, D.; Dixon, W. B.; Hansen-Nygaard, L.; Rastrup-Andersen, J.; Schottlander, M. *J. Mol. Spectrosc.* **1962**, *9*, 124.

Conclusions

MM2 parameters have been developed for divinyl and diphenyl ethers, as well as for a variety of halo-substituted vinyl and aromatic derivatives. Ab initio calculations were used to augment sketchy or lacking experimental data. The new MM2 parameters reasonably reproduce the conformational energies and molecular geometries for a wide variety of structures comprising this general class of organic compounds. Therefore, we recommend that users of MM2 substitute the new divinyl parameters for the ones incorporated into older (1985 and earlier) versions of the program. They should also correct the SSLOPE from 10.88 to 5.44 for the 2–41 atom type[14] and add the new halogen parameters.

Acknowledgment. This study was funded in part by the Agency for Toxic Substances and Disease Registry (ATSDR) under the auspices of the Comprehensive Environmental Response, Compensation, and Liability Act trust fund (Superfund), and in part by the NIH (Grant no. 5 R24RR02165). We are grateful to the Pittsburgh Supercomputing Center and the University of North Carolina Academic Computing Center for providing computational time.

Registry No. TCDD, 1746-01-6; TCDF, 51207-31-9; *cis*-HFC=CFH, 1630-77-9; *cis*-HFC=CHCl, 2268-31-7; *cis*-HBrC=CBrH, 590-11-4; *cis*-HClC=$CHCH_3$, 16136-84-8; *trans*-HFC=CFH, 1630-78-0; *trans*-HFC=CHCl, 2268-32-8; *trans*-HBrC=CBrH, 590-12-5; *trans*-HClC=$CHCH_3$, 16136-85-9; divinyl ether, 109-93-3; diphenyl ether, 101-84-8; furan, 110-00-9; vinyl chloride, 75-01-4; *cis*-1,2-dichloroethylene, 156-59-2; *trans*-1,2-dichloroethylene, 156-60-5; chlorobenzene, 108-90-7; 1,2-dichlorobenzene, 95-50-1; 1,3-dichlorobenzene, 541-73-1; 1,4-dichlorobenzene, 106-46-7; vinyl bromide, 593-60-2; 1,2-dibromoethylene, 540-49-8; bromobenzene, 108-86-1; 1,2-dibromobenzene, 583-53-9; 1,4-dibromobenzene, 106-37-6; vinyl fluoride, 75-02-5; 1,2-difluoroethylene, 1691-13-0; fluorobenzene, 462-06-6; 1,2-difluorobenzene, 367-11-3; 1,3-difluorobenzene, 372-18-9; 1-fluoro-3-chlorobenzene, 625-98-9; 1-bromo-4-fluorobenzene, 460-00-4.

Structurally New Macrocycles from the Resorcinol–Aldehyde Condensation. Configurational and Conformational Analyses by Means of Dynamic NMR, NOE, and T_1 Experiments

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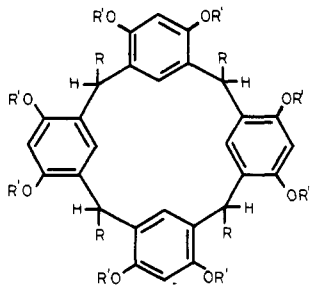
The acid-catalyzed condensation of resorcinol with heptanal or dodecanal followed by acetylation produces three stereoisomeric tetrameric macrocycles. The product distribution is controlled by the relative solubilities of the stereoisomeric octols in the reaction medium. These isomers comprise the previously described boat conformation (C_{2v} symmetry) and chair conformation (C_{2h} symmetry) plus a new one with a diamond-like conformation (C_s symmetry). The corresponding relative configurations of the alkyl substituents, determined from NOE enhancements and NMR spectra, are all-cis, cis-trans-trans, and cis-trans-cis. In all three isomers, the alkyl substituents are in the less hindered axial position. The thermodynamically more stable boat octols can be obtained selectively in high yields (50–80%) by heating the crude initial condensation mixtures at reflux for 4 h.

Introduction

In our search for building blocks for cavitands,[2] we became interested in macrocycles of structure I, which can be easily obtained in high yield by the acid-catalyzed condensation of resorcinol with aldehydes.[3] Although there are many possible stereoisomers of I, only two have been found experimentally. The configuration and conformation of these two isomers of the octaesters R = Ph

(1) (a) Department of Analytical Chemistry. (b) Department of Organic Chemistry.
(2) (a) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826–5828. (b) Cram, D. J. *Science (Washington D.C.)* **1983**, *219*, 1177–1183.
(3) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046–6050 and references cited therein.

0022-3263/88/1953-5475$01.50/0



I

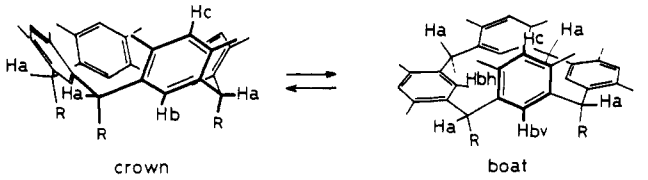
and R = Me have been elucidated by crystal-structure determination[4] and NMR spectroscopy.[5] Although all the R substituents in isomers **1** and **2** are axial, **1** has a boat conformation while **2** has a chair conformation. A procedure for the selective synthesis of isomer **1** (R = Me) has been published.[5] Because our interest was in macrocycles in the boat conformation with long alkyl chains, we have investigated the condensation of resorcinol with heptanal and dodecanal and have studied the stereochemistry of the products by means of ^{1}H NMR, NOE, and T_1 relaxation measurements.

Results and Discussion

Our compounds were synthesized by a previously published procedure.[5] Reaction of equimolar amounts of resorcinol and aldehyde in a 2:2:1 mixture of ethanol, water, and concentrated hydrochloric acid at 25 °C for 12 h gave a phenolic conglomerate, which was acetylated. Purification of the acetylation crude from the reaction with heptanal afforded the three isomers **1a** (26%), **2a** (3%), and **3a** (17%)[6] and of that from dodecanal gave the three isomers **1b** (17%), **2b** (1%), and **3b** (5%).[7] Each triad of octaacetates had almost identical mass spectra but different melting points, R_f values (TLC), and ^{1}H NMR spectra. The octols **4a,b** corresponding to the octaacetates **1a,b**, were obtained selectively in good yields by heating the resorcinol–aldehyde reaction mixture at reflux for 4 h. Upon cooling, a precipitate was formed, which, after crystallization, gave pure **4a** (58%) or **4b** (75%).

The number of possible structural isomers of I depends on the conformation of the macrocyclic ring and on the relative configuration of the R substituents. We discuss the three isomers obtained by condensation of resorcinol with heptanal (**1a–3a**); the interpretation can be extended without modification to the three (**1b–3b**) from the resorcinol–dodecanal condensation.

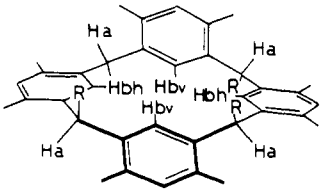
^{1}H NMR Spectra. The room temperature spectrum of **1a** shows a single resonance for protons H_a, H_b, and H_c (Table I).[8] At −60 °C in acetone-d_6, the H_b resonance splits into two broad peaks at 6.6 and 7.9 ppm; H_c becomes very broad, while H_a is unchanged (Table II). These data are explained, as reported for similar compounds (R = Me, R = Ph),[3,5] by the presence of two boat conformations with symmetry C_{2v} and all-cis relative configuration of the substituents. The two conformers interconvert rapidly at room temperature, giving, on the NMR time scale, an average structure with symmetry C_{4v}. The two equivalent



1a ⟶ R = C_6H_{13}
1b ⟶ R = $C_{11}H_{23}$

aromatic protons inside the macrocycle and parallel to the symmetry plane σ_v are labeled H_{bv}, while the perpendicular ones are labeled H_{bh}. The equivalent H_b protons are placed on opposite aromatic rings.

In the room temperature spectrum of **2a** (Table I), H_b and H_c show two resonances each, while H_a gives only one resonance split into a doublet of doublets by coupling with CH_2, clearly due to hindered rotation of the R substituent.[9] No significant changes were observed on heating the sample to 120 °C (DMSO-d_6) or cooling it to −60 °C (toluene-d_8) (Table II). These results indicate a very rigid conformation with the R substituents all either axial or equatorial and with a relative cis-trans-cis configuration.



2a ⟶ R = C_6H_{13}
2b ⟶ R = $C_{11}H_{23}$
2c ⟶ R = CH_3

This situation has been found in an analogous compound (R = Me) and has been attributed to a rigid chair conformation with axial substituents (C_{2h} symmetry), which does not convert to other conformations. We have synthesized this compound (**2c**, Table I) and found that it has chemical shifts, NOE effects, and T_1 similar to those of **2a**. The two H_b peaks identified as H_{bv} and H_{bh} come from hydrogen atoms that lie in the σ_v and σ_h planes of the macrocycle.

Compound **3a** shows spectral features that cannot be explained by either a chair or a boat conformation (Table I). Its room temperature spectrum was not changed significantly at −60 °C or 120 °C (Table II). Furthermore, there are four resonances with the same intensity in the aromatic region. On the other hand, in the H_a region we observe three resonances, a triplet, a doublet of doublets,

(4) (a) Nilsson, B. *Acta Chem. Scand.* **1968**, *22*, 732. (b) Palmer, K. J.; Wong, R. Y.; Jurd, L.; Stevens, K. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1976**, *32*, 847–852. (c) Cram, D. J.; Steward, K. D.; Goldberg, I.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2574–2575.

(5) Högberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498–4500.

(6) Systematic names: **1a**, *r*-2, *c*-8, *c*-14, *c*-20-tetrahexylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol, octaacetate; **2a**, *r*-2, *c*-8, *t*-14, *t*-20-tetrahexylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol, octaacetate; **3a**, *r*-2, *c*-8, *t*-14, *c*-20-tetrahexylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol, octaacetate.

(7) Systematic names: **1b**, *r*-2, *c*-8, *c*-14, *c*-20-tetraundecylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol, octaacetate; **2b**, *r*-2, *c*-8, *t*-14, *t*-20-tetraundecylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol, octaacetate; **3b**, *r*-2, *c*-8, *t*-14, *c*-20-tetraundecylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol, octaacetate.

(8) H_b and H_c in compounds **1** and **2** are distinguished on the basis of T_1 relaxation times (see Table I), which are expected to be reasonably shorter for H_b that for H_c. This assignment agrees with the one proposed by Högberg on the basis of chemical shift.[3]

(9) This is confirmed by the behavior of the analogous compound without the acetate group. In fact, at 120 °C in DMSO-d_6, and H_a resonance becomes a triplet while the rest of the spectrum remains unchanged.

Table I. Chemical Shifts,[a] Multiplicity, and T_1 Relaxation Times[b] at Room Temperature

compd	solvent	H_{bv}	H_{bh}	H_{c1}[c]	H_{c2}[c]	H_a	CH_2	CH_3CO
1a	CD_3COCD_3	7.25 (s) (0.5)		6.88 (s) (7.4)		4.26 (t) (1.0)	2.02 (m) (0.3)	2.31 (s)
2a	CD_3COCD_3	7.30 (s) (0.3)	6.03 (s) (1.3)	7.00 (s) (6.6)	6.81 (s) (6.9)	4.22 (d, d) (1.0)	1.7–1.9 (m) (0.2)	2.38 (s) 1.98 (s)
2c	$CDCl_3$	7.33 (s) (0.4)	5.86 (s) (1.5)	6.92 (s) (5.0)	6.76 (s) (5.3)	4.29 (q) (1.1)	CH_3, 1.43 (d) (0.2)	2.38 (s) 1.95 (s)
3a	CD_3COCD_3	7.96 (s) (0.3)	6.69 (s) (0.5)	6.96 (s) (5.7)	6.89 (s) (6.3)	$H_a(1)$ 4.66 (t) (1.0) $H_a(2)$ 4.36 (d, d) (1.0) $H_a(3)$ 4.24 (t) (1.0)	$CH_2(1)$ 2.16 (m) (0.3) $CH_2(2)$ 1.96 (m) (0.2) $CH_2(3)$ 1.20 (m) (0.5)	2.49 (s) 2.33 (s) 2.31 (s) 2.19 (s)

[a] Chemical shifts are in parts per million with respect to $\delta_{TMS} = 0$. [b] T_1 relaxation times (s) are in parentheses. [c] The chemical shifts of H_{c1} and H_{c2} can be interchanged.

Table II. Chemical Shifts and Multiplicities at Different Temperatures

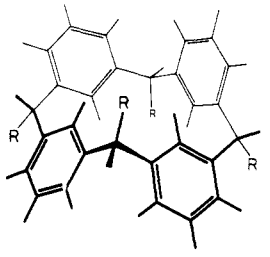
compd	solvent	t, °C	H_{bv}	H_{bh}	H_{c1}	H_{c2}	H_a	CH_3CO
1a	CD_3COCD_3	−60	7.90 (s) (br)[a]	6.65 (s) (br)	7.00 (s) (br)	7.00 (s) (br)	4.07 (t)	2.40 (s), 2.30 (s)
2a	toluene-d_8	−60	7.53 (s) (br)	6.43 (s)	7.14 (s)	6.71 (s)	4.40 (d, d) (br)[b]	1.93 (s), 1.85 (s)
2a	DMSO-d_6	120	7.28 (s)	6.10 (s)	7.10 (s)	6.90 (s)	4.41 (d, d)	2.41 (s), 2.06 (s)
3a	toluene-d_8	−60	7.90 (s)	6.89 (s)	6.98 (s)	6.91 (s)	$H_a(1)$ 4.69 (t) $H_a(2)$ 4.40 (m)[c]	1.99 (s), 1.95 (s) 1.86 (s), 1.82 (s)
3a	DMSO-d_6	120	7.87 (s)	6.65 (s)	7.02 (s)	6.93 (s)	$H_a(1)$ 4.61 (t) $H_a(2)$ 4.34 (t) $H_a(3)$ 4.14 (t)	2.43 (s), 2.40 (s) 2.35 (s), 2.17 (s)

[a] Broad resonance (br). The resonances not labeled br are sharp. [b] H_a broadening is due to a slowing rotation of R substituents. [c] Two resonances overlap, giving a multiplet.

and again a triplet at 4.66, 4.36, and 4.24 ppm, respectively, and with relative areas of 1:2:1. These features can be rationalized with a symmetry plane passing through the two unequivalent H_a protons and perpendicular to the plane of the macrocyclic ring.

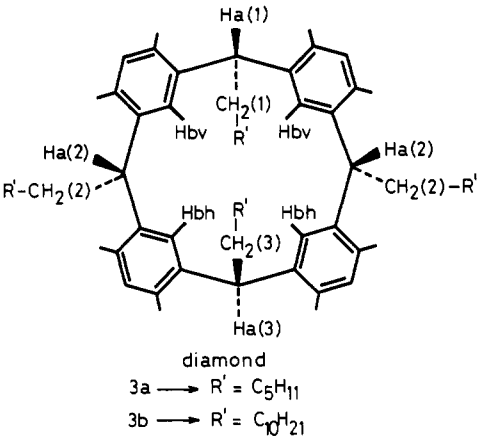
This hypothesis clearly excludes a chair (C_{2h}) or boat (C_{2v}) symmetry, in which the symmetry plane passes through the aromatic protons. The macrocycle appears to have a completely different conformation with a symmetry plane common to the H_a and H_b protons.

The only possible cycle conformation satisfying these requirements is the one shown for **3**, belonging to the symmetry group C_s. The shape of the new isomer can be described as diamond-like.[10]



Now each of the resonances at 7.96 and 6.69 ppm, previously labeled as H_{bv} and H_{bh}, represents two equivalent aromatic protons attached to adjacent rings divided by the symmetry plane (Scheme I). In **1a** and **2a**, they have been assigned to equivalent protons attached to opposite aromatic rings. Further support for this stereostructure for **3** is given by the fact that four resonances are found for CH_3CO (Table I), while one and two resonances are observed for the boat and chair isomers.

Scheme I



The possible interconversion of the diamond conformer with either the boat or the chair form was excluded by examining the CPK model of **3a**. The diamond–boat interconversion requires the inversion of the macrocycle ring, which is highly improbable. The diamond–chair interconversion looks very difficult because of the exceedingly crowded transition state and can be excluded by comparing the behavior of **1a** and **3a** at low temperature (Table II): The boat–crown interconversion in **1a** is frozen in the NMR time scale at −60 °C. The pseudorotation involved in the boat–crown interconversion is much easier than the flipping of any R group through the adjacent acetates, as required by the diamond–chair interconversion. In this situation we should observe a freezing temperature higher than −60 °C, which is not the case. Therefore we conclude that **3a** is a rigid structure.

T_1 Relaxation Times and NOE Measurements. The ^1H NMR spectra do not suffice for assigning the configuration of the R substituents because there are no coupling constants among the protons involved that can be correlated with a geometrical arrangement. For the compounds reported in the literature, this problem has been solved

(10) For a similar shape attribution, see: Jazwinski, J.; Lehn, J. M.; Méric, R.; Vigneron, J. P.; Cesario, M.; Guilhem, J.; Pascard, C. *Tetrahedron Lett.* **1987**, *28*, 3489–3492.

Table III. Percent NOE Enhancements

compd	solvent	proton obsd(proton saturated) = Fd(s) %		
1a	CD_3COCD_3	$H_b(CH_2)$ = +12.9		$H_b(H_a)$ = −3.2
2a	CD_3COCD_3	$H_{bv}(CH_2)$ = +7.1	$H_{bh}(CH_2)$ = +1.3	$H_{bv}(H_a)$ = −6.5
2c	$CDCl_3$	$H_{bv}(CH_3)$ = +15.9	$H_{bh}(CH_3)$ = 0	$H_{bv}(H_a)$ = +1.6
3a	CD_3COCD_3	$H_{bv}(CH_2)(1)$ = +8.3	$H_{bv}(CH_2)(2)$ = +11.1	$H_{bv}(CH_2)(3)$ = +1
		$H_{bh}(CH_2)(1)$ = +0.4	$H_{bh}(CH_2)(2)$ = +4.8	$H_{bh}(CH_2)(3)$ = +8.4
		$H_{bv}(H_a)(1)$ = −1	$H_{bv}(H_a)(2)$ = +0.1	$H_{bv}(H_a)(3)$ = 0
		$H_{bh}(H_a)(1)$ = −1.5	$H_{bh}(H_a)(2)$ = −0.2	$H_{bh}(H_a)(3)$ = −0.3

by crystal-structure determination (R = Ph)[4b] and by using the relative NMR spectrum as a reference for the others (R = Me).[5] Instead we have tried an approach based on NOE enhancements and T_1 relaxation times.

Inspection of CPK models indicated that the relative distances of the H_b protons from the H_a protons and from the CH_2 α to H_a (CH_3 in the case of **2c**) can be correlated with the stereochemistry of the R substituents. In our use of NOE and T_1 measurements to collect information on these distances, we assumed that the motional narrowing conditions apply and that the spin–lattice relaxation mechanism is mainly dipolar and intramolecular for these protons. With these restrictions, the relationships relative to NOE and T_1 are simplified and depend mainly on the distance between the protons.[11]

We designate the NOE enhancements F on different protons as Fd(s), where d is the observed spin and s is the saturated spin. In **2a**, $FH_{bv}(CH_2)$ = +7.1 and $FH_{bv}(H_a)$ = −6.5 (Table III). These values are in accord with a linear system[11] in which the NOE between adjacent protons is positive while that between next nearest neighbors is negative. This implies that the distance between H_{bv} and CH_2 is less than that between H_{bv} and H_a. CPK models of the chair conformation already assigned to **2a** show that this situation occurs when the CH_2 group, and in consequence the R groups, are all axial. Likewise, $FH_{bh}(CH_2)$ and $FH_{bh}(H_a)$ are almost 0, consistent with the greater distance from H_{bh} to CH_2 and H_a.

Values of T_1 relative to H_{bv} and H_{bh} (**2a**, Table I) are in agreement with this last finding, since from them we calculate that the average ratio of the distances of H_{bv} and H_{bh} from CH_2 is 1.3:

$$\frac{r(H_{bh},CH_2)}{r(H_{bv},CH_2)} = \left[\frac{T_1(H_{bh})}{T_1(H_{bv})}\right]^{-6} = 1.3$$

In **2c** we observe similar values for NOE and T_1, confirming the assignment to this compound of a chair conformation with axial substituents. In **1a**, $FH_b(CH_2)$ = +12.9 and $FH_b(H_a)$ = −3.2, also indicating axial substituents.

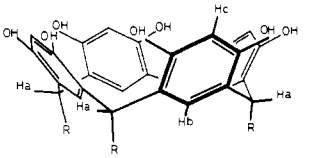
For **3a** the chemical shifts of the CH_2 groups and their correlation with the respective H_a's were derived from a two-dimensional homonuclear COSY. On irradiating the three H_a multiplets (Table III), we find an almost negligible NOE on the aromatic protons H_{bv} and H_{bh}. On the other hand, irradiating $CH_2(1)$ and $CH_2(3)$ gives NOE enhancements on H_{bv} and H_{bh} of +8.3 and +8.4, respectively, which allow us to assign these methylenes to axial positions (Scheme I). Saturating the two equivalent $CH_2(2)$ groups gives positive NOEs on H_{bv} (+11.1) and on H_{bh} (+4.8), which lead us to assign these methylenes to positions close to both sets of H_b aromatic protons. Accordingly they must be axial.

In conclusion we attribute to isomer **3a** a structure in which three of the R substituents point down and one points up with respect to the macrocycle ring plane, with the relative configuration cis-trans-cis [$CH_2(1)$ as reference].

The NOE measurements on **3a** not only give us the positions of the substituents but also confirm the conformation of the macrocycle as derived from symmetry considerations. Any boat or chair conformation could not account for the NOE of both H_{bv} and H_{bh} protons. Furthermore, H_{bh} has a T_1 value of 0.5 s (Table I), which is substantially lower than those of the other compounds ($T_1 \geq 1.3$ s), indicating that the CH_2 groups are close to these aromatic protons.

Conclusion. The relative amounts of the three stereoisomeric octols formed in the condensation reflect a kinetically controlled process driven by crystallization (procedure A). The length of the alkyl chains affects the solubility of the macrocycles, thus the product distribution.[12] The selectivity of the reaction can be improved by changing the solvent mixture and by raising the temperature (procecure B). Under these conditions only the less soluble octols **4a,b** precipitate. Since the reaction is reversible, the other isomers are converted into the boat isomers **4a,b**, which are thermodynamically more stable.

Our results are in agreement with Högberg's assumptions[3] about the origin of stereoselectivity in the resorcinol–aldehyde condensation reaction. The formation of only tetrameric macrocycles,[13] the stereocontrol in the configuration of substituents, and the possibility of producing the boat isomer selectively are the important features of this condensation reaction.



4a ⟶ R = C_6H_{13}
4b ⟶ R = $C_{11}H_{23}$

Experimental Section

ACS grade reagents were used without further purification. Column chromatography was performed by using silica gel 60 (Merck, 230–400 mesh ASTM). Analytical TLC was conducted on precoated Merck silica gel 60 plates. NMR spectra were recorded on a Brucker AM-300 spectrometer equipped with a variable-temperature device. Solutions were prepared by dissolving ≈5 mg of compounds in 0.5 mL of deuteriated solvent and removing oxygen by passing nitrogen into the NMR tube for few minutes. Chemical shifts are given in parts per million (δ_{TMS} = 0) using as an internal reference the solvent peak referred to TMS (2.04 ppm for acetone, 7.25 ppm for chloroform, 2.56 ppm for DMSO). Relaxation times were obtained by using the inversion recovery technique and elaborating the spectral data with a

(11) Noggle, J. H.; Schizmer, R. E. *The Nuclear Overhauser Effect, Chemical Application*; Academic: New York, 1971.

(12) Under the same reaction conditions (procedure A), the condensation of resorcinol with isovaleraldehyde gave only the boat stereoisomer in very high yields (95%) (Cram, D. J.; Dalcanale, E., unpublished results).

(13) For a review of arene–aldehyde condensations, see: Gutsche, C. D. *Topics in Current Chemistry*; Boschke, F. L., Ed.; Springer Verlag: 1984; Vol. 123, p 1.

Brucker library program. NOE enhancements were obtained by using the NOE difference technique: samples were irradiated on resonance and off resonance under the same instrumental conditions. Then from the peak areas (I) of the FT transformed spectra NOE enhancements were evaluated according to the following formula: NOE % = $(I_{on} - I_{off})/I_{off}$. NOE spectra were run at least three times in order to get a reliable average value.

Mass spectra were recorded on a Finnigan MAT 8400 spectrometer, using DCI technique (positive-ion spectrum, current gradient 40 mA/s). Elemental analyses were performed by the microanalytical laboratory of the Donegani Institute. Melting points were measured on a Kofler apparatus and are uncorrected. All products were identified through their elemental analysis and NMR and DCI-MS spectra.

General Condensation Procedures. Procedure A. To a stirred solution of resorcinol (13.2 g, 0.120 mol) in a solvent mixture of ethanol (24 mL), water (24 mL), and concentrated hydrochloric acid (12 mL) cooled to 5 °C was added heptanal (13.7 g, 0.120 mol) dropwise over 1 h. During the addition, the solution became cloudy with the formation of a precipitate. The resulting suspension was stirred overnight at room temperature. The gummy precipitate obtained became crystalline upon addition of water. The solid was filtered, washed to neutrality with water, and dried at 10^{-3} Torr for 8 h (23.6 g).

The crude product, a mixture of the three isomers and oligomers, was acetylated by being dissolved in a hot mixture of acetic anhydride (120 mL) and pyridine (6 mL). The solution was heated to reflux for 30 min, the excess solvent removed by vacuum distillation (20 Torr), and the residue crystallized from methanol (60 mL). The resulting crystals were filtered and dried. The product (5.93 g, 17%) was pure **1a**.

The remaining solution contained the three isomers **1a–3a** plus acetylated oligomers. Concentration of the filtrate afforded a yellow solid (16.04 g), which was chromatographed on silica gel (9:1 ethyl ether/cyclohexane) to give 3.13 g of **1a** (9%, overall 26%), 1.17 g of **2a** (3.4%), and 5.91 g of **3a** (17%).

1a: R_f 0.28 in 9:1 ethyl ether/cyclohexane; mp 172–173 °C; ^{1}H NMR (Me_2CO-d_6) δ 0.90 (t, 12 H, CH_3, J = 6.4 Hz), 1.28 (brm, 32 H, CH_2), 2.02 (brm, 8 H, $CHCH_2$), 2.31 (s, 24 H, $COCH_3$), 4.26 (t, 4 H, H_a, J = 7.4 Hz), 6.88 (s, 4 H, H_b), 7.25 (brs, 4 H, H_c); DCI-MS (isobutane), m/e 1161 (MH^+, 100). Anal. Calcd for $C_{68}H_{88}O_{16}$: C, 70.32; H, 7.64. Found: C, 70.34; H, 7.67.

2a: R_f 0.81 in 9:1 ethyl ether/cyclohexane; mp 214–215 °C; ^{1}H NMR (Me_2CO-d_6) δ 0.85 (t, 12 H, CH_3, J = 6.4 Hz), 1.26 (brm, 32 H, CH_2), 1.75 (brm, 4 H, $CHCH_2$), 1.88 (brm, 4 H, $CHCH_2$), 1.98 (s, 12 H, $COCH_3$), 2.38 (s, 12 H, $COCH_3$), 4.22 (dd, 4 H, H_a, J = 10.0, 4.3 Hz), 6.03 (s, 2 H, H_{bh}), 6.81 (s, 2 H, H_c), 7.00 (s, 2 H, H_c), 7.30 (s, 2H, H_{bv}); DCI-MS (isobutane), m/e 1161 (MH^+, 100). Anal. Calcd for $C_{68}H_{88}O_{16}$: C, 70.32; H, 7.64. Found: C, 70.28; H, 7.76.

3a: R_f 0.45 in 9:1 ethyl ether/cyclohexane; mp 51–52 °C; ^{1}H NMR (Me_2CO-d_6) δ 0.85 (t, 3 H, CH_3, J = 7.2 Hz), 0.93 (m, 9 H, CH_3), 1.03 [brm, 2 H, CH–$CH_2(3)$–CH_2], 1.20 [m, 2 H, CH–$CH_2(3)$], 1.35 (brm, 30 H, CH_2), 1.96 [brm, 4 H, CH–$CH_2(2)$], 2.16 [brm, 2 H, CH–$CH_2(1)$], 2.19 (s, 6 H, $COCH_3$), 2.31 (s, 6 H, $COCH_3$), 2.33 (s, 6 H, $COCH_3$), 2.49 (s, 6 H, $COCH_3$), 4.24 [t, 1 H, $H_a(3)$], J = 7.9 Hz], 4.36 [dd, 2 H, $H_a(2)$, J = 9.9, 5.3 Hz], 4.66 [t, 1 H, $H_a(1)$, J = 8.0 Hz], 6.69 (s, 2 H, H_{bh}), 6.89 (s, 2 H, H_c), 6.96 (s, 2 H, H_c), 7.96 (s, 2 H, H_{bv}); DCI-MS (isobutane), m/e 1161 (MH^+, 100). Anal. Calcd for $C_{68}H_{88}O_{16}$: C, 70.32; H, 7.64. Found: C, 70.35; H, 7.62.

Application of the above procedure to resorcinol (5.50 g, 0.05 mol) and dodecanal (9.21 g, 0.05 mol) in ethanol (10 mL), water (10 mL), and hydrochloric acid (5 mL) gave a gummy precipitate (11.38 g). Also in this case the precipitate began to form during the addition of the aldehyde. Acetylation of the crude product gave a yellow solid, which was crystallized from ethanol (30 mL). The resulting crystals were filtered and dried (4.60 g). TLC analysis showed three main spots. Separation by column chromatography on silica gel (6:4 hexane/ethyl acetate) gave **1b** (3.132 g, 17%), **2b** (0.175 g, 1%), and **3b** (0.857 g, 5%).

1b: R_f 0.23 in 6:4 hexane/ethyl acetate; mp 131–132 °C; ^{1}H NMR (Me_2CO-d_6) δ 0.86 (t, 12 H, CH_3, J = 6.7 Hz), 1.26 (brs, 72 H, CH_2), 1.95 (brm, 8 H, $CHCH_2$), 2.25 (s, 24 H, $COCH_3$), 4.21 (t, 4 H, H_a, J = 7.5 Hz), 6.83 (s, 4 H, H_b), 7.19 (brs, 4 H, H_c); DCI-MS (isobutane), m/e 1441 (MH^+, 100). Anal. Calcd for $C_{88}H_{128}O_{16}$: C, 73.30; H, 8.95. Found: C, 73.25; H, 8.97.

2b: R_f 0.39 in 8:2 hexane/ethyl acetate; mp 48–49 °C; ^{1}H NMR (Me_2CO-d_6) δ 0.87 (t, 12 H, CH_3, J = 6.5 Hz), 1.26 (brs, 72 H, CH_2); 1.72 (brm, 4 H, $CHCH_2$), 1.89 (brm, 4 H, $CHCH_2$), 1.98 (s, 12 H, $COCH_3$), 2.38 (s, 12 H, $COCH_3$), 4.22 (dd, 4 H, H_a, J = 10.0, 4.0 Hz), 6.03 (s, 2 H, H_{bh}), 6.81 (s, 2 H, H_c), 7.02 (s, 2 H, H_c), 7.29 (s, 2 H, H_{bv}); DCI-MS (isobutane), m/e 1441 (MH^+, 100). Anal. Calcd for $C_{88}H_{128}O_{16}$: C, 73.30; H, 8.95. Found: C, 73.08; H, 9.09.

3b: R_f 0.56 in 6:4 hexane/ethyl acetate; oil; ^{1}H NMR (Me_2CO-d_6) δ 0.77 [brm, 2 H, CH–$CH_2(3)$–CH_2], 0.88 (t, 12 H, CH_3, J = 6.3 Hz), 0.99 [brm, 2 H, CH–$CH_2(3)$], 1.29 (brs, 70 H, CH_2), 1.95 [brm, 4 H, CH–$CH_2(2)$], 2.12 (s, 6 H, $COCH_3$), 2.23 [brm, 2 H, CH–$CH_2(1)$], 2.33 (s, 6 H, $COCH_3$), 2.37 (s, 6 H, $COCH_3$), 2.42 (s, 6 H, $COCH_3$), 4.17 [t, 1 H, $H_a(3)$, J = 7.8 Hz], 4.29 [dd, 2 H, $H_a(2)$, J = 9.4, 6.2 Hz], 4.59 [t, 1 H, $H_a(1)$, J = 7.9 Hz], 6.61 (s, 2 H, H_{bh}), 6.81 (s, 2 H, H_c), 6.89 (s, 2 H, H_c), 7.88 (s, 2 H, H_{bv}); DCI-MS (isobutane), m/e 1441 (MH^+, 100). Anal. Calcd for $C_{88}H_{128}O_{16}$: C, 73.30; H, 8.95. Found: C, 73.41; H, 8.58.

Procedure B. To a stirred solution of resorcinol (16.51 g, 0.15 mol) in a solvent mixture of ethanol (60 mL) and concentrated hydrochloric acid (20 mL) cooled to 5 °C, was added heptanal (17.13 g, 0.15 mol) dropwise over 1 h. A precipitate was formed, which dissolved on heating. The solution was refluxed for 8 h and then cooled down to room temperature. A gummy precipitate was formed, which became crystalline upon addition of water. It was filtered, washed to neutrality with water, and dried at 10^{-3} Torr for 8 h (27.3 g). It was then crystallized from methanol to give pure **4a** (17.95 g, 58% yield).

4a: R_f 0.52 in 95:5 ethyl ether/methanol; mp >315 dec; ^{1}H NMR (Me_2CO-d_6) δ 0.88 (t, 12 H, CH_3, J = 6.6 Hz), 1.29 (brs, 32 H, CH_2), 2.28 (brq, 8 H, $CHCH_2$, J = 6.5 Hz), 4.23 (t, 4 H, H_a, J = 6.5 Hz), 6.23 (s, 4 H, H_b), 7.55 s, 4 H, H_c), 8.46 (brs, 8 H, OH); DCI-MS (isobutane), m/e 825 (MH^+, 100). Anal. Calcd for $C_{52}H_{72}O_8$: C, 75.69; H, 8.79. Found: C, 75.55; H, 9.01.

Application of the above procedure to resorcinol (18.06 g, 0.164 mol) and dodecanal (30.23 g, 0.164 mol) gave a yellow precipitate, which was filtered, dried, and crystallized from methanol to give 34.0 g (75%) of pure **4b**.

4b: R_f 0.56 in 95:5 ethyl ether/methanol; mp 300–301 °C dec; ^{1}H NMR (Me_2CO-d_6) δ 0.88 (t, 12 H, CH_3, J = 6.7 Hz), 1.29 (brs, 72 H, CH_2), 2.28 (brq, 8 H, $CHCH_2$), 4.29 (t, 4 H, H_a, J = 7.8 Hz), 6.23 (s, 4 H, H_b), 7.54 (s, 4 H, H_c), 8.42 (brs, 8 H, OH); DCI-MS (isobutane), m/e 1105 (MH^+, 100). Anal. Calcd for $C_{72}H_{112}O_8$: C, 78.21; H, 10.21. Found: C, 78.15; H 10.28.

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Registry No. **1a**, 116670-08-7; **1b**, 112247-08-2; **2a**, 116781-96-5; **2b**, 116780-41-7; **2c**, 74629-75-7; **3a**, 116780-40-6; **3b**, 116780-42-8; **4a**, 116670-09-8; **4b**, 116780-43-9; resorcinol, 108-46-3; heptanal, 111-71-7; dodecanal, 112-54-9.

Supplementary Material Available: ^{1}H NMR spectra of **1a–3a** and **2c** at room temperature, of **1a–3a** at −60 °C, and of **2a–3a** at 120 °C (3 pages). Ordering information is given on any current masthead page.