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Synthesis of Chiral Resorcinarene-based Hosts and a Mass Spectrometric Study of Their Chemistry in Solution and the Gas Phase

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Abstract

The syntheses and characterization of new chiral tetrabenzoxazine and tetrakis-(dialkylaminomethyl) resorcinarenes can be achieved through the reaction of resorcinarene with chiral amines and formaldehyde. In order to examine their host–guest chemistry, chiral quaternary ammonium guests were synthesized by methylation of different amines and amino acid methyl esters through a reductive methylation followed by addition of methyl iodide. Subsequent anion exchange of the iodide against tetraphenylborate helps to improve solubility of the salts in organic solvents. After characterization in solution, mass spectrometry is used to examine the resorcinarenes' chemistry in the gas phase. Interesting implications of the fragmentation behavior for their solution phase chemistry arise, for which a first example is presented. Ammonium ion binding is indicated by mass spectrometry. Nevertheless, chiral recognition between the chiral hosts and pseudoracemic 1:1 mixtures of appropriately deuterium-labeled chiral guest cations is however not observed.

Introduction

Resorcinarenes (Scheme 1, center) are readily available in relatively high yields in the form of *rccc* (all *cis*) isomers by acid-catalyzed cyclocondensation of resorcinol with various aliphatic and aromatic aldehydes [1, 2]. Their conformation is governed by their ability to create a seam of hydrogen bonds along the upper rim. Since the seam has a directionality, the resorcinarene is in principle chiral. However, the formation of hydrogen bonds is rapidly reversible and thus, without any further chiral information, both enantiomers always exist in an equilibrating racemic mixture.

Resorcinarenes have a potential for further functionalization, which makes them excellent building blocks for supramolecular chemistry. They complex various guests and have the ability to interact via π–π interactions and the hydrogen bond-forming phenolic oxygen. This property makes them a very interesting subject for supramolecular research which is a new and rapidly growing field in chemistry concerned with the assembly of molecules into non-covalent arrays. One of the aims of supramolecular chemistry is to mimic biological recognition processes with synthetic molecules, i.e., host–guest (receptor–substrate) chemistry [3, 4]. The potential of resorcinarenes as platforms for multifunctional compounds make them important tools in the synthesis of cavitands [5], dimeric [6] and hexameric [7] capsules, and nanotubes [8].

The aromatic ring of resorcinarenes is highly activated for electrophilic substitutions by the presence of the hydroxyl groups. Fourfold aminomethylation of the resorcinarene core is possible, when secondary amines are reacted with formaldehyde in the presence of the resorcinarene (Scheme 1) in a Mannich-type reaction. When primary amines are used, the intermediate secondary amine reacts intramolecularly with one of the phenolic hydroxyl groups and a second equivalent of formaldehyde, forming tetrabenzoxazines [9–11]. Chirality can be introduced into the benzoxazine resorcinarenes by using chiral amines as starting compounds.

The enantioselective synthesis of α-chiral amines is of prime importance because these chiral synthons are among the most important and commonly found subunits in chiral drugs [12]. These compounds are also useful building blocks for the synthesis of new ligands and natural products. Resorcinarenes bind alkyl ammonium cations in their cavities [13] in solution and in the gas phase and often co-crystallize with them forming capsular structures in the solid state [14]. In alkaline solutions the effect is even further enhanced due to the protonation of the resorcinarene host and the

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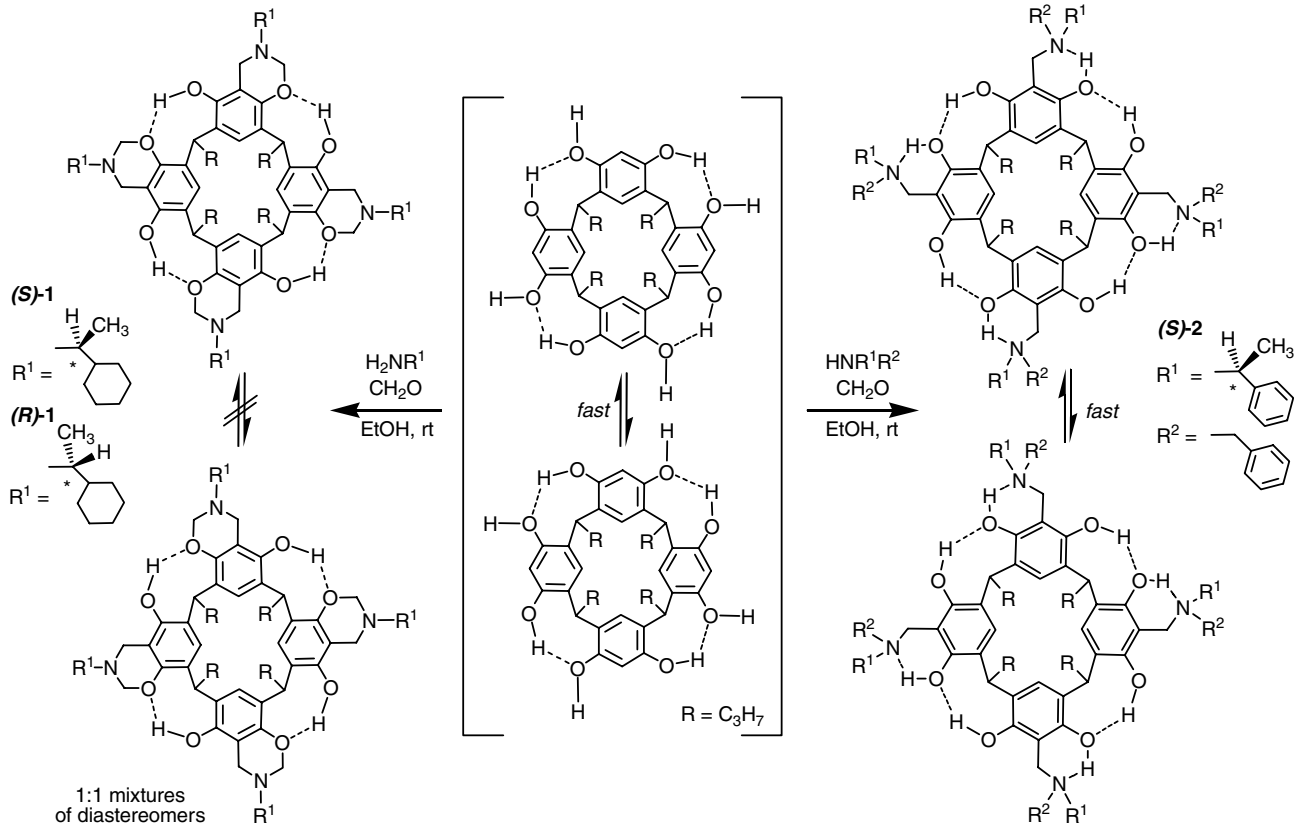


Scheme 1. Synthesis of chiral resorcinarene tetrabenzoxazines **(*R*)-1** and **(*S*)-1** and tetrakis-aminomethylated resorcinarene **(*S*)-2**.

resulting electrostatic interactions between the host anion and guest cation [15].

The investigation of supramolecular, i.e. weakly bound, non-covalent complexes in the gas phase by mass spectrometric means [16] is a rather young research area, which profited much from the development of soft ionization methods in the 1980s, in particular electrospray ionization. A variety of inclusion complexes with crown ethers as chiral hosts have been studied in the gas phase and the effects of the guest configuration have been investigated [17, 18]. Electrospray ionization mass spectrometry (ESI-MS) has also been extensively used to study capsular host–guest complexes of calixarene and resorcinarene dimers [19]. Earlier investigations using the ESI method have shown that resorcinarenes exhibit considerable selectivity when forming complexes with metal ions. An investigation of model systems, consisting of a chiral resorcinarene serving as host and chiral quaternary ammonium salts serving as guests, by mass spectrometry can give information about non-covalent interactions between these components.

In this contribution, we report the synthesis, and characterization of the chiral resorcinarenes **1** and **2** (Scheme 1). Their gas-phase chemistry is examined by ionizing them either as protonated species or as complexes with quaternary ammonium ions, mass selection of the ion of interest and collision-induced decomposition (CID). The complexation ability with ammonium ions extends to chiral ammonium ions. Utilizing Sawada's enantiomer-labeled guest method [20], it should be possible to analyze the hosts capability to bind chiral guests with selectivity [21].

Experimental

General remarks

^{1}H- and ^{13}C-NMR spectra were recorded on Bruker Avance DRX 500 (500 MHz for ^{1}H and, 126 MHz for ^{13}C), DRX 400 (400 MHz for ^{1}H and, 100.8 MHz for ^{13}C), and DRX 300 (300 MHz for 1H and 75.6 MHz for 13C) spectrometers. ^{1}H- and ^{13}C-NMR assignments were mainly based on HMQC, HMBC and 1H, 1H COSY 2D correlation spectra. All signals are expressed as δ values in ppm using the residual solvent signal as an internal standard and coupling constants are given in Hz. Melting points were determined with a Mettler Toledo FP62 capillary melting point apparatus and are uncorrected. Routine mass spectra were carried out with a Micromass LCT ESI-TOF mass spectrometer and elemental analyses were carried out with a Varian ELIII elemental analyzer.

Tetrabenzoxazine **(*R*)-1**

To a solution of resorcinarene (0.5 g, 0.8 mmol) and excess formaldehyde (3 mL) in ethanol (8 mL), R-(−)-1-cyclohexylethylamine (0.9 mL, 6.1 mmol) was added slowly and stirred at rt for 24 h. The precipitate formed was filtered off and washed with ethanol (30 mL) and

dried in vacuum to afford **(*R*)-1** as a mixture of two diastereomers. The ^{1}H-NMR shows two strongly superimposed sets of signals, one for each of the two diastereomers. Yield: 0.67 g (70%); mp: >300 °C. ^{1}H-NMR (500 MHz, $CDCl_3$, 30 °C) δ = 0.98 (44H, m, C_6H_{12}), 1.09–1.47 (32H, m, CH_2CH_3, $^*CHCH_3$), 1.67 (8H, broad, CH_2CH_2), 2.19 (8H, *q* overlapping, $CHCH_2$), 2.62 (4H, quintet overlapping, *J* 6.5, $^*CH$), 3.88 (8H, two pairs of *d* overlapping, *J* 12.6, NCH_2Ar), 4.21 (4H, two *t* overlapping, *J* 7.5, CH), 4.96 (8H, two pairs of *d* overlapping, *J* 9.8, NCH_2O), 7.09 (4H, two *s*, Ar-H), 7.78 (4H, two *s*, Ar-OH) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$, 30 °C) δ = 13.92, 14.39, 14.58, 21.11, 26.56, 26.66, 28.59, 28.64, 30.78, 30.93, 32.45, 35.86, 41.55, 41.89, 43.54, 43.67, 61.17, 61.35, 82.38, 82.67, 110.32, 110.41, 120.95, 121.02, 123.76, 123.83, 124.12, 124.14, 149.01, 149.13, 149.15, 149.24 ppm. $C_{80}H_{116}N_4O_8 \cdot H_2O$ (1279.86): calcd. C 75.08, H 9.29, N 4.38; found C 74.98, H 9.32, N 4.17. ESI-MS: 1335.32 $[M + TMA]^+$, 1262.46 $[M + H]^+$.

Tetrabenzoxazine **(*S*)-1**

To a solution of resorcinarene (0.5 g, 0.8 mmol) and excess formaldehyde (3 mL) in ethanol (8 mL), S-(+)-1-cyclohexylethylamine (0.9 mL, 6.1 mmol) was added slowly and stirred at rt for 24 h. The precipitate formed was filtered off and washed with ethanol (30 mL) and dried in vacuum to afford **(*S*)-1** as a mixture of two diastereomers as detailed above. Yield: 0.57 g (60%); mp: > 300 °C. Analytical data is identical with that of **(*R*)-1**.

Tetrakis-aminomethylated resorcinarene **(*S*)-2**

To a solution of resorcinarene (0.5 g, 0.8 mmol) and excess formaldehyde (3 mL) in ethanol (8 mL), S-(+)-*N*-benzyl-1-methylbenzylamine (1.3 mL, 3.0 mmol) was added slowly and stirred at rt for 24 h. The precipitate formed was filtered off and washed with ethanol (30 mL) and dried in vacuum to afford **(*S*)-2**. Yield: 1.10 g (93%); mp: 142.6 °C. ^{1}H-NMR (500 MHz, $CDCl_3$, 30 °C) δ = 0.89 (12H, t, *J* 7.3, CH_3), 1.18 (8H, m, *J* 7.2, CH_2), 1.42 (12H, d, *J* 6.9, CH_3), 2.18 (8H, m, *J* 6.4, CH_2), 3.14 (4H, d, *J* 12.8, NCH_2Ph), 3.41 (4H, d, *J* 13.5, NCH_2Ph), 3.52 (4H, d, *J* 14.6, NCH_2Ar), 3.86 (4H, q, *J* 6.8, *CH), 3.91 (4H, d, *J* 14.5, NCH_2Ar) 4.11 (4H, t, *J* 7.9, CH), 7.06 (12H, overlap, *Ar*-H, *Ar*-OH), 7.26 (16H, overlap, Ph-H), 7.34 (24H, overlap, Ph-H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$, 30 °C) δ = 13.45, 14.24, 20.42, 32.33, 34.32, 46.19, 54.06, 56.83, 107.28, 122.68, 123.21, 123.31, 126.92, 127.28, 127.96, 128.27, 128.75, 136.54, 138.68, 150.31 ppm. $C_{104}H_{116}N_4O_8$ (1550.11): calcd. C 80.59, H 7.54, N 3.61; found C 81.09, H 7.67, N 3.76. MS: 1624.05 $[M + TMA]^+$, 1550.98 [M + H].

General procedure for the synthesis of the tetra ammonium salts

A solution of the amine (2 mmol), formaldehyde (16 mmol) and palladium on activated charcoal (1 g) in ethanol (25 mL) was shaken for 4 h in a Parr hydrogenator. After filtration, the mixture was concentrated by rotary evaporation and made basic with 2N sodium hydroxide solution and extracted with chloroform (2×40 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Evaporation yielded the permethylated amines (**5**, **6**). A solution of either methyl iodide (6 mmol) or deuterated methyl iodide (6 mmol) and the permethylated amine (2 mmol) in nitromethane (20 mL) was heated at 45 °C for 4 h under argon atmosphere. The excess methyl iodide or deuterated methyl iodide was distilled off and neutralized in 10% NH_4OH solution. The nitromethane was then evaporated to a small volume and ether (90 mL) was added and the iodide salt that precipitated was filtered off and dried to give the iodide salts (**(*R*)-5**, **(*R*)-[D$_3$]-5**, **(*S*)-5**, and **(*S*)-[D$_3$]-5**). A solution of sodium tetraphenylborate (2 mol) in water (30 mL) was added to a stirred solution of the iodide salt (1 mol) in water (25 mL). The precipitate was filtered off and dried in vacuum to give the tetraphenyl borate ammonium salts (**(*R*)-6**, **(*R*)-[D$_3$]-6**, **(*S*)-6** and **(*S*)-[D$_3$]-6**).

(R)-Trimethyl(α-methylphenethyl) ammonium tetraphenylborate **(*R*)-6a**

Yield: 94%; mp: 224.8 °C. ^{1}H-NMR (300 MHz, 30 °C, [D$_6$]-DMSO) δ = 1.69 (3H, d, *J* 6.97, CH_3), 2.92 (9H, s, CH_3), 4.74 (1H, q, *J* 6.97, CH), 6.81 (4H, t, *J* 7.15, Ph-H), 6.95 (8H, t, *J* 7.35, Ph-H), 7.22 (8H, br, Ph-H), 7.48 (3H, m, Ph-H), 7.58 (2H, m, Ph-H) ppm. ^{13}C-NMR (75.6 MHz, 30 °C, [D$_6$]-DMSO) δ = 14.98, 50.91, 73.09, 121.96, 125.76 (^3J (C-^{11}B) 10.8), 129.30, 130.62, 130.87, 133.84, 136.01 (^2J (C-^{11}B) 4.8), 164.16 (^1J (C-^{11}B) 196.2) ppm. $C_{11}H_{18}N \cdot C_{24}H_{20}B \cdot 1.4H_2O$ (508.73): calcd. C 82.63, H 8.08, N 2.75; found C 82.66, H 7.57, N 2.42. MS (FT-ICR): 164.144 $[C_{11}H_{18}N]^+$, 647.460 $[(C_{11}H_{18}N)_2BPh_4]^+$.

(R)-Dimethyldeuteriummethyl(α-methylphenethyl) ammonium tetraphenylborate **(*R*)-[D$_3$]-6a**

Yield: 77%; mp: 223.7 °C. ^{1}H-NMR (300 MHz, 30 °C, [D$_6$]-DMSO) δ = 1.70 (3H, d, *J* 6.97, CH_3), 2.93 (6H, s, CH_3), 4.74 (1H, q, *J* 6.97, CH), 6.80 (4H, t, *J* 7.16, Ph-H), 6.94 (8H, t, *J* 7.16, Ph-H), 7.21 (8H, br, Ph-H), 7.48(3H, m, Ph-H), 7.56 (2H, m, Ph-H) ppm. ^{13}C NMR (75.6 MHz, 30 °C, [D$_6$]-DMSO) δ = 14.95, 50.81, 73.09, 121.95, 125.74 (^3J (C-^{11}B) 10.8), 129.29, 130.61, 130.87, 133.86, 136.00 (^2J (C-^{11}B) 4.8), 164.15 (^1J (C-^{11}B) 196.2) ppm. $C_{11}H_{15}D_3N \cdot C_{24}H_{20}B \cdot H_2O$ (504.55): calcd. C 83.32, H 7.39, N 2.78; found C 82.92, H 7.55, N 2.47. MS (FT-ICR):167.163 $[C_{11}H_{15}D_3N]^+$, 653.498 $[(C_{11}H_{15}D_3N)_2BPh_4]^+$.

(S)-Trimethyl(α-methylphenethyl) ammonium tetraphenylborate **(*S*)-6a**

Yield: 88%; mp: 225.2 °C. ^{1}H-NMR (300 MHz, 30 °C, [D$_6$]-DMSO) δ = 1.70 (3H, d, *J* 6.97, CH_3), 2.92 (9H, s, CH_3), 4.73 (1H, q, *J* 6.97, CH), 6.81 (4H, t, *J* 7.16, Ph-H), 6.95 (8H, t, *J* 7.35, Ph-H), 7.22 (8H, br, Ph-H), 7.48(3H, m, Ph-H), 7.56 (2H, m, Ph-H) ppm. ^{13}C-NMR

(75.6 MHz, 30 °C, [D_6]-DMSO) δ = 14.97, 50.91, 73.10, 121.96, 125.75 (^3J (C-^{11}B) 10.8), 129.30, 130.62, 130.87, 133.85, 135.99 (^2J (C-^{11}B) 4.8), 164.16 (^1J (C-^{11}B) 196.2) ppm. $C_{11}H_{18}N{\cdot}C_{24}H_{20}B$ (483.51): calcd. C 86.95, H 7.92, N 2.90; found C 86.06, H 7.84, N 2.72.MS (FT-ICR): 164.144 $[C_{11}H_{18}N]^+$, 647.474 $[(C_{11}H_{18}N)_2BPh_4]^+$.

(S)-Dimethyldeuteriummethyl(α-methylphenethyl) ammonium tetraphenylborate **(*S*)-[D_3]-6a**
Yield: 87%; mp: 226.3 °C. ^{1}H-NMR (300 MHz, 30 °C, [D_6]-DMSO) δ = 1.70 (3H, d, *J* 6.78, CH_3), 2.93 (6H, s, CH_3), 4.74 (1H, q, *J* 6.97, CH), 6.79 (4H, t, *J* 7.16, Ph-H), 6.93 (8H, t, *J* 7.34, Ph-H), 7.20 (8H, br, Ph-H), 7.49 (3H, m, Ph-H), 7.57 (2H, m, Ph-H) ppm. ^{13}C-NMR (75.6 MHz, 30 °C, [D_6]-DMSO) δ = 14.95, 50.79, 72.89, 121.94, 125.73 (^3J (C-^{11}B) 10.8), 129.29, 130.61, 130.87, 133.87, 135.99 (^2J (C-^{11}B) 4.8), 164.16 (^3J (C-^{11}B) 196.2) ppm. $C_{11}H_{15}D_3N{\cdot}C_{24}H_{20}B{\cdot}C_3H_6O{\cdot}2H_2O$ (522.57): calcd. C 80.45, H 7.52, N 2.68; found C 80.81, H 7.32, N 2.27. MS (FT-ICR): 167.163 $[C_{11}H_{15}D_3N]^+$, 653.512 $[(C_{11}H_{15}D_3N)_2BPh_4]^+$.

(R)-Trimethyl[(α-hydroxymethyl)phenethyl] ammonium tetraphenylborate **(*R*)-6b**
Yield: 78%; mp: 181.3 °C. ^{1}H-NMR (300 MHz, 30 °C, [D_6]-DMSO) δ = 2.95 (1H, t, *J* 11.30, CH_2Ph), 3.18 (9H, s, CH_3), 3.32 (1H, s, CH_2Ph), 3.54 (2H, t, *J* 11.49, CH_2OH), 3.85 (1H, d, *J* 12.44, OH), 5.45 (1H, t, *J* 4.52, CH), 6.80 (4H, t, *J* 7.16, Ph-H), 6.94 (8H, t, *J* 7.54, Ph-H), 7.20 (8H, br, Ph-H), 7.35 (5H, m, Ph-H) ppm. ^{13}C-NMR (75.6 MHz, 30 °C, [D_6]-DMSO) δ = 30.77, 52.40, 56.88, 75.75, 121.94, 125.74 (^3J (C-^{11}B) 10.8), 127.40, 129.10, 129.78, 135.99 (^2J (C-^{11}B) 4.8), 137.27, 164.15 (^1J (C-^{11}B) 196.2) ppm. $C_{12}H_{20}NO{\cdot}C_{24}H_{20}B{\cdot}1.5H_2O$ (540.57): calcd. C 79.99, H 8.02, N 2.59; found C 80.03, H 7.74, N 2.60. MS (FT-ICR): 194.154 $[C_{12}H_{20}NO]^+$.

(R)-Dimethyldeuteriummethyl[(α-hydroxymethyl) phenethyl] ammonium tetraphenylborate **(*R*)-[D_3]-6b**
Yield: 80%; mp: 190.2 °C. ^{1}H-NMR (400 MHz, 30 °C, [D_6]-DMSO) δ = 2.95 (1H, t, *J* 11.37, CH_2Ph), 3.18 (9H, s, CH_3), 3.30 (1H, d, *J* 13.13, CH_2Ph), 3.56 (2H, m, CH_2OH), 3.82 (1H, d, *J* 14.02, OH), 5.45 (1H, t, *J* 4.55, CH), 6.80 (4H, t, *J* 7.20, Ph-H), 6.94 (8H, t, *J* 7.46 Hz, Ph-H), 7.21 (8H, br, Ph-H), 7.35 (5H, m, Ph-H) ppm. ^{13}C-NMR (100.8 MHz, 30 °C, [D_6]-DMSO) δ = 30.76, 52.29, 56.87, 75.66, 121.96, 125.75 (^3J (C-^{11}B) 8.4), 127.41, 129.11, 129.79, 136.00 (^2J (C-^{11}B) 4.2), 137.27, 164.08 (^1J (C-^{11}B) 147.3) ppm. $C_{12}H_{17}D_3NO{\cdot}C_{24}H_{20}B{\cdot}H_2O$ (534.44): calcd. C 80.89, H 7.35, N 2.62; found C 81.01, H 7.56, N 2.51. MS (FT-ICR): 197.173 $[C_{12}H_{17}D_3NO]^+$.

(S)-Trimethyl[(α-hydroxymethyl)phenethyl] ammonium tetraphenylborate **(*S*)-6b**
Yield: 90%; mp: 175.7 °C. ^{1}H-NMR (300 MHz, 30 °C, [D_6]-DMSO) δ = 2.95 (2H, t, *J* 11.30, CH_2Ph), 3.19 (9H, s, CH_3), 3.27 (1H, s, CH_2Ph), 3.54 (2H, m, CH_2OH), 3.81 (1H, d, *J* 14.13, OH), 5.45 (1H, t, *J* 4.33, CH), 6.80 (4H, t, *J* 7.16, Ph-H), 6.94 (8H, t, *J* 7.54, Ph-H), 7.20 (8H, br, Ph-H), 7.35 (5H, m, Ph-H) ppm. ^{13}C-NMR (75.6 MHz, 30 °C, [D_6]-DMSO) δ = 30.77, 52.40, 56.88, 75.75, 121.94, 125.74 (^3J (C-^{11}B) 10.8), 127.40, 129.09, 129.78, 135.99 (^2J (C-^{11}B) 4.8), 137.26, 164.15 (^1J (C-^{11}B) 196.2) ppm. $C_{12}H_{20}NO{\cdot}C_{24}H_{20}B{\cdot}2H_2O$ (549.58): calcd. C 78.68, H 8.07, N 2.55; found C 78.32, H 7.32, N 2.50. MS (FT-ICR): 194.155 $[C_{12}H_{20}NO]^+$.

(S)-Dimethyldeuteriummethyl[(α-hydroxymethyl) phenethyl] ammonium tetraphenylborate **(*S*)-[D_3]-6b**
Yield: 90%; mp: 186.5 °C. ^{1}H-NMR (400 MHz, 30 °C, [D_6]-DMSO) δ = 2.95 (1H, t, *J* 11.37, CH_2Ph), 3.18 (9H, s, CH_3), 3.27 (1H, d, *J* 13.14, CH_2Ph), 3.52 (2H, m, CH_2OH), 3.85 (1H, d, *J* 13.51, OH), 5.46 (1H, br, CH), 6.81 (4H, t, *J* 7.20, Ph-H), 6.95 (8H, t, *J* 7.33, Ph-H), 7.21 (8H, br, Ph-H), 7.34 (5H, m, Ph-H) ppm. ^{13}C-NMR (100.8 MHz, 30 °C, [D_6]-DMSO) δ = 30.77, 52.29, 56.87, 75.66, 121.97, 125.76 (^3J (C-^{11}B) 8.4), 127.41, 129.10, 129.80, 135.98 (^2J (C-^{11}B) 4.2), 137.26, 164.08 (^1J (C-^{11}B) 147.3) ppm. $C_{12}H_{17}D_3NO{\cdot}C_{24}H_{20}B{\cdot}2.5H_2O$ (561.61): calcd. C 77.00, H 7.54, N 2.49; found C 76.52, H 6.93, N 2.33. MS (FT-ICR): 197.174 $[C_{12}H_{17}D_3NO]^+$, 713.536 $[(C_{12}H_{17}D_3NO)_2BPh_4]^+$.

(R)-Trimethyl[(α-hydroxymethyl)-3-methylisobutyl] ammonium tetraphenylborate **(*R*)-6c**
Yield: 86%; mp: 199.2 °C. ^{1}H-NMR (400 MHz, 30 °C, [D_6]-DMSO) δ = 0.94 (3H, d, *J* 6.32, CH_3), 0.99 (3H, d, *J* 6.44, CH_3), 1.51 (1H, m, CH), 1.64 (2H, m, CH_2CH), 3.03 (9H, s, CH_3), 3.25 (1H, br, CH_2OH), 3.72 (1H, br, CH_2OH), 3.87 (1H, br, OH), 5.41 (1H, t, *J* 4.55, CH), 6.82 (4H, t, *J* 7.08, Ph-H), 6.96 (8H, t, *J* 7.46, Ph-H), 7.22 (8H, br, Ph-H) ppm. ^{13}C-NMR (100.8 MHz, 30 °C, [D_6]-DMSO) δ = 21.29, 24.00, 25.74, 33.30, 51.87, 58.18, 73.42, 121.97, 125.76 (^3J (C-^{11}B) 8.4), 136.00 (^2J (C-^{11}B) 4.2), 164.09 (^1J (C-^{11}B) 147.3) ppm. $C_9H_{22}NO{\cdot}C_{24}H_{20}B{\cdot}H_2O$ (497.54): calcd. C 79.67, H 8.91, N 2.82; found C 79.30, H 8.60, N 3.05. MS (FT-ICR): 160.170 $[C_9H_{22}NO]^+$, 639.514 $[(C_9H_{22}NO)_2BPh_4]^+$.

(R)-Dimethyldeuteriummethyl[(α-hydroxymethyl)-3-methylisobutyl] ammonium tetraphenylborate **(*R*)-[D_3]-6c**
Yield: 89%; mp: 214.3 °C. ^{1}H-NMR (400 MHz, 30 °C, [D_6]-DMSO) δ = 0.93 (3H, d, *J* 6.44, CH_3), 0.98 (3H, d, *J* 6.32, CH_3), 1.51 (1H, m, CH), 1.66 (2H, m, CH_2CH), 3.03 (9H, s, CH_3), 3.25 (1H, br, CH_2OH), 3.69 (1H, br, CH_2OH), 3.87 (1H, br, OH), 5.39 (1H, t, *J* 5.06, CH), 6.81 (4H, t, *J* 7.20, Ph-H), 6.95 (8H, t, *J* 7.45, Ph-H), 7.21 (8H, br, Ph-H) ppm. ^{13}C-NMR (100.8 MHz, 30 °C, [D_6]-DMSO) δ = 21.29, 24.00, 25.72, 33.27, 51.76, 58.17, 73.32, 121.95, 125.74 (^3J (C-^{11}B) 8.4), 136.00 (^2J (C-^{11}B) 4.2), 164.08 (^1J (C-^{11}B) 147.3) ppm. $C_9H_{19}NOD_3{\cdot}C_{24}H_{20}B{\cdot}H_2O$ (500.56): calcd. C 79.19, H 8.26, N 2.80; found C 79.28, H 8.58, N 3.05. MS (FT-ICR): 163.189 $[C_9H_{19}D_3NO]^+$, 645.552 $[(C_9H_{19}D_3NO)_2BPh_4]^+$.

(S)-Trimethyl[(α-hydroxymethyl)-3-methylisobutyl] ammonium tetraphenylborate **(*S*)-6c**
Yield: 73%; mp: 196.9 °C. ^{1}H-NMR (300 MHz, 30 °C, [D$_6$]-DMSO) δ = 0.93 (3H, d, *J* 6.21, CH_3), 0.98 (3H, d, *J* 6.22, CH_3), 1.55 (1H, m, CH), 1.66 (2H, m, CH_2CH), 3.04 (9H, s, CH_3), 3.28 (1H, br, CH_2OH), 3.71 (1H, br, CH_2OH), 3.86 (1H, br, OH), 5.39 (1H, t, *J* 4.89, CH), 6.80 (4H, t, *J* 6.97, Ph-H), 6.94 (8H, t, *J* 7.53, Ph-H), 7.20 (8H, br, Ph-H) ppm. ^{13}C-NMR (75.6 MHz, 30 °C, [D$_6$]-DMSO) δ = 21.28, 23.99, 25.72, 33.29, 51.86, 58.17, 73.32, 121.94, 125.73 (^{3}J (C-^{11}B) 10.8), 135.99 (^{2}J (C-^{11}B) 4.8), 164.145 (^{1}J (C-^{11}B) 196.2) ppm. $C_9H_{22}NO{\cdot}C_{24}H_{20}B{\cdot}1.5H_2O$ (506.55): calcd. C 78.25, H 8.95, N 2.77; found C 78.67, H 8.28, N 2.51. MS (FT-ICR): 160.171 $[C_9H_{22}NO]^+$, 639.527 $[(C_9H_{22}NO)_2BPh_4]^+$.

(S)-Dimethyldeuteriummethyl[(α-hydroxymethyl)-3-methylisobutyl] ammonium tetraphenylborate **(*S*)-[D$_3$]-6c**
Yield: 92%; mp: 202.7 °C. ^{1}H-NMR (400 MHz, 30 °C, [D$_6$]-DMSO) δ = 0.93 (3H, d, *J* 6.31, CH_3), 0.98 (3H, d, *J* 6.31, CH_3), 1.54 (1H, m, CH), 1.69 (2H, m, CH_2CH), 3.03 (9H, s, CH_3), 3.27 (1H, br, CH_2OH), 3.69 (1H, br, CH_2OH), 3.87 (1H, br, OH), 5.39 (1H, t, *J* 4.80, CH), 6.81 (4H, t, *J* 7.07, Ph-H), 6.94 (8H, t, *J* 7.33, Ph-H), 7.21 (8H, br, Ph-H) ppm. ^{13}C-NMR (100.8 MHz, 30 °C, [D$_6$]-DMSO) δ = 21.29, 24.00, 25.72, 33.27, 51.76, 58.16, 73.31, 121.95, 125.75 (^{3}J (C-^{11}B) 8.4), 136.00 (^{2}J (C-^{11}B) 4.2), 164.08 (^{1}J (C-^{11}B) 147.3) ppm. $C_9H_{19}NOD_3{\cdot}C_{24}H_{20}B{\cdot}3H_2O$ (536.60): calcd. C 73.87, H 8.45, N 2.61; found C 74.11, H 8.25, N 2.78. MS (FT-ICR): 163.189 $[C_9H_{19}D_3NO]^+$, 645.564 $[(C_9H_{19}D_3NO)_2BPh_4]^+$.

2-Trimethylammonium-(S)-propionic acid methylester tetraphenylborate **(*S*)-6d**
Yield: 60%; mp: 190 °C. ^{1}H-NMR (400 MHz, 30 °C, [D$_6$]-acetone) δ = 7.37–7.33 (m, 8 H, *ortho*-Ph-H); 6.94 (t, ^{3}J = 7.5 Hz, 8 H, *meta*-Ph-H); 6.79 (tt, ^{3}J = 7.3 Hz, ^{4}J = 1.1 Hz, 4 H, *para*-Ph-H); 4.45 (q, ^{3}J = 7.1 Hz, 1 H, CH); 3.85 (s, 3 H, OCH_3); 3.32 (s, 9 H, $N(CH_3)_3$); 1.72 (d, ^{3}J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C-NMR (100.8 MHz, 30 °C, [D$_6$]-acetone) δ = 168.9 (CO); 165.0 (q, $^{1}J_{C\text{-}B}$ = 49.5 Hz, BC); 137.0 (q, $^{2}J_{C\text{-}B}$ = 1.4 Hz, *ortho*-Ph-C); 126.0 (q, $^{2}J_{C\text{-}B}$ = 2.8 Hz, *meta*-Ph-C); 122.3 (*para*-Ph-C); 70.9 (CH-2); 53.9 (OCH_3); 52.7 ($N(CH_3)_3$); 13.2 (CH_3-3) ppm. MS (FT-ICR): 611.44 $[(C_7H_{16}NO_2)_2BPh_4]^+$.

2-Trimethylammonium-(R)-propionic acid methylester tetraphenylborate **(*R*)-6d**
Yield: 75%; mp: 191 °C. ^{1}H-NMR (400 MHz, 30 °C, [D$_6$]-acetone) δ = 7.35–7.39 (m, 8 H, *ortho*-Ph-H); 6.96 (t, ^{3}J = 7.3 Hz, 8 H, *meta*-Ph-H); 6.82 (tt, ^{3}J = 7.1 Hz, ^{4}J = 1.4 Hz, 4 H, *para*-Ph-H); 4.33 (q, ^{3}J = 7.1 Hz, 1 H, CH); 3.82 (s, 3 H, OCH_3); 3.16 (s, 9 H, $N(CH_3)_3$); 1.64 (d, ^{3}J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C-NMR (100.8 MHz, 30 °C, [D$_6$]-acetone) δ = 169.3 (CO); 165.4 (m, $^{1}J_{C\text{-}B}$ = 49.4 Hz, BC); 137.5 (m, $^{2}J_{C\text{-}B}$ = 1.2 Hz, *ortho*-Ph-C); 126.6 (m, $^{3}J_{C\text{-}B}$ = 2.8 Hz, *meta*-Ph-C); 122.8 (*para*-Ph-C); 71.3 (CH-2); 54.4 (OCH_3); 53.0 ($N(CH_3)_3$); 13.6 (CH_3-3) ppm. MS (FT-ICR): 611.45 $[(C_7H_{16}NO_2)_2BPh_4]^+$.

2-Trimethylammonium-(S)-propionic acid methylester tetraphenylborate **(*S*)-[D$_3$]-6d**
Yield: 17%; mp: 192 °C. ^{1}H-NMR (400 MHz, 30 °C, [D$_6$]-acetone) δ = 7.39–7.33 (m, 8 H, *ortho*-Ph-H); 6.95 (t, ^{3}J = 7.2 Hz, 8 H, *meta*-Ph-H); 6.80 (tt, ^{3}J = 7.3 Hz, ^{4}J = 1.1 Hz, 4 H, *para*-Ph-H); 4.38 (q, ^{3}J = 7.2 Hz, 1 H, CH); 3.81 (s, 3 H, OCH_3); 3.24 (s, 6 H, $N(CH_3)_2CD_3$); 1.69 (d, ^{3}J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C-NMR (100.8 MHz, 30 °C, [D$_6$]-acetone) δ = 169.4 (CO); 165.5 (m, $^{1}J_{C\text{-}B}$ = 49.5 Hz, BC); 137.6 (m, $^{2}J_{C\text{-}B}$ = 1.4 Hz, *ortho*-Ph-C); 126.6 (m, $^{3}J_{C\text{-}B}$ = 2.8 Hz, *meta*-Ph-C); 122.8 (*para*-Ph-C); 71.3 (CH-2); 54.4 (OCH_3); 53.0 ($N(CH_3)_2CD_3$); 13.6 (CH_3-3) ppm. MS (FT-ICR): 617.48 $[(C_7H_{13}D_3NO_2)_2BPh_4]^+$.

2-Trimethylammonium-(R)-propionic acid methylester tetraphenylborate **(*R*)-[D$_3$]-6d**
Yield: 80%; mp: 193 °C. ^{1}H-NMR (400 MHz, 30 °C, [D$_6$]-acetone) δ = 7.40–7.35 (m, 8 H, *ortho*-Ph-H); 6.99 (t, ^{3}J = 7.3 Hz, 8 H, *meta*-Ph-H); 6.82 (tt, ^{3}J = 7.2 Hz, ^{4}J = 1.4 Hz, 4 H, *para*-Ph-H); 4.29 (q, ^{3}J = 7.2 Hz, 1 H, CH); 3.81 (s, 3 H, OCH_3); 3.13 (s, 6 H, $N(CH_3)_2CD_3$); 1.62 (d, ^{3}J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C-NMR (100.8 MHz, 30 °C, [D$_6$]-acetone) δ = 169.2 (CO); 165.4 (m, $^{1}J_{C\text{-}B}$ = 49.5 Hz, BC); 137.5 (m, $^{2}J_{C\text{-}B}$ = 1.4 Hz, *ortho*-Ph-C); 126.6 (m, $^{3}J_{C\text{-}B}$ = 2.8 Hz, *meta*-Ph-C); 122.8 (*para*-Ph-C); 71.2 (CH-2); 54.4 (OCH_3); 52.9 ($N(CH_3)_2CD_3$); 13.5 (CH_3-3) ppm. MS (FT-ICR): 617.49 $[(C_7H_{13}D_3NO_2)_2BPh_4]^+$.

3-Methyl-2-trimethylammonium-(S)-butanoic acid methylester tetraphenylborate **(*S*)-6e**
Yield: 27%; mp: 179 °C. ^{1}H-NMR (300 MHz, 30 °C, [D$_6$]-acetone) δ = 7.38–7.31 (m, 8 H, *ortho*-Ph-H); 6.93 (t, ^{3}J = 7.3 Hz, 8 H, *meta*-Ph-H); 6.78 (t, ^{3}J = 7.4 Hz, 4 H, *para*-Ph-H); 4.31 (br, 1 H, CH-2); 4.00 (d, *J* = 3.2 Hz, 3 H, OCH_3); 3.39 (s, 9 H, $N(CH_3)_3$); 2.74 (br, 1 H, CH-3); 1.27 (dd, ^{3}J = 7.0 Hz, ^{4}J = 3.0 Hz, 3 H, CH_3-4); 1.05 (dd, ^{3}J = 7.0 Hz, ^{4}J = 3.4 Hz, 3 H, CH_3-4′) ppm. ^{13}C-NMR (75.5 MHz, 30 °C, [D$_6$]-acetone) δ = 168.2 (CO); 165.5 (m, $^{1}J_{C\text{-}B}$ = 49.5 Hz, BC); 137.7 (m, $^{2}J_{C\text{-}B}$ = 1.4 Hz, *ortho*-Ph-C); 126.6 (m, $^{3}J_{C\text{-}B}$ = 2.8 Hz, *meta*-Ph-C); 122.9 (*para*-Ph-C); 80.3 (CH-2); 54.0 (OCH_3); 53.8 ($N(CH_3)_3$); 27.8 (CH-3); 23.9 (CH_3-4); 20.1 (CH_3-4′) ppm. MS (FT-ICR): 174.15 $C_9H_{20}NO_2^+$, 667.51 $[(C_9H_{20}NO_2)_2BPh_4]^+$.

3-Methyl-2-trimethylammonium-(R)-butanoic acid methylester tetraphenylborate **(*R*)-6e**
Yield: 68%; mp: 184 °C. ^{1}H-NMR (300 MHz, 30 °C, [D$_6$]-acetone) δ = 7.38–7.33 (m, 8 H, *ortho*-Ph-H); 6.94 (t, ^{3}J = 7.4 Hz, 8 H, *meta*-Ph-H); 6.79 (tt, ^{3}J = 7.4 Hz, ^{4}J = 1.4 Hz, 4 H, *para*-Ph-H); 4.25 (d, ^{3}J = 1.5 Hz, 1 H, CH-2); 3.89 (s, 3 H, OCH_3); 3.33 (s, 9 H, $N(CH_3)_3$);

2.69 (m, ^3J = 6.8 Hz 1 H, CH-3); 1.26 (d, ^3J = 7.0 Hz, 3 H, CH_3-4); 1.04 (d, ^3J = 6.8 Hz, 3 H, CH_3-4′) ppm. ^{13}C-NMR (75.5 MHz, 30 °C, [D$_6$]-acetone) δ = 167.5 (CO); 165.0 (m, $^1J_{C\text{-}B}$ = 49.1 Hz, BC); 137.0 (m, $^2J_{C\text{-}B}$ = 1.2 Hz, *ortho*-Ph-C); 126.6 (m, $^3J_{C\text{-}B}$ = 3.0 Hz, *meta*-Ph-C); 122.3 (*para*-Ph-C); 79.6 (CH-2); 53.4 (OCH_3); 53.1 ($N(CH_3)_3$); 27.2 (CH-3); 23.2 (CH_3-4); 19.5 (CH_3-4′) ppm. MS (FT-ICR): 174.15 $C_9H_{20}NO_2^+$, 667.52 $[(C_9H_{20}NO_2)_2BPh_4]^+$.

3-Methyl-2-trimethylammonium-(S)-butanoic acid methylester tetraphenylborate **(*S*)-[D$_3$]-6e**
Yield: 96%; mp: 177 °C. ^{1}H-NMR (300 MHz, 30 °C, [D$_6$]-acetone) δ = 7.38–7.32 (m, 8 H, *ortho*-Ph-H); 6.93 (t, ^3J = 7.4 Hz, 8 H, *meta*-Ph-H); 6.78 (tt, ^3J = 7.0 Hz, ^4J = 1.3 Hz, 4 H, *para*-Ph-H); 4.31 (d, ^3J = 1.5 Hz, 1 H, CH-2); 3.90 (s, 3 H, OCH_3); 3.41 (s, 6 H, $N(CH_3)_2CD_3$); 2.74 (m, ^3J = 6.4 Hz 1 H, CH-3); 1.28 (d, ^3J = 7.0 Hz, 3 H, CH_3-4); 1.06 (d, ^3J = 6.8 Hz, 3 H, CH_3-4′) ppm. ^{13}C-NMR (75.5 MHz, 30 °C, [D$_6$]-acetone) δ = 168.2 (CO); 165.6 (m, $^1J_{C\text{-}B}$ = 49.3 Hz, BC); 137.7 (m, $^2J_{C\text{-}B}$ = 1.2 Hz, *ortho*-Ph-C); 126.6 (m, $^3J_{C\text{-}B}$ = 3.0 Hz, *meta*-Ph-C); 122.9 (*para*-Ph-C); 80.6 (CH-2); 54.0 (OCH_3); 53.7 ($N(CH_3)_2CD_3$); 27.8 (CH-3); 23.9 (CH_3-4); 20.1 (CH_3-4′) ppm. MS (FT-ICR): 177.17 $C_9H_{17}D_3NO_2^+$, 673.55 $[(C_9H_{17}D_3NO_2)_2BPh_4]^+$.

3-Methyl-2-trimethylammonium-(R)-butanoic acid methylester tetraphenylborate **(*R*)-[D$_3$]-6e**
Yield: 68%; mp: 178 °C. ^{1}H-NMR (400 MHz, 30 °C, [D$_6$]-acetone) δ = 7.37–7.33 (m, 8 H, *ortho*-Ph-H); 6.94 (t, ^3J = 7.2 Hz, 8 H, *meta*-Ph-H); 6.79 (tt, ^3J = 7.1 Hz, ^4J = 1.5 Hz, 4 H, *para*-Ph-H); 4.27 (d, ^3J = 1.5 Hz, 1 H, CH-2); 3.89 (s, 3 H, OCH_3); 3.36 (s, 6 H, $N(CH_3)_2CD_3$); 2.71 (m, ^3J = 6.8 Hz 1 H, CH-3); 1.27 (d, ^3J = 7.0 Hz, 3 H, CH_3-4); 1.04 (d, ^3J = 6.8 Hz, 3 H, CH_3-4′) ppm. ^{13}C-NMR (100.6 MHz, 30 °C, [D$_6$]-acetone) δ = 168.1 (CO); 165.6 (m, $^1J_{C\text{-}B}$ = 49.3 Hz, BC); 137.6 (m, $^2J_{C\text{-}B}$ = 1.2 Hz, *ortho*-Ph-C); 126.6 (m, $^3J_{C\text{-}B}$ = 3.0 Hz, *meta*-Ph-C); 122.9 (*para*-Ph-C); 80.2 (CH-2); 54.0 (OCH_3); 53.7 ($N(CH_3)_2CD_3$); 27.8 (CH-3); 23.8 (CH_3-4); 20.1 (CH_3-4′) ppm. MS (FT-ICR): 177.17 $C_9H_{17}D_3NO_2^+$, 673.55 $[(C_9H_{17}D_3NO_2)_2BPh_4]^+$.

4-Methyl-2-trimethylammonium-(S)-pentanoic acid methylester tetraphenylborate **(*S*)-6f**
Yield: 84%; mp: 165 °C. ^{1}H-NMR (300 MHz, 30 °C, [D$_6$]-acetone) δ = 7.36–7.30 (m, 8 H, *ortho*-Ph-H); 6.92 (t, ^3J = 7.4 Hz, 8 H, *meta*-Ph-H); 6.78 (tt, ^3J = 7.2 Hz, ^4J = 1.1 Hz, 4 H, *para*-Ph-H); 4.22 (dd, ^3J = 11.9 Hz, ^4J = 3.2 Hz, 1 H, CH-2); 3.83 (s, 3 H, OCH_3); 3.14 (s, 9 H, $N(CH_3)_3$); 2.01–1.94 (m, CH-3); 1.85 (dt, ^3J = 11.6 Hz, ^2J = 3.2 Hz, 1 H, CH-3′); 1.60–1.46 (m, 1 H, CH-4); 1.08 (dd, ^3J = 6.6 Hz, ^4J = 1.7 Hz, 6 H, CH_3-5) ppm. ^{13}C-NMR (75.5 MHz, 30 °C, [D$_6$]-acetone) δ = 169.1 (CO); 165.5 (m, $^1J_{C\text{-}B}$ = 49.1 Hz, BC); 137.5 (m, $^2J_{C\text{-}B}$ = 1.2 Hz, *ortho*-Ph-C); 126.6 (m, $^3J_{C\text{-}B}$ = 3.0 Hz, *meta*-Ph-C); 122.8 (*para*-Ph-C); 74.8 (CH-2); 54.5 (OCH_3); 53.3 ($N(CH_3)_3$); 36.4 (CH-3); 26.6 (CH-4); 24.2 (CH_3-5); 21.6 (CH_3-5′) ppm. MS (FT-ICR): 188.17 $C_{10}H_{22}NO_2^+$, 695.56 $[(C_{10}H_{22}NO_2)_2BPh_4]^+$.

4-Methyl-2-trimethylammonium-(R)-pentanoic acid methylester tetraphenylborate **(*R*)-6f**
Yield: 88%; mp: 175 °C. ^{1}H-NMR (300 MHz, 30 °C, [D$_6$]-acetone) δ = 7.40–7.34 (m, 8 H, *ortho*-Ph-H); 6.96 (t, ^3J = 7.5 Hz, 8 H, *meta*-Ph-H); 6.82 (tt, ^3J = 7.4 Hz, ^4J = 1.3 Hz, 4 H, *para*-Ph-H); 4.24 (dd, ^3J = 11.9 Hz, ^4J = 3.2 Hz, 1 H, CH-2); 3.86 (s, 3 H, OCH_3); 3.15 (s, 9 H, $N(CH_3)_3$); 2.05–1.97 (m, CH-3); 1.87 (dt, ^3J = 11.4 Hz, ^2J = 3.0 Hz, 1 H, CH-3′); 1.63–1.50 (m, 1 H, CH-4); 1.00 (dd, ^3J = 6.4 Hz, ^4J = 1.5 Hz, 6 H, CH_3-5) ppm. ^{13}C-NMR (75.5 MHz, 30 °C, [D$_6$]-acetone) δ = 169.1 (CO); 165.5 (m, $^1J_{C\text{-}B}$ = 49.1 Hz, BC); 137.5 (m, $^2J_{C\text{-}B}$ = 1.2 Hz, *ortho*-Ph-C); 126.6 (m, $^3J_{C\text{-}B}$ = 3.0 Hz, *meta*-Ph-C); 122.8 (*para*-Ph-C); 74.7 (CH-2); 54.5 (OCH_3); 53.3 ($N(CH_3)_3$); 36.3 (CH-3); 26.6 (CH-4); 24.1 (CH_3-5); 21.6 (CH_3-5′) ppm. MS (FT-ICR): 188.17 $C_{10}H_{22}NO_2^+$, 695.58 $[(C_{10}H_{22}NO_2)_2BPh_4]^+$.

4-Methyl-2-trimethylammonium-(S)-pentanoic acid methylester tetraphenylborate **(*S*)-[D$_3$]-6f**
Yield: 100%; mp: 169 °C. ^{1}H-NMR (400 MHz, 30 °C, [D$_6$]-acetone) δ = 7.38–7.32 (m, 8 H, *ortho*-Ph-H); 6.95 (t, ^3J = 7.5 Hz, 8 H, *meta*-Ph-H); 6.80 (tt, ^3J = 7.5 Hz, ^4J = 1.4 Hz, 4 H, *para*-Ph-H); 4.32 (dd, ^3J = 11.9 Hz, ^4J = 3.2 Hz, 1 H, CH-2); 3.88 (s, 3 H, OCH_3); 3.26 (s, 6 H, $N(CH_3)_2CD_3$); 2.08–2.01 (m, CH-3); 1.93 (dt, ^3J = 11.4 Hz, ^2J = 3.0 Hz, 1 H, CH-3′); 1.63–1.53 (m, 1 H, CH-4); 1.00 (dd, ^3J = 6.6 Hz, ^4J = 1.7 Hz, 6 H, CH_3-5) ppm. ^{13}C-NMR (100.6 MHz, 30 °C, [D$_6$]-acetone) δ = 169.2 (CO); 165.5 (m, $^1J_{C\text{-}B}$ = 49.3 Hz, BC); 137.6 (m, $^2J_{C\text{-}B}$ = 1.2 Hz, *ortho*-Ph-C); 126.6 (m, $^3J_{C\text{-}B}$ = 2.6 Hz, *meta*-Ph-C); 122.8 (*para*-Ph-C); 74.8 (CH-2); 54.5 (OCH_3); 53.3 ($N(CH_3)_2CD_3$); 36.4 (CH-3); 26.7 (CH-4); 24.2 (CH_3-5); 21.7 (CH_3-5′) ppm. MS (FT-ICR): 191.19 $C_{10}H_{19}D_3NO_2^+$, 701.61 $[(C_{10}H_{19}D_3NO_2)_2BPh_4]^+$.

4-Methyl-2-trimethylammonium-(R)-pentanoic acid methylester tetraphenylborate **(*R*)-[D$_3$]-6f**
Yield: 89%; mp: 165 °C. ^{1}H-NMR (300 MHz, 30 °C, [D$_6$]-acetone) δ = 7.38–7.32 (m, 8 H, *ortho*-Ph-H); 6.93 (t, ^3J = 7.4 Hz, 8 H, *meta*-Ph-H); 6.78 (tt, ^3J = 7.2 Hz, ^4J = 1.2 Hz, 4 H, *para*-Ph-H); 4.37 (dd, ^3J = 11.9 Hz, ^4J = 3.4 Hz, 1 H, CH-2); 3.91 (s, 3 H, OCH_3); 3.36 (s, 6 H, $N(CH_3)_2CD_3$); 2.08–2.01 (m, CH-3); 1.93 (dt, ^3J = 11.4 Hz, ^2J = 3.0 Hz, 1 H, CH-3′); 1.66–1.53 (m, 1 H, CH-4); 1.00 (dd, ^3J = 6.6 Hz, ^4J = 3.2 Hz, 6 H, CH_3-5) ppm. ^{13}C-NMR (75.5 MHz, 30 °C, [D$_6$]-acetone) δ = 169.3 (CO); 165.5 (m, $^1J_{C\text{-}B}$ = 49.3 Hz, BC); 137.6 (m, $^2J_{C\text{-}B}$ = 1.2 Hz, *ortho*-Ph-C); 126.6 (m, $^3J_{C\text{-}B}$ = 3.0 Hz, *meta*-Ph-C); 122.9 (*para*-Ph-C); 74.9 (CH-2); 54.6 (OCH_3); 53.5 ($N(CH_3)_2CD_3$); 36.5 (CH-3); 26.8 (CH-4); 24.3 (CH_3-5); 21.7 (CH_3-5′) ppm. MS

(FT-ICR): 191.19 $C_{10}H_{19}D_3NO_2^+$, 701.58 $[(C_{10}H_{19}D_3NO_2)_2\ BPh_4]^+$.

FT-ICR mass spectrometry

ESI mass spectra were recorded with Bruker APEX IV Fourier-transform ion cyclotron resonance (FT-ICR) mass spectrometer with an Apollo electrospray ion source equipped with an off-axis 70° spray needle. Acetonitrile and Chloroform in a 1/1 vv served as the spray solvent and ca. 50 μM solutions of the analytes were used. Analyte solutions were introduced into the ion source with a syringe pump (Cole-Parmers Instruments, Series 74900) at flow rates of ca. 2–3 μl/min. Ion transfer into the first of three differential pump stages in the ion source occurred through a glass capillary with 0.5 mm inner diameter and nickel coatings at both ends. Ionisation parameters were adjusted as follows: capillary voltage: +4.6 to +4.9 kV; endplate voltage: +4.0 to +4.3 kV; cap exit voltage: −300 to −350 V; skimmer voltages: −8 to −12 V; temperature of drying gas: 150–200 °C. The pressure of drying gas was kept in a medium range (ca. 10 psi), while the pressure of nebulizer gas was set to ca. 15 psi. The ions were accumulated in the instrument's hexapole for 1.8–2.5 s, introduced into the FT-ICR cell which was operated at pressures below 10^{-10} mbar, and detected by a standard activation and detection sequence. For each measurement, 16–128 scans were averaged to improve the signal-to-noise ratio.

Results and discussion

Synthesis

The room temperature reaction of resorcinarene with excess formaldehyde and (*R*)-(−)-1-cyclohexylethylamine or (*S*)-(+)-1-cyclohexylethylamine, respectively, in ethanol provides tetrabenzoxazines **(*R*)-1** and **(*S*)-1** with 60–70% yield. Two different orientations of the new six-membered rings are possible which would translate into a mixture of 16 potential isomers for the tetrabenzoxazines. However, due to the seam of hydrogen bonds connecting the free OH groups on each of the four resorcinol rings to the oxazine oxygen atom of the adjacent one, only two different isomers are formed. They bear all oxazines in a clockwise or all in a counterclockwise orientation with respect to the resorcinarene scaffold. This element of chirality is not dynamic anymore like the hydrogen-bonding pattern in the parent resorcinarene. Together with the chiral information of the four amines used in the synthesis, the product of the reaction is thus a mixture of diastereomers. According to ^{1}H-NMR data, no significant diastereoselectivity is observed likely due to the fact that the amine stereocenters diverge from the seam of hydrogen bonds and do not interact strongly enough with it.

The same reaction with secondary *S*-(+)-*N*-benzyl-1-methylbenzylamine gave tetra-Mannich base **(*S*)-2** with 93% yield (Scheme 1). As with the parent resorcinarene, the seam of hydrogen bonds can quickly interconvert between two different orientations and may well involve intramolecular hydrogen bonding between the second OH group and the amine.

The structures and their chirality and dynamic properties are expressed in the NMR spectra (Figure 1). The ^{1}H-NMR spectra of **(*R*)-1** and **(*S*)-1** are identical and exhibit two sets of signals, one for each of the two diastereomers. The OH groups and the signal of the resorcinol ring protons both appear doubled between 7 and 8 ppm. Both appear in a 1:1 ratio indicating that no diastereoselectivity is operative in the synthesis. The multiplet at around 5 ppm corresponds to the diastereotopic methylene protons linking the nitrogen and phenolic oxygens in the oxazine rings. Closer inspection shows it to consist of two strongly overlapping pairs of doublets. The methine protons of the resorcinarene

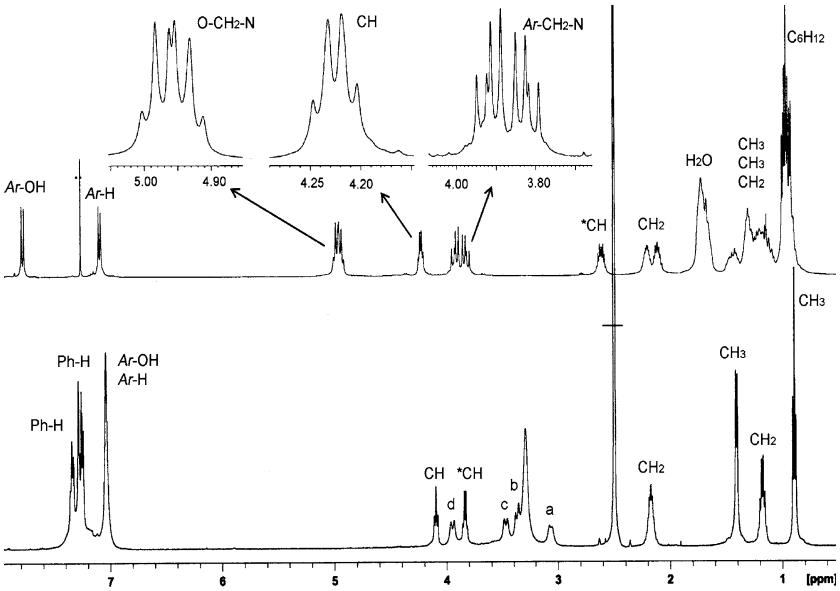


Figure 1. Top: ^{1}H-NMR spectrum of **(*R*)-1** in $CDCl_3$ at 30 °C. Bottom: ^{1}H-NMR spectra of **(*S*)-2** in DMSO at 30 °C.

scaffold appear at 4.2 ppm as two overlapping triplets. The diastereotopic protons of the Ar–CH_2–N group are easily identified as two slightly overlapping pairs of doublets. The remaining signals are more difficult to interpret due to strong overlap and non-resolved couplings. Nevertheless, they can be assigned to the remaining protons in the molecules.

For **(*S*)-2**, the NMR spectra show only one set of signals in line with the quick interconversion of hydrogen-bonding patterns of opposite directionality. Some broadening of the signals is observed which may indicate that this exchange process occurs. Four doublets (a–d in Figure 1, bottom) are observed between 3 and 4 ppm which correspond to the Res–CH_2–N and N–CH_2–Ph methylene groups. The fact that two doublets are found for each indicates that these protons are diastereotopic and thus prove the presence of the chiral information within the amine substituent.

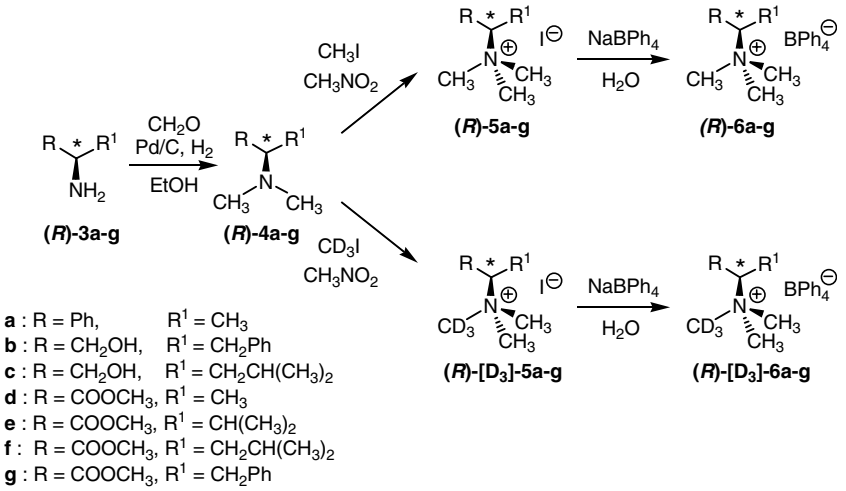
In order to determine chiral recognition by mass spectrometry, one needs to generate a pseudo-racemate of either the guest or the host. In our case, it is quite simple to perform isotopic labeling of the ammonium ions which are to be used as the guests. When the host is mixed with an excess of a 1:1 mixture of the two guest enantiomers, only one of which is deuterium labeled, two diastereomeric host–guest complexes can be formed. Only one of these contains the isotope label and thus has a mass different from the other complex. For this purpose, the ammonium salts shown in Scheme 2 were prepared according to a procedure by Undheim et al. [22] (Scheme 2). Since direct permethylation usually leads to a product mixture and because the use of base racemizes the amino acid derivatives **3d--g**, a two-step synthesis involving reductive methylation with formaldehyde followed by methylation of the tertiary amine with methyl iodide (CH_3I or CD_3I, respectively) was applied. The synthesis terminates with an anion exchange of iodide against tetraphenyl borate in order to avoid interference of the iodide with the hydrogen bonding at the upper rim of the host molecules and to increase the solubility of the salts in organic solvents. The purity of all the ammonium salts was confirmed by NMR spectroscopy and by ESI-TOF mass spectrometry. CD spectra (Figure 2) confirm that racemization did not occur during the synthesis.

Mass spectrometry and gas-phase fragmentation of **(*S*)-2**

For a mass spectrometric analysis, **(*S*)-2** can easily be ionized through electrospray ionization from methanol as the spray solvent. In this case, protonated ions are formed, presumably protonated at one of the amines. Another approach uses ammonium ions, e.g. tetramethyl ammonium (TMA) which bind to the cavity of the resorcinarenes. Both methods successfully work for **(*S*)-2**.

For an examination of the gas-phase fragmentation reactions, the ions of interest are mass-selected (monoisotopic ions only) in the analyzer cell of the Fourier-transform ion-cyclotron-resonance mass spectrometer. Subsequent collisions with argon as the collision gas induce fragmentation (CID = collision-induced dissociation). The results for both the protonated molecule and its TMA adduct are shown in Figure 3. Product signals appear at repetitive distances of Δm = 211 Da which corresponds to the loss of the amine shown in the inset of Figure 3. The same distances are observed between the product signals for the TMA adduct. While this fragmentation reaction occurs up to four times for the protonated resorcinarene, only three fragmentation steps are seen for the TMA adduct. Instead a rather intense signal for the TMA cation is seen. Consequently, the loss of the neutral host generating bare TMA^+ competes with the elimination of the amine.

Scheme 3 summarizes these fragmentation reactions and provides a plausible mechanism. Intramolecular hydrogen bonding between one of the OH groups on a resorcinol ring and the amine nitrogen supports a



Scheme 2. Synthesis of chiral, quaternary ammonium ions suitably labeled for their use in mass spectrometric experiments aiming at a detection of chiral recognition in the gas phase. The anion exchange to BPh_4^- helps to avoid interference of hydrogen bonding with the iodide. The (*S*)-series was prepared through the same synthetic steps just starting from the corresponding (*S*)-enantiomer of the precursors.

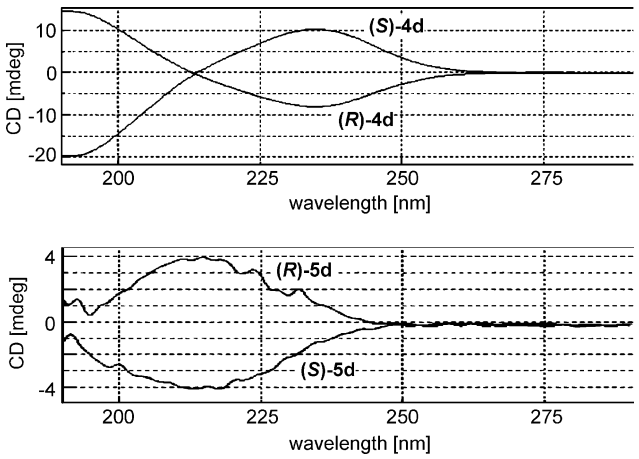


Figure 2. CD spectra of intermediate **(*S*)-** and **(*R*)-4d** and iodides **(*S*)-** and **(*R*)-5d** as representative examples.

1,4-elimination proceeding through a six-membered transition structure. Since the proton binds much more strongly to the host than the TMA cation, all four amines can be expelled. For the TMA adduct, the TMA binding energy limits the energy demand of the 1,4-elimination reactions. The fourth reaction is not observed any more. From these experiments, it is impossible to determine whether the bare TMA cation is formed only from the last intermediate. It may well also be generated from the parent ion or the other elimination intermediates to some extent.

Mass spectrometry and gas-phase fragmentation of **(*S*)-1** *and* **(*R*)-1**

(*S*)-1 and **(*R*)-1** can be ionized analogously by protonation or TMA adduct formation. Instead of a 1,4-elimination, another reaction proceeds here upon collisional activation (Figure 4): The loss of Δm = 139 Da indicates that cyclohexyl-ethyl-substituted imines are liberated in a retro-Diels–Alder reaction. Again, up to four subsequent reaction steps are observed for the protonated molecule, while loss of the host giving rise to the bare TMA cation competes with the retro-Diels–Alder reaction for **(*S*)-1•**TMA^+ (Scheme 4).

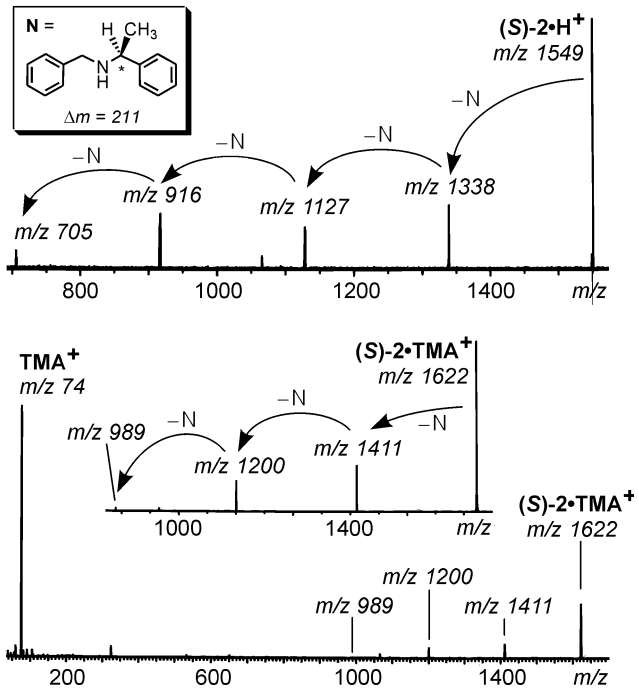


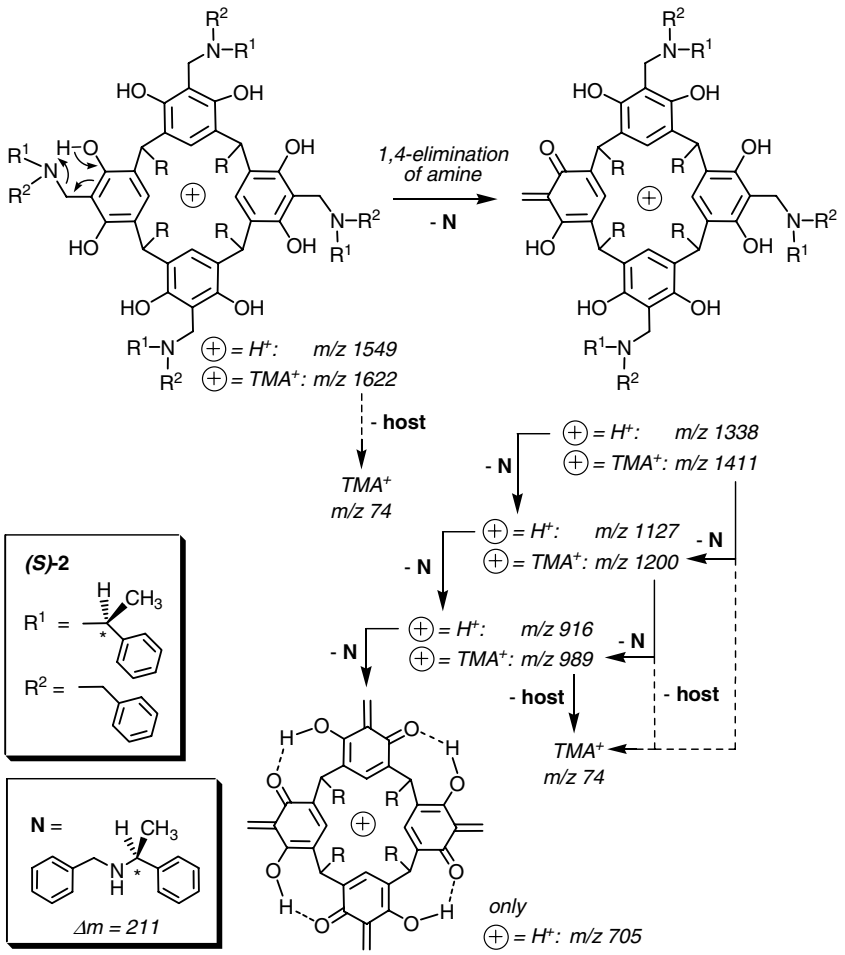
Figure 3. Collision-induced fragmentation (CID) of protonated **(*S*)-2** (top) and its adduct with a tetramethyl ammonium cation (bottom).

In the synthesis of **1**, side products are formed which did not undergo oxazine ring formation. Instead one, two, or even three rings remain open with the resorcinol rings aminomethylated. From the raw product, ionization through protonation and mass selection of the resulting ions is possible so that they can be subjected to a collision experiment without interference of the major product or any other side product. Figure 5 shows the CID spectrum of the compound which bears two oxazoline rings and two amino methyl groups. Three different positional isomers are possible, one of which carries the two aminomethyl groups on opposing sides of the resorcinarene scaffold. The two remaining isomers with their aminomethyl groups adjacent to each other are again a pair of diastereomers. They all have the same elemental composition and thus cannot be distinguished by mass spectrometry. Nevertheless, the CID mass spectrum nicely shows that both reactions, 1,4-amine elimination and retro-Diels–Alder reactions, can occur in any sequence. They both efficiently compete with each other indicating that their activation barriers do not differ significantly.

Chiral recognition between chiral ammonium cations and chiral resorcinarenes?

With the formation of the tetramethylammonium adducts, the resorcinarenes under study have already shown their capability to bind ammonium ions as their guests. Similarly, chiral analogues form complexes. In order to evaluate the extent by which chiral recognition can be achieved, pseudo-racemates were prepared from one unlabeled guest enantiomer and the other deuterium-labeled enantiomer. ESI mass spectra of the pseudo-racemates yield intense signals for anion-bridged dimers. Homo- and heterodimers of the ammonium ions appear with a statistical 1:2:1 ratio, when an exact 1:1 mixture is used. Thus, these mass spectra can be used to make sure that the both cations are present in exactly equal amounts.

Then, part of this stock solution was mixed with one of the resorcinarenes. Since one of the host–guest complexes is labeled with a CD_3 group the two diastereomeric host–guest complexes overlap with their isotope patterns. Nevertheless, the relative ratio of both complexes can be analyzed by isotope pattern analysis. The result is shown in Figure 6 exemplarily for three different amino acid derivatives. In none of the cases studied, significant differences between the intensities of the two complexes were observed. This lack of chiral recognition is confirmed by the control experiment in which the other guest enantiomer was deuterium labeled.



Scheme 3. Fragmentation mechanism and pathways for the consecutive 1,4-eliminations of the amine N from protonated **(*S*)-2** and its adduct with tetramethyl ammonium cations (TMA^+).

One might ask, why there is no chiral recognition expressed in the mass spectra. Molecular modeling [23] may help to find an answer. Figure 7 shows the structures of **(*R*)-1** with both enantiomers of guest cation **6a**$^+$ as an example. It is clearly visible, that the cyclohexyl side chains as well as the methyl groups attached to the chiral center nicely accommodate both cations with similar ease. Consequently, the flexibility of the single bonds connecting the stereogenic center to the resorcinarene scaffold allows these substituents to easily adjust to the cation structure. No pronounced effect can thus be expected as observed in the experiments.

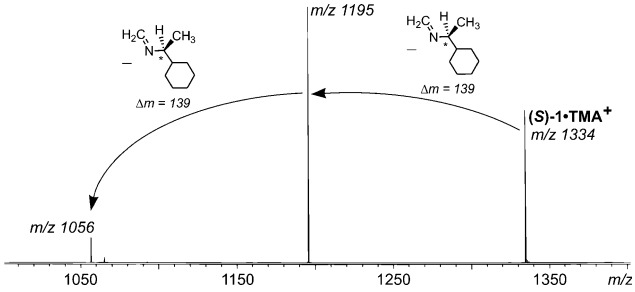
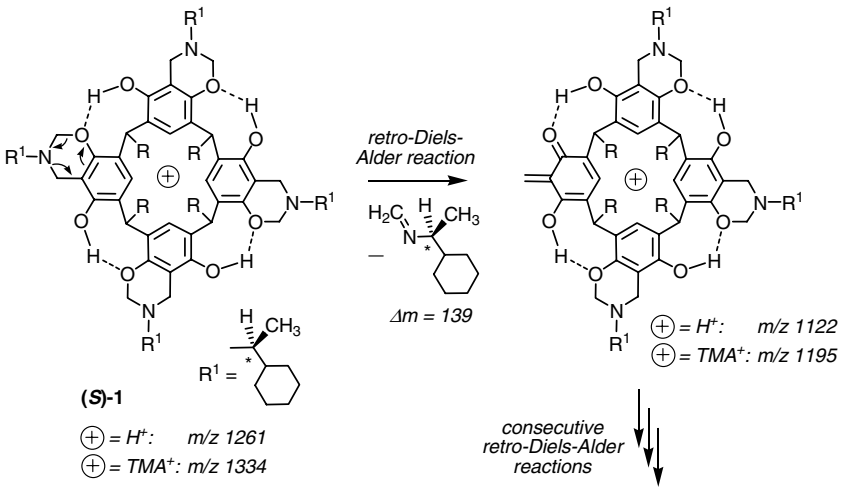


Figure 4. CID mass spectrum of the mass-selected TMA adduct of **(*S*)-1**.

Mass spectrometry as a means to study the kinetics of solution-phase reactions of **(*S*)-2**

While the ESI-FTICR mass spectrum of a freshly prepared sample of **(*S*)-2** in methanol was almost perfectly clean, additional signals raised over time with a repetitive peak spacing of Δm = 179 Da (Figure 8). This mass difference corresponds to the replacement of an amine substituent (Δm = 211 Da) by a methoxy group (Δm = 32 Da, thus 211−32 = 179 Da) originating from the solvent. Three such replacements are possible giving rise to ions at m/z 1550, m/z 1371, m/z 1192, and m/z 1013. The replacement of the last amine was however not observed. Instead, a signal rose at m/z 1045 which formally corresponds to a methanol adduct of the product of three amine/methanol exchanges.

Our first interpretation that the replacement can only take place, when a second amine is present to assist implies that the last step is the formation of a host–guest complex with methanol. However, this interpretation is not very satisfying. First, why should the other host compounds not form such methanol adducts? Second, why is the formation of the last methanol adduct at m/z 1045 so slow, although one would certainly expect a fast exchange reaction in solution? Third, any attempt to



Scheme 4. Retro-Diels–Alder reactions rationalize consecutive imine losses.

rationalize the assistance by a second amine arm in the replacement of another one by molecular modeling failed.

Consequently, we ruled out this interpretation. Scheme 5 shows another possibility to account for the data obtained. Replacement of up to three amine substituents is possible without removing all amines from the molecule. Thus, protonation is easily possible and for the parent compound and the three first exchange products, the protonated ions are observed in the mass spectra. Upon replacement of the last amine, no site is left, which could easily be protonated. Instead, quite many free amines are present in solution. This is the reason why the final product is visible in the mass spectrum as a complex with the ammonium ion generated from the liberated amine. This explanation also answers the questions above: The last step is slow, because its rate-determining step is the replacement of the last amine, not the formation of the methanol complex. As long as an amine incorporated in the resorcinarene is protonated, complex formation with another ammonium ion is unlikely due to charge repulsion. Finally, all four amines can be exchanged; no assistance from any other group in the molecule is necessary.

Figure 8 (bottom) provides a kinetics plot of the data collected. As a first approximation, one may assume the intensities obtained from the mass spectra to correlate with solution concentrations. This assumption is certainly not fully true, but at least for the first steps, the ions are quite similar to each other. The last step, i.e. replacement of the last amine and complex formation with the ammonium ion, generates a somewhat different ion, for which this assumption may not be valid anymore. Nevertheless, we decided to simulate the kinetics of the amine/methanol exchange reaction on the basis of this data with the Freeware Chemical Kinetics Simulator [24]. At least, a semiquantitative picture should be extractable from this simulation. Indeed, the following four rate constants were obtained from a simulation which excellently fitted the experimental data:

$$k_1 = 1.21 \cdot 10^{-5}\,\mathrm{mol\,l^{-1}\,s^{-1}}$$
$$k_2 = 1.80 \cdot 10^{-5}\,\mathrm{mol\,l^{-1}\,s^{-1}}$$
$$k_3 = 1.55 \cdot 10^{-5}\,\mathrm{mol\,l^{-1}\,s^{-1}}$$
$$k_4 = 0.90 \cdot 10^{-5}\,\mathrm{mol\,l^{-1}\,s^{-1}}$$

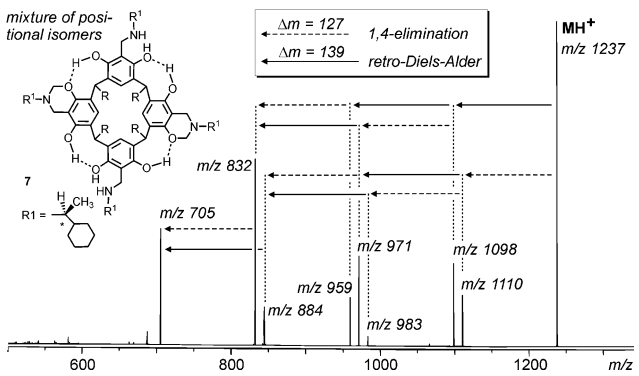


Figure 5. CID mass spectrum of a mixture of the three possible positional isomers bearing two oxazine rings and two aminomethyl groups at the resorcinarene scaffold.

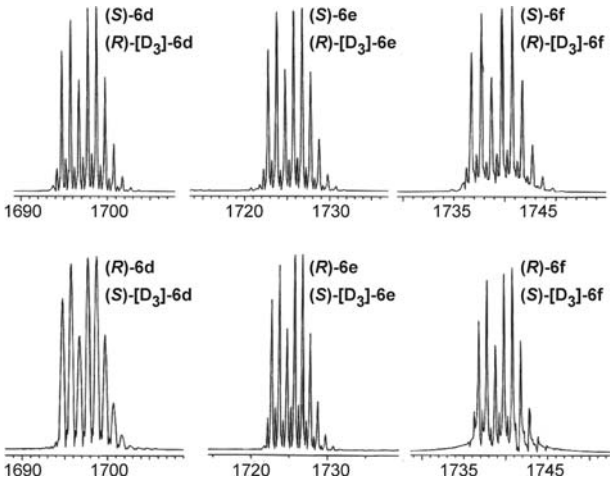


Figure 6. Isotope pattern regions of the ESI-FTICR mass spectra of (***S*)-2** with pseudo-racemates of the two guests given in the figure. The bottom row represents control experiments with a reversed labeling of the two guest enantiomers as compared to the top row.

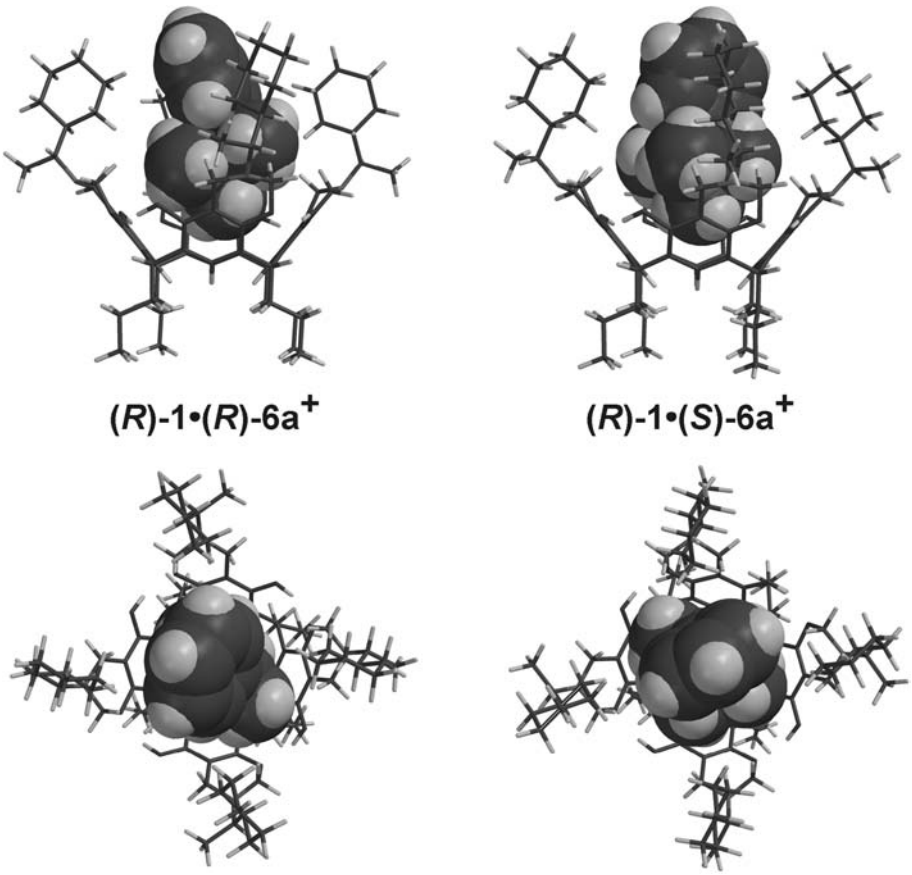


Figure 7. Side (top) and top view (bottom) of the host guest complexes of **(*R*)-1** with the two enantiomers of **6a**$^+$.

Without overinterpreting the data, it is clear that all four rate constants are at least in the same order of magnitude. This is in good agreement with the assumption that all four amines can be replaced by methanol independently from each other.

Together with the gas-phase results discussed above, the question arises, by which mechanism the exchange proceeds. No acids or bases were added to the sample solution in addition to the tetrakis-aminomethylated resorcinarene, which itself is a base. Consequently, the formation of the corresponding benzyl cations as intermediates is not very likely, since they could easily be neutralized through deprotonation of one of the resorcinol OH groups. We believe that the mechanism depicted in Scheme 6 is more convincing. 1,4-elimination of the amine through a six-membered transition structure could be followed by a hydrogen-bond assisted Michael addition of methanol, which is present in a large excess. Of course, a similar reaction could proceed intermolecularly, but the concentration in the sample prepared for mass spectrometric experiments was in the lower micromolar regime. Consequently, the reaction likely proceeds intramolecularly.

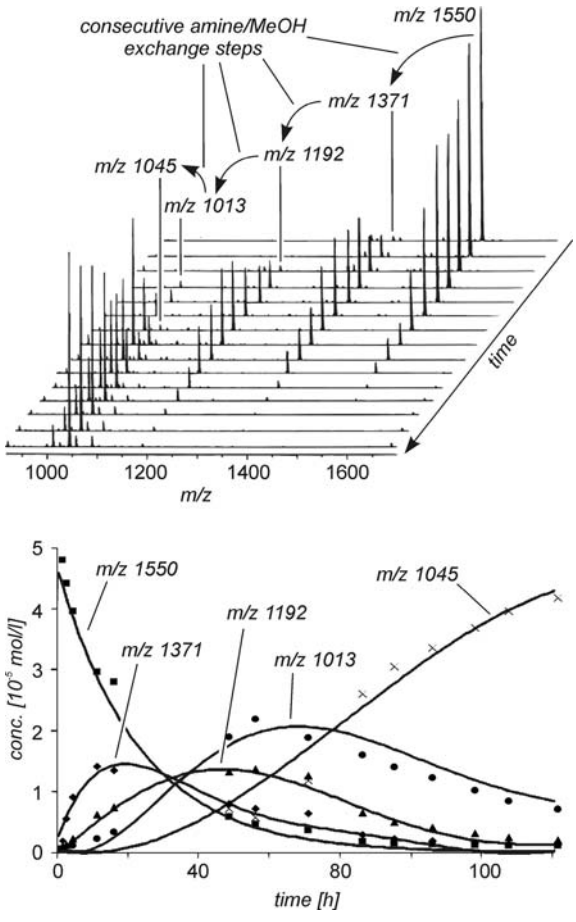
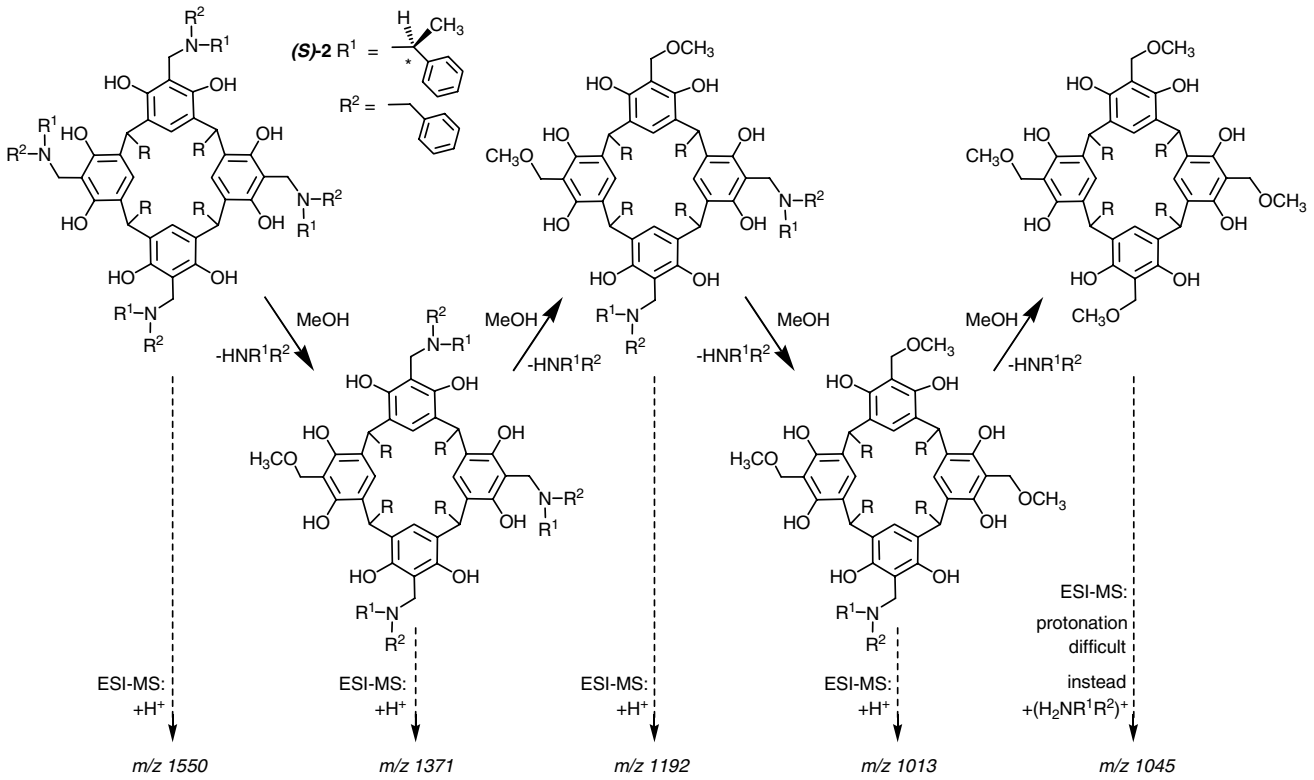
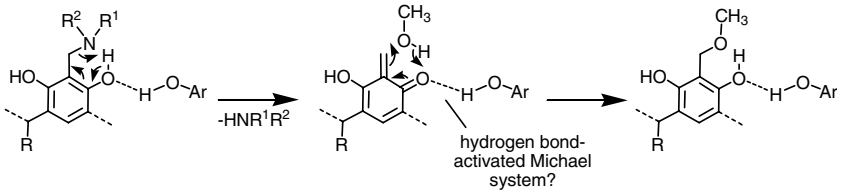


Figure 8. Change of the ESI-FTICR mass spectrum of a methanol solution of **(*S*)-2** over time (top) . Kinetics plot for the reactions monitored assuming that – as a first approximation – intensities can be translated into concentrations in solution (bottom).



Scheme 5. Consecutive replacement of amines by methanol occurring in solution and the corresponding ions observed in the ESI-FTICR mass spectra. Note that the last resorcinarene does not bear any amine and thus is more difficult to protonate. Consequently, it forms a complex with the ammonium ion resulting from the liberated amine.



Scheme 6. Plausible mechanism for the amine/methanol exchange reaction in solution.

Whatever the final details of the mechanism are, this reaction may synthetically be useful, because almost any nucleophile strong enough to replace the amine or present in a sufficiently large excess can be introduced into the resorcinarene scaffold. By such a reaction, the versatility of resorcinarenes for the generation of building blocks for supramolecular chemistry is significantly enhanced.

Conclusions

We have presented the syntheses and characterization of two different types of chiral resorcinarenes. Although these compounds did not reveal the desired chiral recognition with chiral ammonium guests in a mass spectrometric analysis, they give rise to a very clear-cut and easy-to-analyze fragmentation behavior. For **1**, retro-Diels–Alder reactions within the benzoxazines are observed. For **2**, intramolecular 1,4-eliminations proceed with a similarly high activation barrier as evidenced by ions bearing both types of substituents in the same molecule. Mass spectrometry has also been used to examine the kinetics of solution phase reaction. The gas-phase results imply that a similar reaction proceeds in solution. However, the reaction product is not stable, but undergoes reaction with methanol which was used as the spray solvent. The reaction observed in solution is synthetically useful for the generation of differently substituted resorcinarenes as building blocks for supramolecular chemistry.

Acknowledgements

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