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The Synthesis of Oxazaborolo-benzoxazaborinine Derivatives of Resorcinarene from (1*S*,2*R*)-ephedrine

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Abstract

The oxazaborolo-benzoxazaborinine derivatives (**3**) of resorcinarene have been synthesized from (1*S*,2*R*)-ephedrine. The reaction yields the crown and diamond conformers of the bora derivative of resorcinarene in high diastereomeric excess (de > 97%). The crystallographic structure of the crown conformer of (**3**) was determined.

Introduction

Resorcinarenes are cavity-shaped macrocycles which can be easily synthesized from resorcinol and aldehydes [1]. The synthesis of the chiral resorcinarenes [2] is interesting not only for the preparation of novel chiral supramolecular structures but also for their potential use in the study of chiral discrimination as well as their application as chiral catalysts for asymmetric reactions. Although some examples of using the resorcinarene derivatives in the study of chiral discrimination appear in the literature [3], no data have been found concerning application of these derivatives in asymmetric reactions. An atom having the properties of Lewis acid can be introduced into the resorcinarene derivative [4], making it possible to use such a structure as a potential supramolecular catalyst for a number of asymmetric reactions (see Figure 1).

Results and Discussion

The first stage of the presented synthesis was the preparation *via* Mannich reaction of the aminomethylene derivative (**2**) of resorcinarene starting from (1*S*,2*R*)-ephedrine (see Scheme 1).

Subsequently, the hydroxy groups of the phenolic ring and the (1*S*,2*R*)-ephedrine, and the electron lone pair at the nitrogen atom of the derivative **2** were linked using $PhB(OH)_2$, to yield the oxaborolo-benzoxazaborinine derivative of resorcinarene. The reaction was performed in toluene and water was removed azeotropically from the reaction mixture. After evaporation of the solvent, the residue was taken up in acetone, and a crystalline solid precipitated. Thin-layer chromatography using ethyl acetate: *n*-hexane indicated a mixture of two reaction products. These products were separated *via* column chromatography, using ethyl acetate:*n*-hexane as an eluent. The analysis of the ^1H and ^{13}C NMR spectra proved that the major reaction product is the crown conformer of the bora derivative of resorcinarene, and the other product is the diamond conformer. These products **3** feature a high diastereomeric excess, more than 97%. An overall yield up to 60% of this synthesis is also quite good.

Crystallization of the crown conformer of the derivative **3** from acetone afforded crystals suitable for X-ray analysis. Figure 2 presents the crystallographic structure of the crown conformer of **3**.

The crystallographic analysis shows that the closure of all the resorcinol rings to form the oxazaborolo-benzoxazaborinine derivative is clockwise when viewed from inside the cavity. The benzoxazaborinine rings are oriented towards the resorcinarene cavity, whereas the phenyl groups on boron protrude outwards the cavity. This diastereoisomer, when crystallized from acetone, contains an acetone molecule within the cavity with its methyl group pointing towards the π-basic socket of the resorcinarene as a result of CH–π interactions with the resorcinol rings. This derivative adopts the crown conformation in the solid state and it is stabilized by hydrogen bonds between the phenolic hydroxy groups; the distances between the oxygen atoms are: 2.687 Å (O19A—O13D), 2.686 Å (O19B—O13A), 2.757 Å (O19C—O13B), 2.904 Å (O19D—O13A). The lengths of nitrogen–boron bonds are as follows: 1.704 Å

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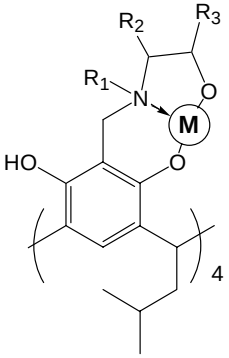


M = Lewis atom

Figure 1. The general structure of novel resorcinarene derivatives.

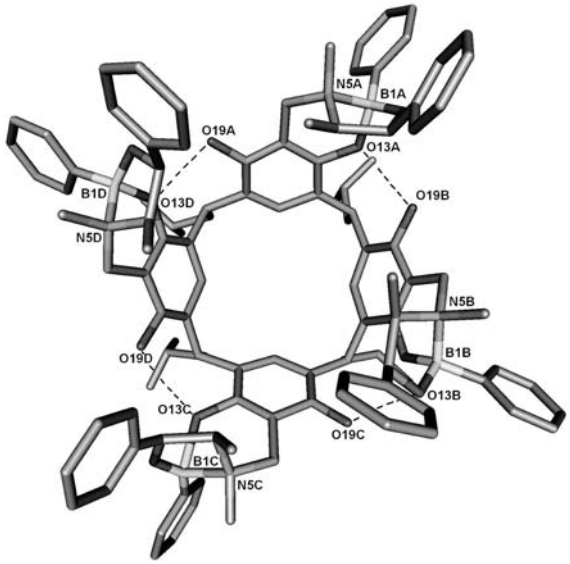
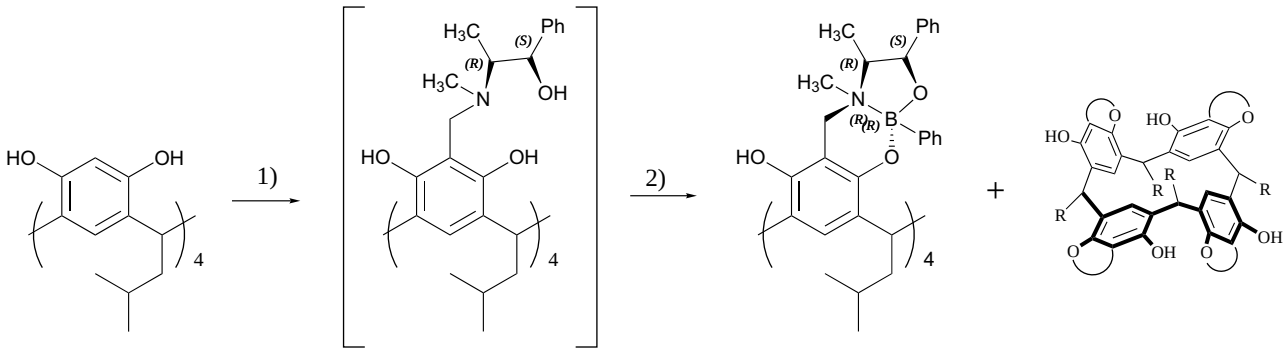


Figure 2. The crystallographic structure of the oxazaborolo-benzoxazaborinine derivative of resorcinarene from (1*S*,2*R*)-ephedrine. The top view of the crystallographic structure; dotted lines denote the hydrogen bonds, selected atom are labeled. The hydrogen atoms are omitted for clarity.

(N5A—B1A), 1.575 Å (N5B—B1B), 1.916 Å (N5C–B1C), 1.676 Å (N5D—B1D); these lengths are similar to that of other derivatives of this type [5]. The selected crystallographic data, the distances between the oxygen atoms and the bond lengths between nitrogen–boron atoms are listed in Table 1.

Figure 3 compares the representative ranges of the ^{1}H NMR spectra of the crown and diamond conformers of the derivative **3** in chloroform. In particular, the presence of four doublets of the ephedrine methine protons (—CH—Ph) of the diamond conformer is noteworthy in comparison to one doublet appearing for the crown conformer (δ : 5.42, 5.47, 5.52, 5.56 ppm, and 5.48 ppm, respectively). Besides, in the range diagnostic for hydroxy protons (—OH), there are four signals observed for the diamond conformer (δ : 8.16, 8.73, 8.74, 8.91 ppm) *versus* one signal observed for the crown conformer (δ: 8.71 ppm). The diastereotopic aminomethylene protons (—CH_2—N—) give rise to one pair of doublets in the case of the crown conformer (δ: 3.62 and 4.23 ppm, $J = 16.18$ Hz), whereas there are two pairs of doublets and one doublet of doublets (dd) having a twofold intensity for the diamond conformer (δ: 4.05 and 4.41 ppm, $J = 15.71$ Hz; 4.11 ppm (dd), $J = 6.74$ Hz; 4.17 and 4.31 ppm, $J = 8.97$ Hz, respectively). These values of chemical shifts of aminomethylene protons of the crown conformer of **3** are consistent with the chemical shifts observed for the bora-oxazino-oxazolidine derivative of resorcinarene prepared from L-prolinol [4]. The most characteristic it is however the chemical shift of proton H_5. It is at: $\delta = 4.59$ ppm for crown conformer as well as $\delta = 4.68$ and 4.57 ppm for diamond conformer and it is in good agreement with chemical shifts for these conformers well known with literature [6].

An analysis of the ^{13}C NMR spectrum of the diamond conformer confirms its structure. Four signals are observed for each of the carbon atoms bearing the



1 **2** **3** (crown) **3** (diamond)

1) (+)-ephedrine, CH_2O, MeOH, rt; 2) $PhB(OH)_2$, toluene, reflux

Scheme 1.

Table 1. Crystallographic data and selected O—O and N—B bond length (Å) for derivate **3**

Formula	$C_{124}H_{152}\ B_4\ N_4\ O_{16} * 4\,C_3H_6O$
M	1997.74
a/Å	15.773(1)
b/Å	27.349(1)
c/Å	32.273(1)
α/deg	90.00
β/deg	90
γ/deg	90.00
V/Å^3	13921.8(11)
D_{calc}/g cm^{-3}	0.953
Z	4
Cyst. syst.	Orthorhombic
Space group	P212
R	0.174
O19A—O13D	2.687
O19B—O13A	2.686
O19C—O13B	2.757
O19D—O13A	2.815
N5A—B1A	1.704
N5B—B1B	1.634
N5C—B1C	1.916
N5D—B1D	1.676

methylene and methine protons which are marked in Figure 3. Moreover, there are eight signals (δ: 148.66, 149.24, 149.35, 149.38, 149.50, 149.56, 149.86, 150.42 ppm) for the aromatic carbon atoms bearing the oxygen atoms. All this evidence verifies the formation of the diamond conformer of the bora-derivative of resorcinarene. However, this is not sufficient to ascertain the direction of closure of the oxazine ring and the location of the oxazolidine ring of this derivative.

The presented cyclization reaction results in formation of new stereogenic centers at the nitrogen and boron atoms. In the case of the crown conformer, the nitrogen and boron atoms adopt the (*R*) configuration as shown in Scheme 1.

In summary, clipping of the aminomethyl derivative (**2**) of resorcinarene and (1*S*,2*R*)-ephedrine using phenylboronic acid yields two conformers of the oxazaborolo-benzoxazaborinine derivative (**3**) of resorcinarene, viz., the crown conformer **3** and the diamond conformer **3**. The crystallographic structure of the crown conformer was determined.

Experimental

General

^{1}H and ^{13}C NMR spectra were measured at 25 °C on Bucker at 250 MHz. Mass spectra were obtained on a Finnigan MAT-711A mass spectrometer. All solvents and chemicals were obtained commercially and used as received. Optical rotations were measured at 20 °C on Perkin-Elmer-241 polarimeter. Chromatographic separations were performed on silica gel 60 (SiO_2, Merck, particle size 0.040–0.063 mm, 230–240 mesh).

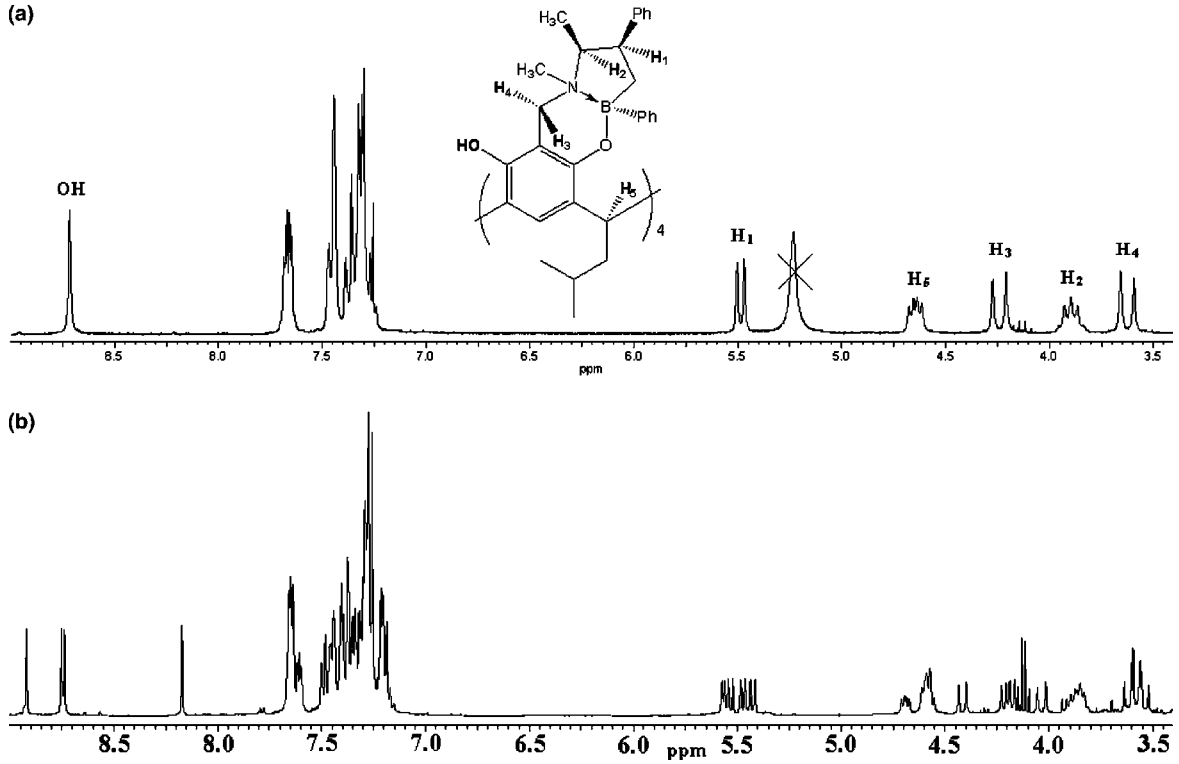


Figure 3. A comparison of the selected ^{1}H NMR spectra of (a) the crown conformer, and (b) the diamond conformer of **3** in $CDCl_3$.

General procedure for preparation of compound 3

The reaction was conducted without isolation of the aminomethylene derivative of resorcarene (**2**), using 4 equiv of formaldehyde and 4 equiv of the (1*S*,2*R*)-ephedrine. The reaction was carried out in methanol. The solvent was evaporated after 24 h. Toluene and 5 equiv of $PhB(OH)_2$ were added to the residue, followed by azeotropic removal of water for 4 h. After stripping of the solvent, the residue was taken up in acetone, and a crystalline solid precipitated, yield 60%. Thin-layer chromatography using ethyl acetate : *n*-hexane indicated a mixture of two reaction products. The conformers mixture of enantiomers was chromatographed on silica gel, with ethylacetate : *n*-hexane.

Spectroscopic data: **3** *(crown)*
Yield 40%, mp > 300 °C; $[\alpha]^{25}_D$ +54.0 ($c = 1.1$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.82 (d, $J = 6.72$ Hz, 12H), 0.90 (d, $J = 6.41$ Hz, 12H), 1.02 (d, $J = 6.72$ Hz, 12H), 1.62 (m, 6H), 1.91 (m, 4H), 2.12 (s, 12H), 2.49 (m, 4H), 3.62 (d, $J = 16.18$ Hz, 4H), 3.89 (m, 4H), 4.23 (d, $J = 16.18$ Hz, 4H), 4.64 (m, 4H), 5.48 (d, $J = 8.85$ Hz, 4H), 7.22–7.40 (m, 24H), 7.41–7.49 (m, 12H), 7.61–7.69 (m, 8H), 7.58 (m, 12H), 8.71 (s, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 10.34, 22.31, 23.67, 26.23, 31.01, 41.40, 43.12, 51.46, 53.39, 60.32, 103.10, 123.77, 124.46, 126.63, 127.47, 127.81, 128.22, 132.71, 140.82, 149.54, 149.9 FAB-MS (NBA) *m*/*z*: 1997.7948 (calcd. 1997.7441).

3 *(Diamond)*
Yield 20%, mp > 300 °C; $[\alpha]^{25}_D$ +57.2 ($c = 1.02$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.55 (d, $J = 7.18$ Hz, 3H), 0.79 (d, $J = 7.18$ Hz, 3H), 0.80–0.90 (m, 32H), 0.99 (d, $J = 3.14$ Hz, 6H), 1.01 (d, $J = 3.14$ Hz, 6H), 1.08 (d, $J = 6.73$ Hz, 6H), 1.11 (d, $J = 6.73$ Hz, 6H), 1.23–1.28 (m, 10H), 1.59 (m, 6H), 1.85 (m, 3H), 1.94–2.03 (m, 8H), 2.04 (s, 3H), 2.06–2.13 (m, 12H), 2.16 (s, 15H), 3.37 (t, $J = 3.17$ Hz, 5H), 3.50–3.64 (m, 5H), 3.80–3.95 (m, 3H), 4.03 (d, $J = 15.71$ Hz, 1H), 4.11 (dd, $J = 6.74$, 1H), 4.17 (d, $J = 8.97$ Hz, 1H), 4.21 (d, $J = 8.97$, 1H), 4.41 (d, $J = 15.71$ Hz, 1H), 4.53–4.63 (m, 3H), 4.68 (dd, $J = 5.83$ Hz, 1H), 7.15–7.50 (m, 60H), 7.57–7.67 (m, 12H), 8.16 (s, 1H), 8.73 (s, 1H), 8.75 (s, 1H), 8.92 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 5.34, 5.40, 5.52, 12.76, 17.29, 17.353, 17.67, 17.82, 18.11, 18.17, 18.76, 21.26, 21.33, 21.36, 21.528, 24.68, 24.77, 25.77, 25.92, 26.04, 26.178, 26.33, 29.57, 29.66, 30.07, 30.81, 30.93, 30.98, 31.07, 31.22, 31.54, 31.89, 41.43, 41.46, 42.70, 42.99, 43.02, 43.06, 43.17, 43.20, 49.45, 50.95, 50.98, 51.18, 51.21, 51.30, 51.51, 51.57, 59.99, 60.08, 60.32, 60.58, 70.83, 102.82, 103.32, 103.44, 109.06, 123.04, 124.30, 124.75, 124.96, 125.45, 126.21, 126.60, 126.74, 127.07, 127.40, 127.97, 128.19, 132.62, 132.73, 133.15, 139.78, 140.84, 140.93, 148.66, 149.24, 149.35, 149.38, 149.50, 149.56, 149.86, 150.42. FAB-MS (NBA) *m*/*z*: 1997.8543 (calcd. 1997.7441).

X-ray crystal structure analysis of **3** *(crown)*

Formula $C_{112}H_{128}B_4N_4O_{12} * 4C_3H_6O$, $M = 1997.74$, light yellow crystal $0.45 \times 0.25 \times 0.15$ mm, $a = 15.773(1)$, $b = 27.349(1)$, $c = 32.273(1)$ Å, $V = 13921.8(11)$ Å^3, $\rho_{calcd} = 0.953$ g cm^{-3}, $\mu = 0.62$ cm^{-1}, empirical absorption correction via SORTAV ($0.973 \le T \le 0.991$), $Z = 4$, orthorhombic, space group $P2_12_12_1$ (No. 19), $\lambda = 0.71073$ Å, $T = 198$ K, ω and φ scans, 59340 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.50$ Å^{-1}, 13815 independent ($R_{int} = 0.146$) and 9550 observed reflections [$I \ge 2\sigma(I)$], 1007 refined parameters, $R = 0.174$, $wR^2 = 0.375$, Flack parameter 1(3), hydrogens calculated and refined as riding atoms.

Structure analysis was done as confirmation of the chemical composition. The result suffers from the weakly diffracting crystals. The molecule is heavily disordered, one of the subunits (B1C—C31C) can only be refined with one relative ordered subunit (B1A—C31A) as a model (SAME command) and with isotropic thermal parameters. The phenyl groups were refined as rigid groups, in addition the group C26D—C31D also only with isotropic thermal parameters.

The solvent molecules are refined with geometrical restrains (FLAT), two of the four are only with isotropic thermal parameters and using the best as a model (SAME command).

The highest remaining electron density is located in the region of the worse subunit C, trials to refine some positional disorder including this electron density did not improve the model.

Data sets were collected with a Nonius KappaCCD diffractometer, equipped with a rotating anode generator Nonius FR591. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN [7], absorption correction SORTAV [8], structure solution SHELXS-97 [9], structure refinement SHELXL-97 (G.M. Sheldrick, Universität Göttingen, 1997). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 183690. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, CambridgeCB2 1EZ, UK [fax: int. code +44(1223)336-033, e-mail: deposit@ccdc.cam.ac.uk].

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