Selective Derivatization of Resorcarenes. 3. C_2-Symmetrical and Transcavity Bridged Bis-Benzoxazines Derived from C_{2v}-Symmetrical Tetratosylates[⊥]

Alexander Shivanyuk,[†] Christian Schmidt,[†] Volker Böhmer,*[,†] Erich F. Paulus,[‡] Oleg Lukin,[§] and Walter Vogt[†]

Contribution from the Institut für Organische, Chemie, Johannes Gutenberg-Universität Mainz, J.-J.-Becher-Weg 34 SB1, D-55099 Mainz, Germany, Hoechst-Marion-Roussel-Deutschland GmbH, D-65926 Frankfurt/Main, Germany, and Institute of Organic Chemistry, Polish Academy of Science, 01-224 Waszawa, ul. Kasprzaka 44, Poland

Received August 19, 1997. Revised Manuscript Received February 17, 1998

Abstract: The regioselective condensation of resorcarene tetratosylates **3**/**4** with formaldehyde and various primary amines readily gives bis-benzoxazines **5**/**6** in 65−86% yield. The chiral, C_2-symmetrical structure of these compounds has been proved by NMR-spectroscopy and single-crystal X-ray analysis. Bis-benzoxazines **5f** and **5i** assume in the crystalline state a boat conformation in which the two resorcinol rings bearing the oxazine fragments are nearly parallel. The tosylated resorcinol units are horizontally arranged in a propeller-like fashion, and two intramolecular hydrogen bonds are formed between the phenolic hydroxy groups and the oxygens of the neighboring sulfonyl fragments. Molecular mechanics calculations suggest that the regioselective formation of the C_2-isomer is caused by the repulsion between the substituents or the unpaired electrons at the nitrogen atoms of the two benzoxazine rings and by slightly better geometrical conditions for intramolecular S═O···H−O hydrogen bonding in comparison with the meso-isomer. The aminomethylation of tetratosylate **3** with appropriate diamines leads to the first examples of 1,3-bridged derivatives of resorcarenes. Chiral (C_2-symmetrical) or meso- (C_s-symmetrical) compounds can be obtained depending on the length of the bridging chain. In the case of 1,3-diaminopropane a 1,3-diazacyclohexane (hexahydropyrimidine) bridge is formed by additional condensation with formaldehyde.

Introduction

Resorcarenes **1** are macrocyclic compounds readily available by acid catalyzed condensation of resorcinol with various aldehydes.[1] Their all-cis (rccc) isomers have been widely used as building blocks for the construction of "container molecules" like cavitands, carcerands, and hemicarcerands[2] or for even larger molecular structures.[3,4] Recently the formation of hydrogen bonded, self-assembled "super-cavities" has been observed for the rccc-isomers,[5] while several rctt isomers form unusually strongly solvated structures in the crystalline state.[6]

C_{2v}-symmetrical tetrasubstituted derivatives of rccc resorcarenes in which two opposite resorcinol rings are completely acylated can be prepared by reaction with dialkylchlorophosphates[7] or arylsulfonyl chlorides.[8] Although these compounds are promising starting materials for the synthesis of further functionalized resorcarenes, not much is known so far about their reactivity.[9]

We therefore undertook a detailed study of the condensation of tetratosylates **3**/**4** with primary amines and formaldehyde, as an example of an electrophilic substitution. This reaction was highly regioselective in the case of resorcarenes **1**, leading exclusively to tetrabenzoxazines **2** with C_4-symmetry due to their stabilization by intramolecular O−H···O hydrogen bonding.[10] In addition it was diastereoselective in the case of chiral amines bearing the chirality center in α-position.[11] While a selective substitution of the resorcinol units could be expected for **3**/**4**

[⊥] The crystallographic data (without structure factors) of the structures described in this publication have been submitted as "supplementary publication no. CCDC-101414" to the Cambridge Crystallographic Data.

[†] University of Mainz.

[‡] Hoechst-Marion-Roussel-Deutschland GmbH.

[§] Institute of Organic Chemistry, Polish Academy of Sciences.

(1) For a recent review on resorcarenes, see: Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663−2704. For a more general review on calixarenes, including resorcarenes, see: Böhmer, V. *Angew. Chem.* **1995**, *107*, 785−818. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745.

(2) Cram, D. J.; Cram, J. M. Container Molecules and Their Guests; In *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, U.K., 1994.

(3) Timmerman, P.; Verboom, W.; van Veggel, F. C. J. M.; van Hoorn, D.; Reinhoudt, D. N. *Angew. Chem.* **1994**, *106*, 1313−1315. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1292−1295.

(4) Chopra, N.; Sherman, J. C. *Angew. Chem.* **1997**, *109*, 1828−1830. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1727−1729.

(5) MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469−472.

(6) Shivanyuk, A.; Paulus, E. F.; Böhmer, V.; Vogt, W. *Angew. Chem.* **1997**, *109*, 1358−1360. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1301−1303.

(7) Kalchenko, V. I.; Rudkevich, D. M.; Shivanyuk, A. N.; Pirozhenko, V. V.; Tsymbal, I. F.; Markovsky, L. N. *Zhurn. Obsch. Khim. (Russ)* **1994**, *64*, 731; *Chem. Abstr.* **1995**, *122*, 314652u.

(8) Lukin, O. V.; Pirozhenko, V. V.; Shivanyuk, A. N. *Tetrahedron Lett.* **1995**, *36*, 7725−7728.

(9) Single examples comprise the acylation of the remaining hydroxy groups in tetraphosphates and the aminomethylation of the unsubstituted resorcinol rings. Shivanyuk, A. N.; Kalchenko, V. I.; Pirozhenko, V. V.; Markovsky, L. N. *Zhurn. Obsch. Khim. (Russ)* **1994**, *64*, 1558; *Chem. Abstr.* **1995**, *122*, 314625u.

(10) (a) Arnecke, R.; Böhmer, V.; Paulus, E. F.; Vogt, W. *J. Am. Chem. Soc.* **1995**, *117*, 3286−3288, and references cited there. (b) Airola, K.; Böhmer, V.; Paulus, E. F.; Rissanen, K.; Schmidt, C.; Thondorf, I.; Vogt, W. *Tetrahedron* **1997**, *53*, 10709−10724.

S0002-7863(97)02928-4 CCC: $15.00
Published on Web 04/29/1998

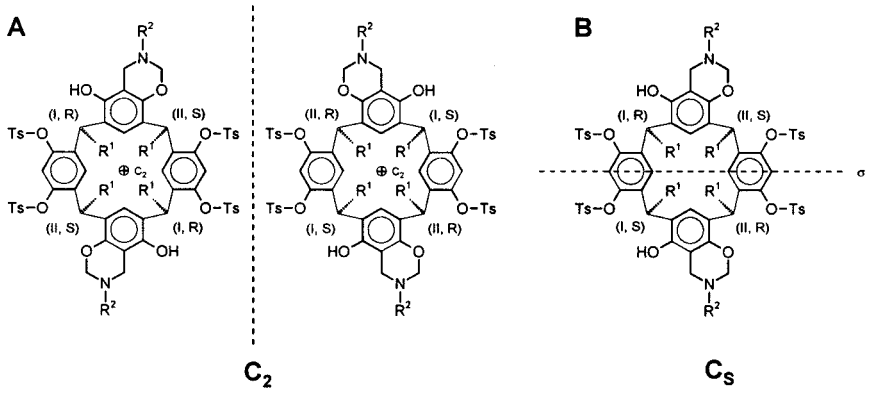
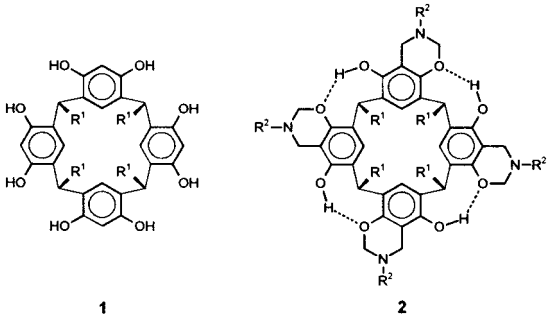


Figure 1. Schematic representation of the two possible regioisomers **A** and **B** of bis-benzoxazines **5**/**6** and of their stereochemical properties.

the question was, if regio- and diastereoselectivity would exist also in these cases. Furthermore, we were interested in the trans-cavity bridging of resorcarenes by a covalent connection of opposite resorcinol rings[12] which should be possible by using appropriate diamines. By variation of their chain length, on the other hand, further information about potential selectivities should be available.



1 **2**

Results and Discussion

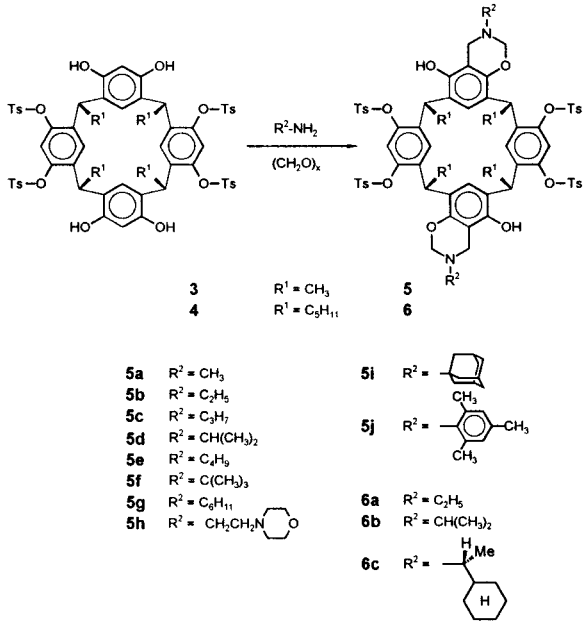
Reactions with Monoamines. The condensation of tetratosylates **3**/**4** with various primary amines and formaldehyde (room temperature, acetic acid as catalyst) gives the bis-benzoxazines **5**/**6** usually as a precipitate (65−74% yield after purification) (Scheme 1).

By subsequent acid-catalyzed cleavage of the oxazine rings (BuOH/HCl/H_2O, 120 °C) the secondary diamines **10a**,**b** are available,[13] as shown for **5c** and **5f**.

The FD-mass spectra of **5**/**6** confirm the expected formation of two benzoxazine structures. For **5** two intensive peaks were found, corresponding to the molecular ion and to a fragment without a R^2-N-CH_2 moiety. In the series **5b**−**5f** the ratio of the intensity of these two peaks increased in the order R^2 = *t*-Bu < *i*-Pr < *n*-Bu < *n*-Pr < Et.

There are two possible regioisomers for bis-benzoxazines **5**/**6** (Figure 1), the chiral structure **A** with a "trans" orientation of the oxazine rings (clockwise or counterclockwise), which has a 2-fold axis and the mesoform **B** with a "cis" orientation and a symmetry plane passing through the tosylated resorcinol rings.

Scheme 1



The ^{1}H NMR spectra of all bis-benzoxazines **5** and **6** contain three signals of equal intensity for the protons of the resorcinol rings and two sets of signals for the protons of the bridges and the tosyl fragments in accord with the pattern expected for the chiral structure **A** (Figure 2a).

In solution molecules **5**/**6** assume one of two possible boat conformations[14] based on NOE experiments (Figure 2a) and the large difference between the signals g and e (e.g., $\Delta\delta = 0.6$ ppm for **5d**) where the high field signal g corresponds to the endo protons of the horizontal aryl rings that are shielded by the vertical rings.

A bis-benzoxazine **6c** is also isolated if the condensation of **4** is carried out with (−)-*R*-α-cyclohexylethylamine. Its ^{1}H NMR spectrum (Figure 2b) shows two sets of all signals (ratio 60:40) which can be interpreted as the result of two possible diastereomers with C_2-symmetry.[15]

Single Crystal X-ray Structures. Crystallization of bis-benzoxazines proved difficult, and diffraction quality crystals could only be obtained from solvent mixtures such as EtOH/CH_2Cl_2/benzene (**5f**) and EtOH/CH_2Cl_2/$CHCl_3$ (**5i**).

(11) (a) El Gihani, M. T.; Heaney, H.; Slawin A. M. Z. *Tetrahedron Lett.* **1995**, *36*, 4905−4908. (b) Iwanek, W.; Mathay, J. *Lieb. Anal.* **1995**, 1463−1469. (c) Arnecke, R.; Böhmer, V.; Friebe, S.; Gebauer, S.; Krauss, G. J.; Thondorf, I.; Vogt, W. *Tetrahedron Lett.* **1995**, *36*, 6221−6224.

(12) Adjacent resorcinol units have been bridged by the condensation of resorcarenes such as **3**/**4** with diamines and formaledhyde: Airola, K.; Böhmer, V.; Paulus, E. F.; Rissanen, K.; Schmidt, C.; Thondorf, I.; Vogt, W. *Tetrahedron* **1997**, *53*, 17691−17698.

(13) Compare: (a) Matsushita, Y.; Matsui, T. *Tetrahedron Lett.* **1993**, *34*, 7433−7437. (b) Schneider, U.; Schneider, H.-J. *Chem. Ber.* **1994**, *127*, 2455−2459.

(14) (a) Högberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498−4500. (b) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046−6050. (c) Abis, L.; Dalcanale, E.; Du vosel, A.; Spera, S. *J. Chem. Soc., Perkin. Trans. 2* **1990**, 2075−2080.

(15) This is in contrast to the diastereoselectivity found for resorcarenes, compare ref 11.

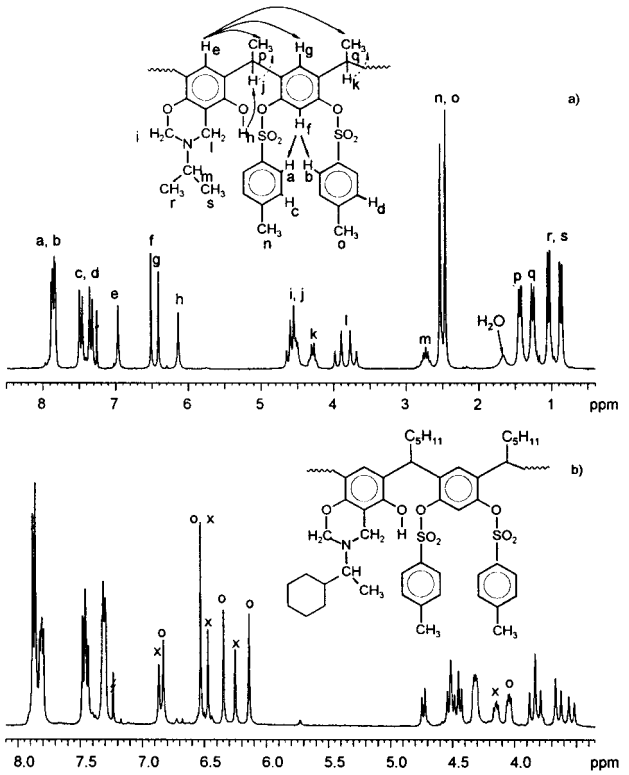


Figure 2. (a) ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of bis-benzoxazine **5d**. The indicated assignment of the signals was achieved by a combination of NOE (arrows) and COSY experiments (dashed arrows). The singlet of the OH-groups disappears after exchange with CH_3OD. Irridation of signal g did not give any NOE with p and q, indicating also that **5d** adopts a boat conformation. (b) Section of the ^{1}H NMR spectrum of bis-benzoxazine **6c**. Signals of the major (x) and minor (o) diastereomers (ratio 60:40) are indicated.

As shown in Figure 3 the molecule **5f** is indeed chiral (structure **A**) and adopts the boat conformation in which the two tosylated resorcinol rings are nearly horizontal and those bearing the oxazine moieties are vertical. Both oxazine rings are oriented inward with the *tert*-butyl groups assuming the axial positions, similar to known structures from tetra-benzoxazine derivatives **2**.[16] Two crystallographically independent molecules of **5f** are found in the asymmetric unit (Figure 3a,b) differing mainly in the arrangement of the tosylate fragments. Their resorcarene skeleton, including the oxazine rings, is very similar in shape (rms = 0.2 Å).

The distances between the oxygens of the phenolic hydroxy groups and the oxygens of the adjacent sulfonyl groups are within the range 2.78−2.82 Å indicating intramolecular O−H···O═S hydrogen bonds which become optimal by orientation of the tosyl groups toward the center of the molecule.

As Figure 3c shows, the boat conformation of the resorcarene skeleton of **5f** is strongly distorted like a two-bladed propeller, as demonstrated by the dihedral angle between the tosylated resorcinol rings (18.7°/19.8° for the two crystallographically independent molecules). The vertical rings, on the other hand, are slightly bent inward (dihedral angle 19.3°/19.6°). This distorted structure can be considered to be a direct manifestation of a resorcarene conformation with "induced" chirality.[17]

The conformation of **5i** is similar to that of **5f**, although in this case the substituents at the nitrogens, the two adamantyl groups have an *out axial* orientation (Figure 4a). Thus, an extended cavity is formed which is filled with disordered solvent molecules. The resorcarene skeleton of **5i** is again strongly distorted (the interplanar angle between the tosylated resorcinol rings is about 18°), and the tosyl residues have a similar arrangement with two intramolecular O−H···O═S hydrogen bonds (O−O distances 2.77/2.79 Å). One of the non-hydrogen bonded tosyl residues was found to be disordered over two positions with about 50% occupancy.

The rather "irregular shape" of **5i** prevents a dense packing of the molecules in the crystal lattice. The gaps or channels thus formed are filled with disordered solvent molecules which also explains why single crystals can be obtained only from complex mixtures of solvents.

Table 1. Crystallographic Data for Bis-Benzoxazines **5f** and **5i**[a]

	5f	**5i**
formula	$C_{72}H_{78}O_{16}N_2S_4$	$C_{84}H_{90}O_{16}N_2S_4 \times CHCl_3 \times CH_2Cl_2$
formula weight	1356.7	1724.52
space group	*P*-1	*P*-1
crystal system	triclinic	triclinic
crystal color	colorless	colorless
crystal size	0.5 × 0.25 × 0.1 mm^3	0.55 × 0.24 × 0.04 mm^3
T (K)	293 (2)	293(2)
a (Å)	17.147(1)	11.293(1)
b (Å)	21.677(1)	14.133(1)
c (Å)	23.859(1)	28.650(2)
α (deg)	77.27(1)	86.19(1)
β (deg)	70.00(1)	81.67(1)
γ (deg)	86.71(1)	69.60(1)
V (Å^3)	8127.3(2)	4239.9(4)
Z	4	2
D_c (g/cm^3)	1.145	1.351
F(000)	2964	1804
μ (cm^{-1})	0.18	0.37
$2\theta_{max}$ (deg)	41.64	43.94
(*hkl*)	$-17<h<17$	$-11<h<11$
	$-21<k<21$	$-14<k<14$
	$-23<l<23$	$-30<l<30$
$\Delta\omega$ (grad)	0.3	0.3
time (min/frame)	0.5	0.5
R(merg) (%)	5.37	4.93
R_σ (%)	9.97	8.18
uniq reflec	16782	10168
reflections	30962	18825
$I > 2\sigma(I)$	8655	5443
$R_{2\sigma(I)}$ $(F)^b$ (%)	9.22	8.20
$wR(F^2)^{c,d}$ (%)	30.4	25.6
S	1.032	1.012
weighting factor *A*	0.1824	0.1125
weighting factor *B*	0	6.0453
Δ/σ (max)	0.002	0.002
$\Delta(\rho)$ (e$^-$/Å^3)	−0.49...0.88	−0.41...0.67
no. of parameters	1779	1053
no. of restrains	0	36

[a] The structures were corrected for Lorentz, polarization, and absorption effects. [b] Minimization of $(F_o^2 - F_c^2)^2$. [c] Weighting scheme $w = 1/[\sigma^2(F_o^2) + (A\cdot P)^2 + B\cdot P]$; $P = (\mathrm{Max}(F_o^2, 0) + 2\cdot F_c^2)/3$. [d] Calculated for all reflections.

Reactions with Diamines. The condensation of **3** with formaldehyde and aliphatic diamines carried out under high dilution conditions furnished the first resorcarene derivatives in which two opposite resorcinol units are covalently linked.[12] This macrotricyclic skeleton was confirmed by FD-mass spectra which showed only the molecular ion in these cases. The chiral structure of **7a**−**c** (yield of pure products 17−53%) was proved again by ^{1}H NMR spectroscopy (Figure 5).

The crystal structures of **5f** and **5i** suggest, however, that a C_2-symmetrical bridging should not be possible with shorter

(16) Compare for instance refs 10−12.

(17) Such a chiral distortion of the resorcarene conformation was postulated by Aoyama in order to explain strong Cotton effects upon complexation of chiral polyols by resorcarenes **1**, see: Kikuchi, Y.; Kobayashi, K.; Aoyama, Y. *J. Am. Chem. Soc.* **1992**, *114*, 1351−1358.

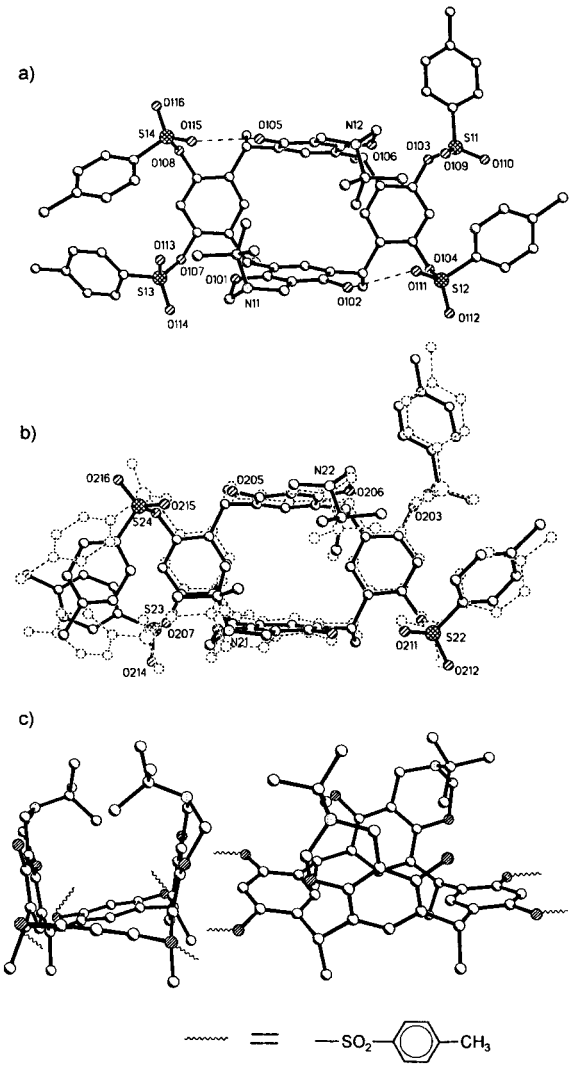


Figure 3. Single-crystal X-ray structure of **5f**. **(**a) One of the two crystallographically independent molecules with the numbering of the heteroatoms. Hydrogen atoms are omitted for clarity, intramolecular hydrogen bonds are indicated by dashed lines. (b) Superimposition with the second molecule which differs mainly in the orientation of the tosylate groups. (c) Views of the resorcarene skeleton only, showing its propeller-like distortion.

diamines. In fact the reactions with ethylenediamine, 1,1-dimethyl ethylenediamine, or *N*-methyl ethylenediamine gave exclusively the macrobicyclic dibenzoxazines **8a** (89%) and **8b** (62%) or the monobenzoxazine **9** (79%), respectively. No benzoxazine is formed with 1,3-diaminopropane where the condensation with an additional molecule of formaldehyde leads instead to a hexahydro pyrimidine ring. **11b** is obtained in 91% showing that the *N*,*N*-acetal is more stable under these conditions than the *O*,*N*-acetal.

The ^{1}H NMR spectrum of **8a** (Figure 5) shows five signals for the aromatic protons of the resorcinol rings (with the theoretical ratio of 1:1:1:1:2), in full agreement with the C_s-symmetrical structure **B**. The signals corresponding to the tosylated resorcinol rings of **8a** are split and strongly shifted in comparison with **7**, while the singlet for the two protons of the other aryl rings does not change its position. This allows the conclusion that all compounds **5**−**8** adopt a similar boat conformation in solution with the tosylated resorcinol rings in an horizontal arrangement.

The ^{1}H NMR spectra of **8b** and **9** (Figure 5) contain six singlets for the protons of the resorcarene skeleton as expected

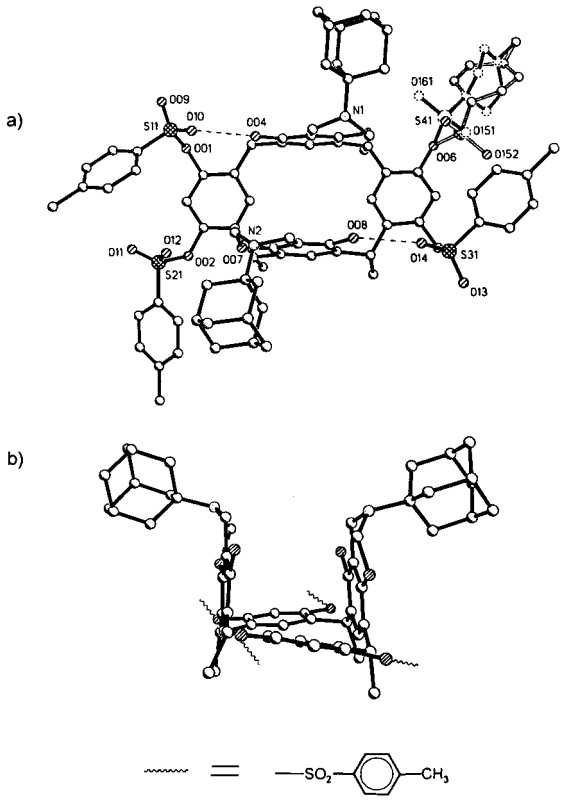


Figure 4. Single-crystal X-ray structure of **5i**. (a) Molecular conformation and numbering of the heteroatoms. The two positions of the disordered tosyl residue are shown. (b) Distortion of the resorcarene skeleton and orientation of the oxazine residues.

for asymmetric molecules. The similarity of the aryl signals for **8b** and **9** suggests a cis orientation of the tertiary amino group (−CH_2−N(CH_3)−CH_2) in **9** hydrogen bonded in $CDCl_3$ by the adjacent OH group.

Critical inspection of the high resolution ^{1}H NMR spectrum of **7b** shows also some small peaks that are analogous to **8a**, and the same has been observed sometimes for compounds **5**/**6**. This suggests, that in such cases a very small amount (<5%) of the C_s-isomer is present, indicating a relatively small energy difference between the two regio isomers **A** and **B**.

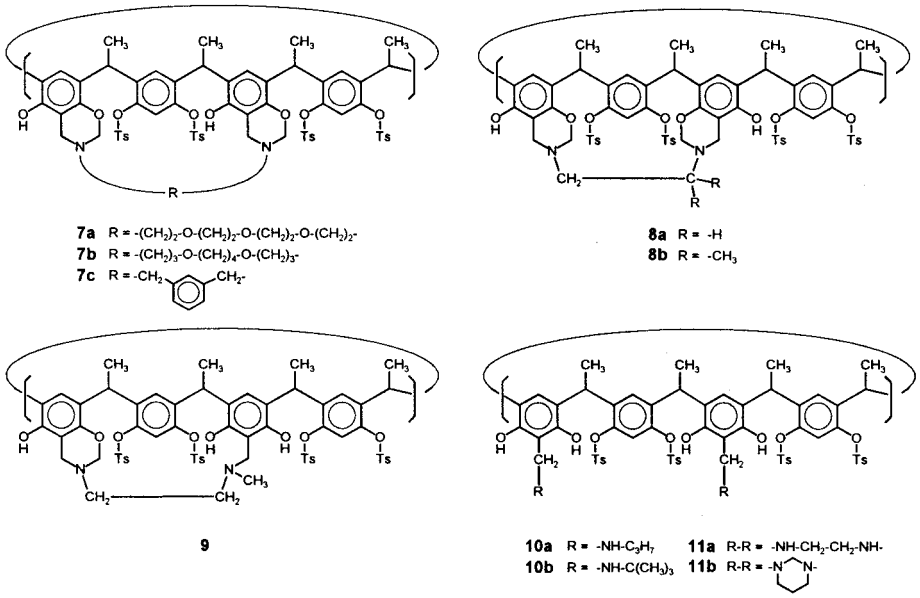
Hydrolysis of **8a** to the secondary amine **11a** (85%) was possible, while the *N*,*N*-acetal ring in **11b** could not be hydrolyzed. Interestingly, the ^{1}H NMR spectrum of **11b** reveals C_s-symmetry at 0 °C, showing five signals for the aromatic protons of the resorcinol rings and two sets of signals for the tosyl groups[18] as found for **8a**. This proves, in combination with a pair of doublets for the Ar−CH_2−N protons, that the diamino bridge is bent to one side. C_{2v}-symmetry is found for **11a** with a slightly longer chain and for the open chain diamines **10**.

Computational Simulations. Possible conformers for bis-benzoxazines **5** may differ by (a) the inclination of the resorcinol rings of the resorcarene skeleton, (b) the orientation of the nitrogen atoms of the benzoxazine rings (*out* or *in*), (c) the orientation of the substituents at the nitrogen (*axial* or *equatorial*), and (d) the relative orientations of the tosyl residues.

MM-calculations predict a boatlike conformation as the energy minimum for tetratosylate **3**, in which the free resorcinol rings are nearly parallel (dihedral angle 3.7°) and the tosylated resorcinol rings are bent outward. The energy calculated for

(18) Kolehmainen, E.; Rissanen, K.; Böhmer, V. et al.; detailed publication in preparation.

Chart 1



the alternative boat conformation with the free resorcinol rings bent outward was higher by about 8 kcal/mol. Two opposite tosyl groups oriented toward the center form stronger OH···O═S hydrogen bonds (O···O-distance 2.9 Å) than the two others (O···O-distance 3.1 Å). The resorcarene skeleton itself is slightly distorted like a two-bladed propeller (dihedral angle of the tosylated resorcinol units 4.3°) due to the tendency to form two hydrogen bonds as strong (O···O-distances as short) as possible.[19]

For **5f** the lowest energy corresponds to a similar boat conformer having the nitrogen atoms oriented *in* and their *tert*-butyl groups assuming the *axial* position (Figure 6a), usually the most stable orientation in 1,3-oxazines.[20] In comparison with conformations with an *out* orientation of the nitrogen atoms (Figure 6b) this ensures a maximum distance between their unshared electron pairs. The resorcarene skeleton shows a propeller-like distortion with a dihedral angle of 16.4° between the tosylated resorcinol units. Comparison with the 4.3° calculated for **3** suggests that, in fact, this distortion is mainly due to the oxazine rings. The tosyl residues themselves are oriented in a propeller like (C_2-symmetrical) fashion, which leads to two short O−H···O═S hydrogen bonds (O···O-distance 2.9 Å). The calculated energies for other conformations are higher by at least 3.2 kcal/mol (Figure 6b).[21]

The lowest energy conformation is rather similar to the conformations found in the crystalline state. In particular the dihedral angles between the tosylated (16.4°) and vertical (17.4°) resorcinol rings are in good agreement with the values found in the crystalline state (18.7°/19.8° and 19.3°/19.6°, respectively). The main differences concern the arrangement of the tosyl groups in the neighborhood of the benzoxazine fragments, which are not involved in intramolecular hydrogen bonds. A superimposition of the resorcarene skeleton (including the benzoxazine structures but excluding the *tert*-butyl groups and the tosyl residues) leads to rms values of 0.29 and 0.34 Å for the two crystallographically independent molecules.

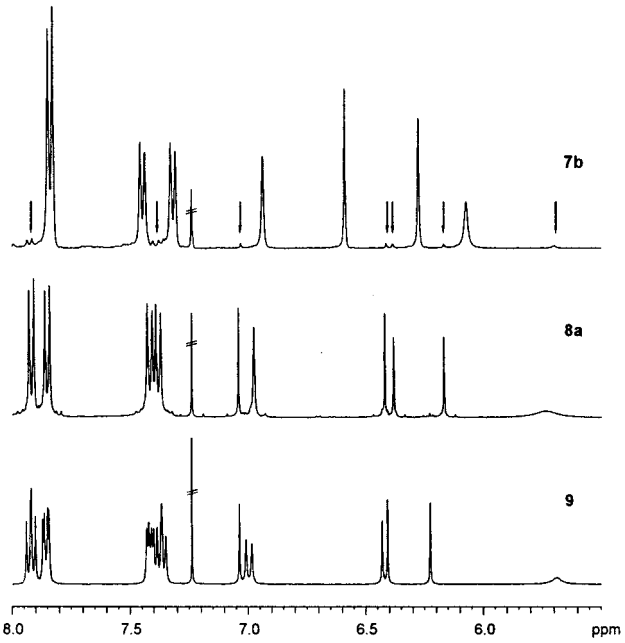


Figure 5. Section of the ^{1}H NMR spectra (400 MHz, $CDCl_3$) of the macrotricyclic bis-benzoxazines **7b** and **8a**, showing the difference between the C_2- and C_s-symmetrical arrangement of the two benzoxazine structures and of the analogous asymmetric mono-benzoxazine **9**. Signals belonging to the "cis" isomer of **7b** are indicated with arrows.

For the meso-form **B** (Figure 1) with a cis orientation of the oxazine rings an *out/out-eq/eq* conformation with a single (!) strong intramolecular O−H···O═S hydrogen bond (O···O-distance 2.9 Å) is predicted, in which the resorcarene skeleton is only slightly distorted (dihedral angles between tosylated and vertical resorcinol rings are 0° and 4.1°, respectively). The H-bonded tosyl group points toward the center of the macrocycle similar to the tetratosylate **3** and the chiral isomer **5f**. The isomers **A** and **B** can be interconverted by cleaving one O−CH_2 bond, rotating around the Ar−CH_2 bond, and forming the opposite O−CH_2 bond. This process occurs under acidic catalysis[11] and resembles the regrouping of hydrogen bonds in secondary amines such as **10**. Therefore it seems justified, to

(19) Experimentally such a conformation was detected by ^{1}H-NMR spectroscopy at 205 K, where the spectrum corresponds to C_2-symmetry, while a fast exchange between the pairs of tosyl groups leads to time-avaraged C_{2v}-symmetry at room temperature: Lukin, O. V.; Shivanyuk, A. to be published.

(20) Katritzky, A. R.; Shcherbakova, I. V.; Mancheno, B.; Tack, R. D. *Magn. Reson. Chem.* **1993**, *31*, 615−617.

(21) Similar conformations and energy differences resulted for bis-benzoxazines formally obtained with methyl-, ethyl-, and isopropylamine.

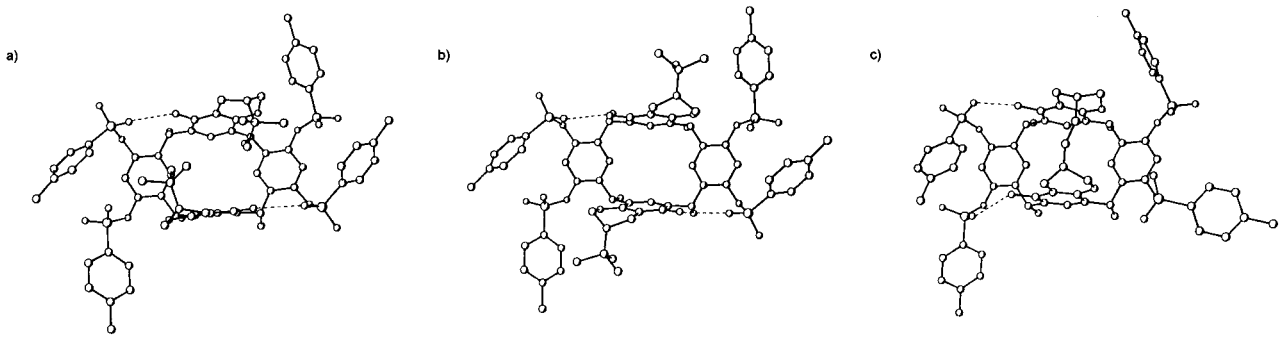


Figure 6. Energy minimized conformation (*in*/*in*, *ax*/*ax*) of bis-benzoxazine **5f** (a) in comparison with the *out*/*out*, *ax*/*ax* conformation (relative energy 3.2 kcal/mol (b), and the minimized structure of bis-benzoxazine **8a** (c).

compare also the relative energies for **A** and **B**. This reveals that the lowest energy conformation of **B** is less favored by 5.5 kcal/mol in comparison to **A**.

MM calculations for the bridged compounds **8a** and **9** showed that in both cases the cis orientation (with an intramolecular O−H···N bond for **9**) was most advantageous (Figure 6c). All attempts to optimize the trans isomers resulted in highly distorted structures with unreasonably high energies. In the optimized structures of **8a** and **9** the methylene groups of the bridge assume an *axial-in* position (similar to the crystal structure of **5f**).

Molecular dynamics simulations were performed (vacuum, 300 K), starting with the minimized structure of **5f**. Every 10−12 ps fast inversions of the oxazine rings and their nitrogens occur, making the benzoxazine structure "planar" on time average. However, no change of the conformation of the resorcarene skeleton (e.g., an interconversion to the other boat conformation) and no significant change of the orientation of the tosyl fragments occurs over the whole simulation time of 120 ps, suggesting that this conformation is maintained "time averaged" also in solution. This is in agreement with dynamic ^{1}H NMR studies ($CDCl_3$) which show only a downfield shift for the OH-signal and a slight broadening of the signals of the benzoxazine protons when the temperature is decreased from 295 to 218 K.

Concluding Remarks

The regioselective formation of tetrabenzoxazines **2** is due to the fact that among the four possible regioisomers only the C_4-symmetrical isomer enables the formation of four intramolecular O−H···O hydrogen bonds. For bis-benzoxazines **5** and **6** two intramolecular O−H···O═S hydrogen bonds are possible in principle for both isomers **A** and **B**. However, the starting tetratosylate **3** prefers the conformation in which the tosylated resorciol rings are oriented outward and in which, by a slight C_2-symmetrical distortion of the resorcarene skeleton, two distal hydrogen bonds are stronger. Since this boat conformation also exists in **5** and **6**, the orientation of the oxazine rings must be trans as in the C_2-symmetrical isomer **A** to avoid steric and electrostatic repulsion of the N−R^2 groups. In combination with the tendency to obtain the most favorable intramolecular hydrogen bonds this leads to an overall propeller-like distortion which involves the resorcarene skeleton itself as well as the arrangement of the tosyl groups. The energetic preference of the C_2-symmetrical isomer **A** over the C_s-symmetrical isomer **B** cannot be very high, however, since the macrotricyclic compounds **8** are easily formed in high yield even without high dilution conditions.

Experimental Part

Reagents and Methods. Resorcarenes **1**[22] and their tetratosylates **3** and **4**[14] were synthesized as described previously. Melting points were determined with a MEL TEMP 2 capillary melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker AC200 (200 MHz), Bruker AM 400 (400 MHz), and Bruker DRX 500 (500 MHz) spectrometers, and NOE, COSY, and HMBC− experiments were performed by a Bruker AM 400 (400 MHz) spectrometer. FD mass spectra were recorded with a Finnigan MAT 90 (5 kV/10 mA/min).

General Procedure for the Synthesis of Bis-Benzoxazines 5 and 6. The tetratosylate **3** or **4** (0.25 mmol) was dissolved in EtOH (30 mL). An aqueous solution of formaldehyde (40%, 8 mL), glacial acetic acid (0.5 mL), and finally the primary amine (1.5 mmol) was added with intensive stirring. A colorless precipitate formed after a while, which was filtered off after 24 h, washed with EtOH, and recrystallized. Further experimental details, yields, and analytical data are given subsequently for selected examples only.

Bis-benzoxazine 5f: Yield 71%; mp 159−161 °C (EtOH/CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 (d, J = 8.0 Hz, 4H), 7.80 (d, J = 8.0 Hz, 4H), 7.44 (d, J = 8.0 Hz, 4H), 7.31 (d, J = 8.0 Hz, 4H), 6.99 (s, 2H), 6.57 (s, 2H), 6.38 (s, 2H), 6.30 (s, 2H), 4.86 (d, J = 10.6 Hz), 4.66 (d, J = 10.6 Hz), 4.53 (q, J = 6.9 Hz, 2H), 4.31 (q, J = 6.9 Hz, 2H), 3.96 (m, 4H), 2.52 (s, 6H), 2.45 (s, 6H), 1.40 (d, J = 6.9 Hz, 6H), 1.23 (d, J = 6.9 Hz, 6H), 0.91 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.54, 149.57, 146.31, 145.22, 143.85, 141.38, 138.54, 131.62, 130.36, 129.82, 128.73, 127.94, 127.46, 122.34, 121.73, 116.22, 114.66, 111.31, 78.17, 54.32, 41.21, 31.60, 30.76, 28.16, 22.28, 21.77, 21.63, 19.69; FD-MS m/z 1356.3 (22%, M^+), 1270.3 (100%, $M^+ - CH_2NBu^t$). Anal. Calcd for $C_{72}H_{78}N_2O_{16}S_4$: C, 63.80; H, 5.76; N, 2.10. Found: C, 63.79; H, 5.69; N, 2.17.

Bis-benzoxazine 5j: Yield 86%; mp 195−197 °C (EtOH/CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 4H), 7.78 (d, J = 8.4 Hz, 4H), 7.41 (d, J = 8.4 Hz, 8H), 7.16 (s, 2H), 7.12 (s, 2H), 6.96 (s, 2H), 6.80 (s, 4H), 6.71 (s, 2H), 6.21 (s, 2H), 5.95 (s, 2H), 4.60−4.15 (m, 10H), 7.91 (d, J = 17.4 Hz, 2H), 2.47 (s, 6H), 2.21 (s, 12H), 2.09 (s, 6H), 2.04 (s, 6H), 1.45 (d, J = 6.7 Hz, 6H), 1.30 (d, J = 7.0 Hz, 6H); FD-MS m/z 1479.5 (12%, M^+), 1333.0 (100% $M^+ - CH_2NC_6H_2(CH_3)_3$). Anal. Calcd for $C_{82}H_{82}N_2O_{16}S_4 \cdot H_2O$: C, 65.76; H, 5.65; N, 1.87. Found: C, 65.99; H, 5.71; N, 1.85.

Bis-benzoxazine 6b: Yield 88%; mp 176−178 °C (EtOH/CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 4H), 7.80 (d, J = 8.2 Hz, 4H), 7.46 (d, J = 8.2 Hz, 4H), 7.32 (d, J = 8.2 Hz, 4H), 6.89 (s, 2H), 6.50 (s, 2H), 6.48 (s, 2H), 6.25 (s, 2H), 4.73 (d, J = 10.2 Hz, 2H), 4.66 (d, J = 10.2 Hz, 2H), 4.32 (dd, J = 9.9 Hz, J = 4.6 Hz, 2H), 4.16 (dd, J = 8.9 Hz, J = 5.5 Hz, 2H), 4.00 (d, J = 17.1 Hz, 2H), 3.64 (d, J = 17.1 Hz, 2H), 2.57 (m, 2H), 2.51 (s, 6H), 2.44 (s, 6H), 1.95−1.11 (m, 24 H), 0.96 (d, J = 6.2 Hz, 6H), 0.75 (m, 18H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.21, 150.81, 146.31, 145.57, 145.19, 143.87, 140.19, 137.61, 131.53, 130.42, 129.82, 128.87, 127.77, 122.75, 120.39, 114.24, 113.58, 109.59, 78.85, 51.48, 44.18, 36.88, 36.65, 35.76, 33.81, 31.73, 31.63, 27.78, 27.33, 22.54, 21.84, 21.71, 20.51, 13.98; FD-MS m/z 1551.2 (69%, M^+), 1481.2 (100%, $M^+ - CH_2NPr^i$). Anal. Calcd for $C_{86}H_{106}N_2O_{16}S_4$: C, 66.55; H, 6.80; N, 1.80. Found: C, 66.56; H, 6.75; N, 1.80.

General Procedure for the Synthesis of Bridged Resorcarenes. To a solution of formaldehyde (40%, 1.5 mL) and glacial acetic acid (0.05 mL) in 200 mL of ethanol (800 mL) a solution of tetratosylate **3** (0.5 g, 0.43 mmol) and diamine (0.45 mmol) in ethanol (25 mL) was

slowly added (over 2 h) at 80 °C. The reaction mixture was refluxed for further 2 h. The solution was evaporated in vacuum, and the oily residue triturated with methanol. The obtained white powder was recrystallized from chloroform/methanol. Further data are given for selected examples only.

Bis-benzoxazine 7a: Yield 53%; mp 132−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.3 Hz, 8H), 7.45 (d, J = 8.3 Hz, 4H), 7.33 (d, J = 8.3 Hz, 4H), 6.97 (s, 2H), 6.60 (s, 2H), 6.34 (s, 2H), 6.18 (br s, 2H), 4.49 (q, J = 6.9 Hz, 2H), 4.45 (d, J = 9.7 Hz, 2H), 4.36 (d, J = 9.7 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.92 (d, J = 17.1 Hz, 2H), 3.68−3.52 (m, 14H), 3.59 (m, 2H), 2.51 (s, 6H), 2.45 (s, 6H), 2.32 (m, 2H), 1.40 (d, J = 6.9 Hz, 6H), 1.26 (d, J = 7.1 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.84, 150.42, 146.26, 145.34, 143.92, 141.49, 138.50, 133.89, 131.80, 130.35, 129.87, 128.40, 128.06, 126.83, 122.09, 121.72, 117.00, 114.70, 108.37, 79.51, 70.54, 70.29, 67.80, 48.08, 46.99, 31.98, 31.20, 27.18, 21.83, 21.72, 19.46. The molecular peak was not found in the FD-MS spectrum of this compound. Anal. Calcd for $C_{72}H_{76}N_2O_{19}S_4 \cdot H_2O$: C, 60.92; H, 5.54; N, 1.97. Found: C, 61.13; H, 5.51; N, 1.83.

Bis-benzoxazine 8a: Yield 89%; mp 195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91, 7.85 (d, J = 8.3 Hz, each 4H), 7.41, 7.38 (d, J = 8.2 Hz, each 4H), 7.04 (s, 1H), 6.97 (s, 2H), 6.42 (s, 1H), 6.38 (s, 1H), 6.17 (s, 1H), 5.74 (s, 2H), 4.64 (d, J = 10.0 Hz, 2H), 4.44−4.36 (m, 6H), 3.93 (d, J = 17.4 Hz, 2H), 3.51 (d, J = 16.6 Hz, 2H), 2.48 (s, 6H), 2.46 (s, 6H), 2.53−2.36 (m, 4H), 1.39 (d, J = 6.9 Hz, 6H), 1.28 (d, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.46, 150.06, 146.47, 145.16, 144.97, 144.92, 140.70, 139.19, 134.14, 131.81, 130.44, 129.94, 128.42, 128.33, 127.35, 126.47, 122.49, 122.10, 117.17, 115.92, 113.25, 109.31, 82.76, 53.26, 46.29, 32.54, 30.65, 21.80, 21.70, 20.39, 19.83; FD-MS m/z 1269.7 (100%, M^+). Anal. Calcd for $C_{66}H_{64}N_2O_{16}S_4 \cdot 1.5H_2O$: C, 61.14; H, 5.21; N, 2.16. Found: C, 61.07, H, 5.24, N, 2.18.

Bis-benzoxazine 8b: Yield 62%; mp 257 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95, 7.92, 7.88, 7.87 (d, J = 8.3 Hz, each 2H), 7.43, 7.42, 7.39, 7.37 (d, J = 8.3 Hz, each 2H), 7.06 (s, 1H), 6.99 (s, 1H), 6.98 (s, 1H), 6.41 (s, 1H), 6.37 (s, 1H), 6.24 (s, 1H), 5.89 (s, 1H), 5.71 (s, 2H), 5.02 (dd, J = 11.1 Hz, J = 1.5 Hz, 1H), 4.66 (d, J = 11.1 Hz, 1H), 4.62 (d, J = 9.6 Hz, 1H), 4.47(q, J = 6.9 Hz, 1H), 4.41 (q, J = 7.2 Hz, 2H), 4.30 (q, J = 7.1 Hz, 1H), 4.08 (dd, J = 9.7 Hz, J = 1.8 Hz, 1H), 4.00, 3.92 (d, J = 18.6 Hz, each 1H), 3.66, 3.51 (d, J = 16.1 Hz, each 1H), 2.50 (s, 6H), 2.48 (s, 3H), 2.47 (s, 3H), 1.74, 1.60 (d, J = 14.5 Hz, each 1H), 1.42, 1.38 (d, J = 6.9 Hz, each 3H), 1.31, 1.27 (d, J = 7.2 Hz, each 3H), 1.23, 1.06 (s, each 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.91, 151.05, 150.53, 148.91, 146.43, 145.12, 145.00, 144.70, 141.14, 140.77, 139.67, 138.54, 134.35, 134.05, 131.93, 131.83, 130.45, 130.43, 130.17, 129.94, 129.92, 128.48, 128.42, 128.30, 127.29, 126.61, 122.82, 122.19, 122.03, 121.93, 117.18, 115.97, 115.14, 113.12, 111.31, 108.09, 84.81, 77.73, 59.76, 58.45, 57.90, 49.35, 40.56, 32.62, 32.49, 31.11, 30.32, 24.67, 23.90, 21.81, 21.70, 20.80, 20.43, 20.35, 19.35, 18.43; FD-MS m/z 1297.8 (100%, M^+).

Mono-benzoxazine 9: Yield 79%; mp 227−228 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92, 7.91 (d, J = 8.2 Hz, each 2H), 7.86, 7.85 (d, J = 8.4 Hz, each 2H) 7.42, 7.41 (d, J = 8.2 Hz, each 2H) 7.37, 7.35 (d, J = 7.7 Hz, each 2H), 7.04 (s, 1H), 7.01 (s, 1H), 6.99 (s, 1H), 6.43 (s, 1H), 6.41 (s, 1H), 7.23 (s, 1H), 5.69 (s, 1H), 4.60 (d, J = 9.6 Hz, 1H), 4.50−4.28 (m, 5H), 3.88, 3.70 (d, J = 15.2 Hz, each 1H), 3.51 (d, J = 15.1 Hz, 1H), 3.49 (br d, J = 16.2 Hz, 1H), 2.49, 2.48, 2.46, 2.45, 2.39 (s, each 3H), 2.5−2.45 (m, 1H), 2.33 (m, J = 12.3 Hz, J = 5.6 Hz, 1H), 2.07 (m, J = 12.5 Hz, J = 4.8 Hz, 1H), 1.84 (m, J = 12.6 Hz, J = 5.5 Hz, 1H), 1.42, 1.35 (d, J = 6.9 Hz, each 3H), 1.29, 1.27 (d, J = 6.8 Hz, each 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.44, 150.52, 150.40, 150.20, 146.42, 145.11, 145.03, 144.96, 144.79, 144.69, 140.92, 140.81, 139.35, 139.24, 134.24, 133.81, 131.91, 131.89, 130.44, 130.41, 129.96, 129.80, 128.70, 128.45, 128.32, 127.44, 126.54, 123.62, 122.19, 122.10, 117.17, 116.01, 115.22, 113.41, 109.55, 106.80, 83.63, 58.43, 56.32, 47.76, 46.53, 44.63, 32.63, 30.95, 30.48, 21.80, 21.71, 21.22, 20.31, 20.16, 19.51; FD-MS m/z 1271.5 (100%, M^+). Anal. Calcd for $C_{66}H_{66}N_2O_{16}S_4 \cdot H_2O$: C, 61.48; H, 5.32; N, 2.17. Found: C, 61.38, H, 5.37, N, 2.13.

Diamine 11b: Yield 91%; mp 272 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 0 °C) δ 7.93, 7.89 (d, J = 8.1 Hz, each 4H), 7.45, 7.39 (d, J = 8.1 Hz, each 4H), 7.06 (s, 2H), 6.95 (s, 1H), 6.42 (s, 1H), 6.26 (s, 1H), 6.19 (s, 1H), 5.91 (s, 2H), 4.47(q, J = 6.4 Hz, 2H), 4.41 (q, J = 7.0 Hz, 2H), 3.58, 3.36 (d, J = 12.7 Hz, each 2H), 2.95 (m, 3H), 2.51 (s, 6H), 2.48 (s, 6H), 2.05 (d, J = 9.3 Hz, 1H), 1.94 (t, J = 11.2 Hz, 2H), 1.75 (q, J = 12.2 Hz, 1H), 1.58 (d, J = 12.6 Hz, 1H), 1.42 (d, J = 6.4 Hz, 6H), 1.35 (d, J = 7.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.17, 151.22, 146.42, 145.12, 144.87, 141.08, 139.58, 133.86, 131.78, 130.42, 129.92, 128.49, 126.85, 125.94, 123.96, 122.12, 117.27, 116.20, 113.85, 109.96, 72.17, 53.07, 49.91, 32.79, 31.96, 31.35, 24.94, 21.76, 20.50, 19.62; FD-MS m/z 1271.4 (100%, M^+).

General Procedure for the Preparation of Secondary Amines. A solution of the bis-benzoxazine (100 mg), half concentrated hydrochloric acid (4 mL), and *n*-butanol (50 mL) was heated under reflux. While water and formaldehyde were removed by azeotropic distillation additional half concentrated hydrochloric acid (two times 4 mL) was added. The remaining *n*-butanol was finally evaporated, and the crude product recrystallized from chloroform/methanol. Yields and analytical data are given for two examples.

Diamine 10b: Yield 80%; mp 266 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 8H), 7.37 (d, J = 7.6 Hz, 8H), 7.19 (s, 2H), 6.82 (s, 2H), 6.16 (s, 2H), 4.42 (q, J = 6.0 Hz, 4H), 3.97 (br s, 4H), 2.44 (s, 12H), 1.35−1.27 (m, 30H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.55, 145.69, 144.73, 139.21, 132.67, 130.17, 128.54, 127.49, 127.16, 125.99, 115.14, 113.71, 57.86, 31.69, 25.89, 21.76, 20.43; FD-MS m/z 1260.7 (100% $M^+ - NBu^t$).

Diamine 11a: Yield 85%; mp 278−280 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 8H), 7.36 (d, J = 8.0 Hz, 8H), 7.24 (s, 2H), 6.46 (s, 2H), 6.32 (s, 2H), 4.47 (q, J = 5.9 Hz, 4H), 4.14 (s, 4H), 3.06 (s, 4H), 2.42 (s, 12H), 1.35 (d, J = 6.0 Hz, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.53, 146.35, 144.73, 139.57, 131.57, 130.25, 128.30, 127.33, 126.50, 122.32, 116.62, 108.09, 43.00, 41.90, 32.10, 21.58, 20.63; FD-MS m/z 1246.2 (100%, M^+).

Crystallizations. All attempts to obtain single crystals of bis-benzoxazines **5** using various pure solvents and mixtures of two solvents were hitherto unsuccessful in our hands. The slow recrystallization of dibenzoxazine **5f** from EtOH/CH_2Cl_2 for instance gave no crystals but a fine powder which seemed to need an additional component in the solvent mixture to become crystalline. After addition of benzene to the mother liquor the powder was dissolved again by heating. Colorless crystals formed overnight, which, however, after a rather short time were covered by precipitating powder. This precipitation was overcome by the addition of more benzene and repeated crystallization. Crystals of compound **5i** were obtained by similar manner from EtOH/$CHCl_3$/CH_2Cl_2.

X-ray Structure Determination. Crystals of **5f** and **5i** were unstable without solvent and were sealed in a capillary containing the mother liquor. Measurements were performed at 23 °C by a Siemens three circle diffractometer with CCD, Siemens-rotating anode, Mo Kα-radiation (graphite monochromated λ = 0.7107 Å). Structures were solved and refined using direct methods[23] (refinement with full matrix versus F^2). Full crystallographic details and tables of coordinates, temperature factors, and bond distances and angles are given in the Supporting Information.

Molecular Mechanics Calculations and Molecular Dynamics Simulations. Molecular mechanics calculations were performed using the MMX force field as implemented in PCMODEL 5.13.[24] Geometry optimization was accomplished with conjugate gradient procedure. A root-mean-square (rms) gradient of 0.001 kcal/mol or less was assumed as a condition of energy convergence. A value of 1.5 D was assumed for the dielectric constant.

Both possible boat conformations (with the unsubstituted resorcinol rings parallel and the tosylated ones coplanar and vice versa) were taken

(22) Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305−1312.

(23) (a) Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467−473. (b) Sheldrick, G. M. SHELXL-96, Program for the Refinement of Crystal Structures. Universität Göttingen, Germany, 1996.

(24) (a) PCMODEL is distributed by Serena Software, Dr. Kevin E. Gilbert, P. O. 3076, Bloomington, IN 47402. (b) Discover, version 2.9.5; May 1994; Biosym Technologies, 9685 Scranton Road San Diego, CA 92121-4778.

as a starting point for the tetratosylate **3**, and the arrangement of the tosyl groups was optimized by variation of the torsion angle for the Ar−OTs and ArO−Ts bonds in 12 steps of 30°. While these angles were fixed, the rest of the molecule was minimized. From the 144 conformers thus obtained, the conformer with the minimum energy was further optimized without any restriction of the conformational mobility. This was repeated then analogously for the remaining tosyl groups. The same computational procedure was applied to all possible conformers of bisbenzoxazine **5f**, differing in the orientation of the nitrogen (*in*, *out*) and the *tert*-butyl groups (*eq*, *ax*).

Molecular dynamics simulations were carried out using the CVFF force field as implemented in the InsightII (Discover 2.9.5) program package. A value of 1.5 D was assumed for the dielectric constant. The minimized structures were used as starting points for MD simulations. The structures were equilibrated for 20 ps in all cases before the main simulations were started. The time step in all MD simulations performed was 1 fs. MD simulations were carried out at 300 K for 120 ps.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the European Community. We are grateful to Dr. E. Kolehmainen (Jyväskylä) for the measurement of ^{13}C-NMR and low temperature ^{1}H-NMR spectra.

Supporting Information Available: Experimental details, yields, NMR-spectral data for the compounds **5a**−**e**, **5g**−**i**, **6a**, **6c**, **7b**−**c**, and **10a** not described in detail above and crystal structural data including tables of atomic coordinates, anisotropic thermal parameters, bond lengths and angles, and torsion angles for compounds **5f** and **5i** (61 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA9729286