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Regioselective Formation of Dissymmetric Resorcarene Derivatives with C_4-Symmetry

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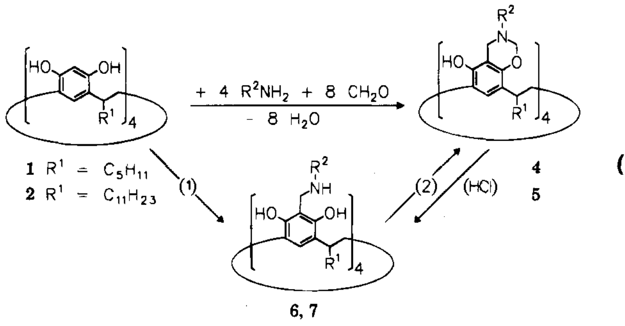
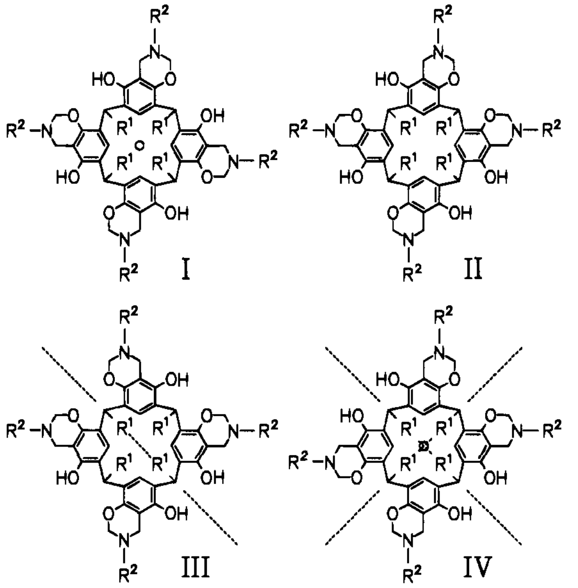
Resorcarenes[1] (e.g., **1**, **2**) are cyclic tetramers, easily obtained as the *all-cis* isomer by acid-catalyzed condensation of resorcinol with a variety of aldehydes.[2] They have been used as starting materials for the synthesis of cavitands,[3] velcrands,[4] and even more complex compounds such as carcerands,[5] hemicarcerands,[6] and holands.[7]

Obvious places for the chemical modification of resorcarenes are the phenolic hydroxy groups and the 2 position of the resorcinol units. While the aminomethylation with secondary amines has been studied by several groups,[8] we were interested in the condensation of resorcarenes with primary amines and excess formaldehyde leading to the formation of oxazine[9] structures (eq 1). In this way, not only can additional functionalities be introduced (while simultaneously enlarging the cavity),[10] but this reaction also offers interesting stereochemical aspects. As demonstrated in Chart 1, four regioisomers may be formed in principle, two of which (**I**, **II**) are chiral. Here the dissymmetric compound **I** with a 4-fold axis is especially interesting.[11]



(1)

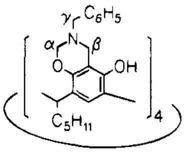
Chart 1



We have studied this condensation with several resorcarenes and a variety of primary amines, aliphatic as well as aromatic. For two resorcarenes (**1**, **2**) and five amines (**3a–e**), we have obtained only a single product in each case (**4a–e**, **5a–e**) (see Table 1) in excellent yield simply by refluxing the resorcarene (1 mol) with the amine (5 mol) and formaldehyde (10 mol) in an appropriate mixture of toluene and ethanol.[12] This suggests that the scope of the reaction is probably quite general.

^{1}H- and ^{13}C-NMR spectra of **4** and **5** are in complete agreement with the C_4-symmetrical structure **I**. In all cases, only one singlet is observed for the OH and Ar-H protons and one set of signals for the residues R^1 and R^2. To distinguish **I** from **IV**, the observation of only one triplet for the methine proton -C*H*R^1- and one singlet for the methine carbon -*C*HR^1- in the different solvents (CDCl$_3$, acetone-d_6, benzene-d_6) is important.

The methylene groups of the oxazine rings appear as two pairs of doublets (AB systems) (α, 4.885/4.807; β, 4.030/3.860; values for **4b**), and a third pair of doublets (γ, 3.807/3.743) is observed from the benzylic group in **4b** (as well as in **5b**). The latter is easily identified, since it is the only one which is observed in **4b′**, a compound formed with (CD$_2$O)$_n$.



	α	β	γ
4b	CH_2	CH_2	CH_2
4b'	CD_2	CD_2	CH_2
4b"	CH_2	CD_2	CH_2
4b'''	CD_2	CH_2	CH_2

The exclusive formation of a single reaction product in high yield can be understood by the fact that *four* intramolecular

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(1) Among various not entirely convincing names proposed for these compounds we choose the shortest one: Böhmer, V. *Angew. Chem.*, in press.

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(9) The newly formed rings should be named more exactly benzodihydro-1,3-oxazine rings.

(10) Three samples of this type have been briefly mentioned.[8b] However, there is no stereochemical characterization of the products given, nor is the stereochemical problem discussed at all.

(11) A C_4-symmetrical arrangement of intramolecular hydrogen bonds is found in the crystalline state for a resorcarene derivative obtained by aminomethylation with dipropylamine.[8a]

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Table 1. Yields (%) of Tetraoxazine Derivatives **4** (R^1 = n-C_5H_{11}) and **5** (R^1 = n-$C_{11}H_{23}$)

	amine **3** (R^2)	oxazine derivative	
		4	**5**
a	$CH_2CH_2CH_2CH_3$	88	89
b	$CH_2C_6H_5$	75	93
c	1-admantyl	65	73
d	p-$C_6H_4NO_2$	55	62
e	p-$C_6H_4OC_6H_5$	49	53

hydrogen bonds (O—H···O) are possible *only* in **I**. It suggests that at least the second step (2) in eq 1, the formation of the oxazine[9] ring, is reversible. This was shown by treating **4b′** with $(CH_2O)_n$ under the reaction conditions and observing the appearance of the doublets α in **4b″** belonging to the O-CH_2-N group.

The oxazine rings in **4** can be hydrolyzed under acidic conditions, leading to the secondary amines **6** and **7**.[12] Heating with formaldehyde regenerates **4**; if this is done with $(CD_2O)_n$, **7b** is converted to **4b‴**, showing only the AB systems α and β, which confirms again that the latter belongs to the Ar-CH_2-N group.

The structure and the C_4-symmetry of **5d** were confirmed by single crystal X-ray analysis.[13] In the solid state, the molecule resides on a crystallographic 2-fold axis, and some deviations from an "ideal" 4-fold symmetry are present.[14] They may be expressed, for instance, by the dihedral angles between the best plane of the methine carbons and the resorcinol rings, which are 132.2° and 123.8°. The oxazine[9] rings are tilted in such a way that the p-nitroaniline rings (which are axial with respect to the oxazine rings) are bent inwards, assuming dihedral angles of 73° and 59° with the resorcinol planes. The cavity thus formed may be described by the distances between opposite -O-CH_2-N carbons (12.32 and 11.43 Å) and between the best planes through the methine carbons and the nitrogen atoms of the nitro groups (8.7 Å). Due to the flexibility of the oxazine[9] ring, a larger cavity with the nitroaniline rings bent outwards may be also assumed in solution. Intramolecular hydrogen bonds are indicated by the O−O distances (2.77 and 2.78 Å) of adjacent resorcinol units.

Although the chirality of compounds **4** and **5** follows from their structure,[13] it has not yet been detected in solution. Doubling of peaks in the ^1H NMR spectrum in the presence of Pirkle's reagent was not observed, and all attempts to separate the enantiomers by chromatography on various chiral stationary phases have failed so far.[15] Obviously a necessary condition for chiral recognition is that the interacting chiral groups are of comparable size. In the present case, chirality of **4**, **5** manifests on a nanometer scale, which is larger than that of possible reagents or groups normally used to form diasteromeric complexes and to distinguish enantiomeric structures. Thus, the challenging problem appears to monitor the "nanochirality" of these and other large intrinsically asymmetric molecules and superstructures by appropriate nanochiral tools.

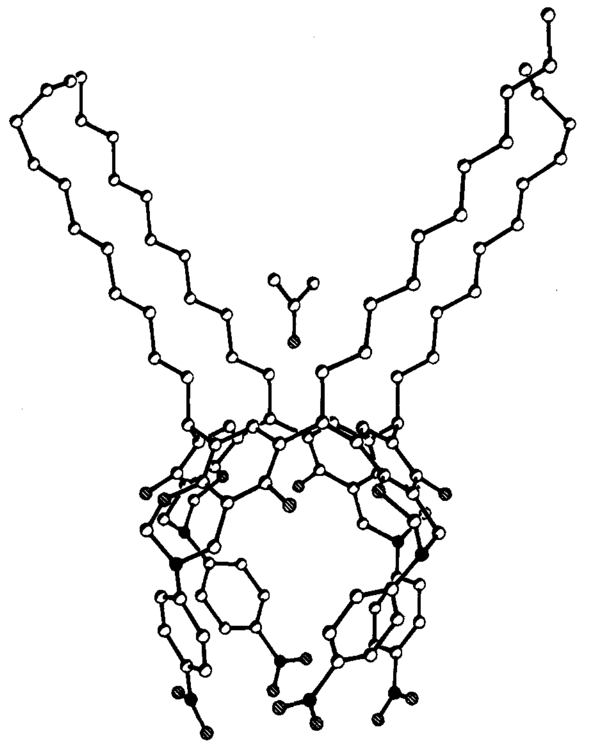

Figure 1. Molecular conformation of **5d**. Two molecules of acetone are included, one on a fixed position between the aliphatic chains (shown), and the other one disordered in the cavity (ommitted for clarity). Solid and hatched circles represent nitrogen and oxygen atoms, respectively.

Independently, compounds like **4** or **5** and the corresponding hydrolysis products **6** and **7** are interesting starting materials for a variety of more sophisticated molecules.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and by the European Community.

Supplementary Material Available: Description of the synthesis and ^1H NMR data of two representative examples (**5a**, **5b**) (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(12) All compounds gave satisfactory ^1H and ^{13}C NMR spectra, elemental analyses, and mass spectra.

(13) Single crystals of **5d** were obtained by recrystallization from acetone/ethanol (9:1), $C_{104}H_{132}N_8O_{16}\cdot 2CH_3COCH_3$, M_r = 1866.4, monoclinic, space group $C2/c$, a = 20.039(4), b = 17.041(3), and c = 31.453(6) Å, β = 105.72(3)°, V = 10339(6) Å^3, z = 4, D_x = 1.199 g·cm^{-3}, λ (Mo Kα) = 0.710 73 Å, μ = 0.07 mm^{-1}, F(000) = 4016.0, T = 193 K. Refinement (not yet finished) based on *all* 7642 unique reflections led to R = 0.15 and wR = 0.14. All calculations were done with the programs SHELX86, SHELXTL-PLUS, and SHELXL (Sheldrick, G. M., University of Göttingen, Germany).

(14) Several calix[4]arenes with C_4-symmetry were obtained from m-substituted phenols which assume a pinched-cone conformation with C_2-symmetry in the crystalline state: Andreetti, G. D.; Böhmer, V.; Jordon, J. G.; Tabatabai, M.; Ugozzoli, F.; Vogt, W.; Wolff, A. *J. Org. Chem.* **1993**, *58*, 4023−4032.

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