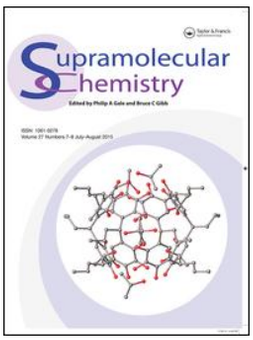


Supramolecular Chemistry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gsch20

Synthesis of quinoxaline cavitand baskets

Alessia Favero, Andrea Rozzi, Chiara Massera, Alessandro Pedrini, Roberta Pinalli & Enrico Dalcanale

To cite this article: Alessia Favero, Andrea Rozzi, Chiara Massera, Alessandro Pedrini, Roberta Pinalli & Enrico Dalcanale (2021): Synthesis of quinoxaline cavitand baskets, Supramolecular Chemistry, DOI: 10.1080/10610278.2021.1917768

To link to this article: https://doi.org/10.1080/10610278.2021.1917768

Published online: 02 May 2021.

SUPRAMOLECULAR CHEMISTRY
https://doi.org/10.1080/10610278.2021.1917768

Taylor & Francis
Taylor & Francis Group

ARTICLE

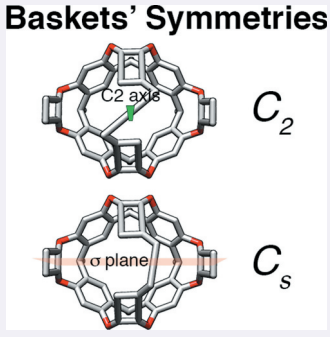
Synthesis of quinoxaline cavitand baskets

Alessia Favero, Andrea Rozzi, Chiara Massera, Alessandro Pedrini, Roberta Pinalli and Enrico Dalcanale

Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma, Italy and INSTM Parma Research Unit, Italy

ABSTRACT

The unique temperature, solvent and pH driven*vase* to *kite* equilibrium in quinoxaline cavitands allows the reversible uptake and release of guests. However, the cavity breathing associated with this conformational switch reduces the strength of complexation. A limited number of solutions have been proposed for the cavity rigidification, using either H-bonding, metal coordination or covalent connections. Here we report the synthesis and structural characterisation of quinoxaline-based cavitand baskets, which present two distal quinoxaline walls linked together. Baskets A and B were obtained through a bridging reaction starting from an AC di-quinoxaline bridged cavitand using two different di-quinoxaline moieties. In both cases, two isomers were obtained: isomer C_2, with the linking unit crossing the cavity mouth, and isomer C_s, having the linker sideways. The isomers were identified through ^{1}H NMR analysis. In the case of basket A-C_s, the resolved molecular structure confirmed the C_s symmetry of the basket.



ARTICLE HISTORY
Received 16 March 2021
Accepted 9 April 2021

KEYWORDS
Quinoxaline cavitands; cavity partial rigidification; X-ray crystal structure; upper rim bridging

1 Introduction

The unique temperature, solvent and pH driven vase-kite equilibrium in quinoxaline cavitands [1] has attracted the attention of several researchers [2–4], since this conformational switch allows the reversible uptake and release of candidate guests [5] (Figure 1).

Quinoxaline cavitands in the vase form have shown peculiar molecular recognition properties in the gas-phase [6,7], in solution [8,9] and at the solid-gas interface [10,11], leading to their use in sensors for the detection of aromatic volatile organic compounds [12–14]. The vase-kite equilibrium can be suppressed in favour of the vase form *via* H-bonding [15], metal coordination [16] or covalent connections. Covalent rigidification was obtained by introducing four lateral bridging units linking the four quinoxaline walls (Chart 1a). This rigidification has further sharpened the molecular recognition properties of the resulting cavitands, leading to a sensor for the detection of benzene at ppb levels in air [17]. An intermediate level of rigidification has been reported by Diederich's group by replacing two distal quinoxaline walls with diazaphthalimide walls, connected via diacetylenic or *p*-xylylene bridges (Chart 1(b,c)) [18,19]. In this way, the upper mouth of the cavity is partially sealed, leaving the other two quinoxaline walls as gates for the opening and closing of the cavity. In this case, the residual vase-kite conformational switch is also pH driven. These molecular baskets have shown enhanced molecular recognition properties compared to the parent flexible cavitand, coupled with the ability to open the lateral portals for guest release.

CONTACT Enrico Dalcanale enrico.dalcanale@unipr.it Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parco Area delle Scienze 17/A, Parma 43124, Italy

Dedicated to the memory of David Gutsche

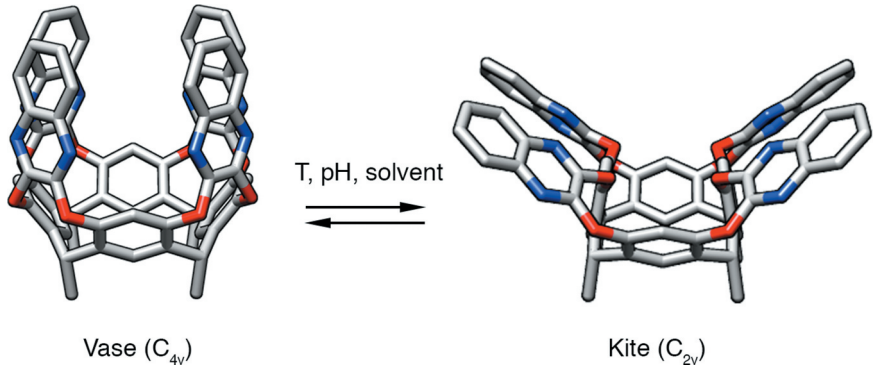


Figure 1. Vase-kite switching by controlling temperature, pH and solvent polarity.

Intrigued by the possibility to use quinoxaline cavitand baskets as selective preconcentration units in sensors, we explored different synthetic pathways for the synthesis of molecular baskets featuring exclusively quinoxaline walls. Here we report the results of this study.

2 Materials and methods

2.1 Chemicals

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of argon using anhydrous solvents (either freshly distiled, passed through activated alumina columns or stored on molecular sieves for at least 48 h). All commercially obtained reagents were used as received unless otherwise specified. Silica column chromatography was performed using silica gel 60 (Fluka 230–400 mesh or Merck 70–230 mesh). Automatic purification was performed on COMBIFLASH NextGen 300. Silica cartridges (Purezza-Daily Open-Load Flash Cartridge Silica 60A 50um-Size 40) were purchased from SEPACHROM.

^{1}H and ^{13}C NMR spectra were obtained using a Bruker AVANCE 300 (300 MHz) and a Bruker AVANCE 400 (400 MHz) spectrometer at 298 K. All the chemical shifts (δ) were reported in ppm relative to the proton resonances resulting from incomplete deuteration of the NMR solvents. High-resolution MALDI-TOF was performed on an AB SCIEX MALDI TOF-TOF 4800 Plus (matrix: α-cyano-4-hydroxycinnamic acid).

4-hydroxy-2-nitroaniline and 1,3-diphenylpropane were purchased by Fluorochem. Products **5** and **6** were obtained following a literature procedure [20], as well as **AB-2QxCav** and **AC-2QxCav** [21].

2.2 Synthesis of 4,4'-(ethane-1,2-diylbis(oxy))bis (2-nitroaniline) (1)

To a solution of 4-hydroxy-2-nitroaniline (500 mg, 3.24 mmol) in dry ACN (15 mL), K_2CO_3 (1.345 g, 9.73 mmol) was added. After 5 min, ethylene di(*p*-toluenesulfonate) was added (1.803 g, 4.87 mmol) and the reaction mixture was stirred at 80°C for 24 h. The solvent was removed and water was added to the solid crude. The crude was sonicated for 15 min and filtered through a Büchner funnel to afford a red solid. The target compound was obtained after recrystallisation from dichloromethane (DCM) as a dark red powder (374 mg, 69%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm = 7.63 (d, 2H, J = 2.8 Hz), 7.13 (dd, 2H, J_o = 6.0 Hz, J_m = 3.0 Hz), 6.77 (d, 2H, J = 9.0 Hz), 4.29 (s, 4 H).

ESI-MS: m/z 357.19 $[M+ Na]^+$; m/z 373.26 $[M + K]^+$.

2.3 Synthesis of 4,4'-(ethane-1,2-diylbis(oxy))bis (benzene-1,2-diamine) (2)

To a solution of compound **1** (374 mg, 1.12 mmol) in EtOH (40 mL), $SnCl_2$*$2H_2O$ (2.52 g, 11.16 mmol) was added in one portion and the solution was stirred at 80°C for 17 h. The eluent was evaporated under vacuum to give a dark solid, which was maintained under inert atmosphere and carried to the next step without further purification (307 mg, quantitative yield).

2.4 Synthesis of 6,6'-(ethane-1,2-diylbis(oxy))bis (quinoxaline-2,3-diol) (3)

To a solution of compound **2** (307 mg, 1.12 mmol) in HCl 4 N (18 mL), oxalic acid (242 mg, 2.69 mmol) was added and the mixture was stirred at 110°C for 16 h. The reaction mixture was filtered through a Büchner funnel. The obtained solid was washed with water and subsequently dried under vacuum to give a dark purple solid (394 mg, 92%).

^{1}H NMR (DMSO-d_6, 300 MHz): δ ppm = 11.83 (d, 2H, OH, J = 16 Hz), 7.05 (d, 2 H, J = 8.7 Hz), 6.78 (dd, 2 H, J_o = 11.3 Hz, J_m = 2.6 Hz), 6.72 (s, 2 H, J = 2.5 Hz), 4.25 (s, 4 H).

2.5 Synthesis of 1,2-bis((2,3-dichloroquinoxalin-6-yl)oxy)ethane (4)

To a solution of **3** (200 mg, 0.52 mmol) in dry 1,2-dichloroethane (30 mL), dry DMF (5 drops) and $POCl_3$ (1.95 mL, 20.90 mmol) were added. The mixture was stirred at 80°C

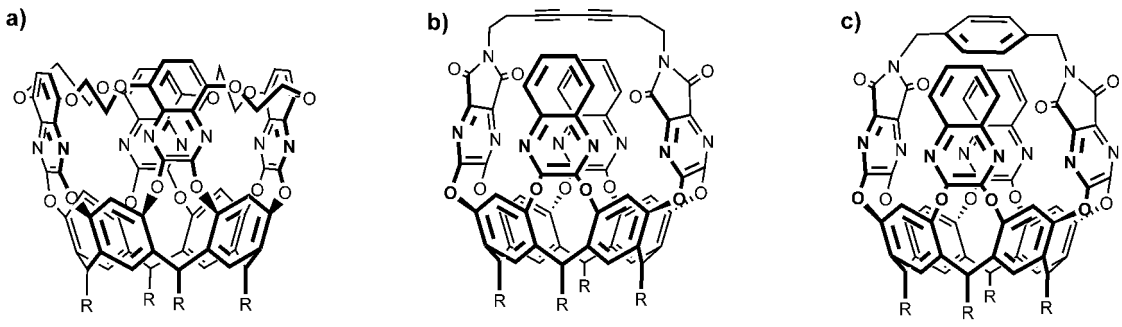


Chart 1. Possible rigidification of the quinoxaline cavitand. (**a)** Connection of all the quinoxaline moieties with ethoxy bridges; partial rigidification connecting two distal diazaphthalimide walls via (**b)** diacetylenic and (**c)** *p*-xylylene bridges.

for 16 h, then cooled to room temperature and the solvent removed under vacuum. The crude was suspended in MeOH and filtered through a Büchner funnel to give a brownish solid (490 mg, 96%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm = 7.93 (d, 2 H, J = 9.2 Hz), 7.49 (dd, 2 H, J_o = 9.3 Hz, J_m = 2.7 Hz), 7.38 (d, 2 H, J = 2.8 Hz), 4.55 (s, 4 H).

ESI-MS: m/z 456.97 $[M + H]^+$.

2.6 Synthesis of baskets A

In a Schlenk flask, **AC-2QxCav** (53 mg, 0.05 mmol) was dissolved in 70 mL of dry DMF in an inert atmosphere. After the addition of K_2CO_3 (41 mg, 0.3 mmol) and ethylenedioxy bis-dichloroquinoxaline **4** (23 mg, 0.05 mmol), the reaction was stirred at 80°C for 16 h. The solvent was removed under vacuum, H_2O was added to the crude, and the suspension was sonicated and filtered. Purification by flash column chromatography over silica gel and subsequent preparative TLCs using DCM/MeOH 98:2 as eluent in both cases, afforded pure **A-C$_s$** (3 mg, 12%) followed by **A-C$_2$** (1.3 mg, 5%).

A-C$_s$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 8.38 (s, 2 H, ArH_{up}), 8.33 (m, 2 H, QxH), 8.12 (s, 2 H, ArH_{up}), 8.03 (m, 2 H, QxH), 7.87 (m, 2 H, QxH), 7.73 (m, 2 H, QxH), 7.40 (d, 2 H, QxH, J = 9.21 Hz), 7.20 (s, 2 H, ArH_{down}), 7.08 (s, 2 H, ArH_{down}), 6.65 (dd, 2 H, QxH, J^1 = 9.21 Hz, J^2 = 2.58), 5.96 (d, 2 H, QxH, J = 2.58 Hz), 5.86 (t, 1 H, J = 8.25 Hz), 5.64 (t, 1 H, J = 8.32 Hz), 5.58 (t, 2 H, J = 8.32 Hz), 3.69 (m, 2 H), 3.30 (m, 2 H), 2.39 (m, 2 H), 2.27 (m, 2 H), 2.15 (m, 4 H), 1.41 (m, 32 H), 0.99 (m, 12 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 154.06, 153.60, 152.87, 152.66, 152.54, 152.52, 151.56, 150.72, 140.48, 140.16, 139.47, 135.78, 135.59, 135.49, 135.02, 129.47, 129.10, 128.76, 128.46, 128.26, 124.00, 123.20, 122.82, 119.64, 109.20, 64.98, 34.46, 34.12, 33.96, 33.57, 31.98, 31.93, 31.81, 31.52, 30.69, 29.41, 29.34, 28.04, 27.90, 22.69, 22.65, 14.10, 14.06.

MALDI-TOF: m/z 1387.6232 calculated for $C_{86}H_{83}N_8O_{10}$ $[M + H]^+$, found 1387.6268; m/z 1409.6052 calculated for $C_{86}H_{82}N_8NaO_{10}$ $[M+ Na]^+$, found 1409.6017.

A-C$_2$ ^{1}H NMR (CDCl3, 400 MHz): δ ppm = 8.27 (s, 2 H, ArHup), 8.25 (m, 2 H, QxH), 8.00 (m, 2 H, QxH), 7.98 (s, 2 H, ArHup), 7.87 (t, 2 H, QxH, J = 7.03 Hz), 7.77 (t, 2 H, QxH, J = 6.90 Hz), 7.46 (d, 2 H, QxH, J = 9.12 Hz), 7.36 (d, 2 H, QxH, J = 8.07 Hz), 7.22 (s, 2 H, ArHdown), 7.01 (s, 2 H, ArHdown), 6.65 (dd, 2 H, QxH, J = 6.78), 6.32 (d, 2 H, QxH, J = 2.55 Hz), 5.65 (t, 2 H, J = 8.11 Hz), 5.57 (t, 2 H, J = 8.20 Hz), 3.99 (m, 2 H), 3.40 (m, 2 H), 2.33 (m, 4 H), 2.18 (m, 4 H), 1.35 (m, 32 H), 0.94 (m, 12 H).

^{13}C NMR (CDCl3, 100 MHz): δ ppm = 154.11, 153.63, 152.85, 152.70, 152.57, 152.53, 151.59, 150.74, 140.50, 140.19, 139.45, 135.71, 135.53, 135.42, 135.11, 129.47, 129.13, 128.77, 128.48, 128.25, 124.06, 123.21, 122.84, 119.67, 109.24, 65.03, 34.41, 34.14, 33.99, 33.58, 32.00, 31.95, 31.84, 31.55, 30.72, 29.43, 29.37, 28.09, 27.94, 22.73, 22.68, 14.12, 14.07.

MALDI-TOF: m/z 1387.6232 calculated for $C_{86}H_{83}N_8O_{10}$ $[M + H]^+$, found 1387.6254 $[M + H]^+$; m/z 1409.6052 calculated for $C_{86}H_{82}N_8NaO_{10}$ $[M+ Na]^+$, found 1409.6063.

2.7 Synthesis of N,N′-(propane-1,3-diylbis(2-nitro-4,1-phenylene))diacetamide (7)

Compound **6** (360 mg, 1.59 mmol) was suspended in 15 mL of acetic anhydride, and the suspension was cooled down in an ice bath. *p*-Toluenesulfonic acid (665 mg, 3.5 mmol) and KNO_3 (353 mg, 3.5 mmol) were added and the mixture was stirred overnight at room temperature. The reaction was quenched with 200 mL of water and the formed precipitate was sonicated, filtered off on a frit glass (G4), recovered with 20 mL of ethyl acetate, sonicated and filtered again. The obtained crude was purified with an automatic flash column in a linear gradient Hex = > AcOEt in 20 minutes. 475 mg of product **7** were obtained with an overall yield of 74%.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 10.26 (s, 2 H), 8.69 (d, J = 8.7 Hz, 2 H), 8.02 (d, J = 2.0 Hz, 2 H), 7.48 (dd, J = 8.7, 2.0 Hz, 2 H), 2.79–2.65 (m, 4 H), 2.31 (s, 6 H), 1.99 (t, J = 7.7 Hz, 2 H).

ESI-MS: m/z 271.13 $[M\text{-}NO_2^-]^+$, 317.15 $[M + H]^+$.

2.8 Synthesis of 4,4′-(propane-1,3-diyl)bis (2-nitroaniline) (*8*)

Product **7** (425 mg, 1.06 mmol) was suspended in 20 mL of ethanol and 2 mL of water. An excess of sodium hydroxide was added (400 mg, 10 mmol) and the reaction was stirred at 80°C for 5 h. The solvent was evaporated at reduced pressure and the crude extracted with 3 × 20 mL of AcOEt. The organic phase was dried over anhydrous sodium sulphate and filtered. The crude was purified by flash chromatography using Hex:AcOEt as eluent in a linear gradient from 7:3 to 1:1 mixture in 20 min. The desired product was obtained as yellow solid (302 mg, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.91 (d, J = 2.0 Hz, 2 H), 7.19 (dd, J = 8.5, 2.1 Hz, 2 H), 6.75 (d, J = 8.5 Hz, 2 H), 2.60–2.52 (m, 4 H), 1.88 (tt, J = 8.9, 6.9 Hz, 2 H).

ESI-MS: m/z 339.17 $[M+ Na]^+$.

2.9 Synthesis of 4,4′-(propane-1,3-diyl)bis (benzene-1,2-diamine) (intermediate 9) and 6,6′-(propane-1,3-diyl)bis(quinoxaline-2,3-diol) (*10*)

Product **8** (302 mg, 955 µmol) was dissolved in 20 ml of THF, obtaining a clear yellow solution. The temperature was risen to 60°C under nitrogen. Hydrazine 80% (300 µL, 7.64 mmol) was added, followed by a catalytic amount of Nickel Raney. After 30 minutes the reaction was quenched. The unstable intermediate **9** was obtained after filtration of the catalyst on a glass filter under an inert atmosphere. The immediate addition of 10 mL of HCl 4 M to the filtrate preserved the intermediate from degradation. THF was removed under reduced pressure and the aqueous phase became pale yellow. The solution was immediately poured into a 100 mL round-bottom flask and oxalic acid (198 mg, 2.20 mmol) was added. The temperature was raised to 100°C and the reaction was left stirring overnight. The white precipitate formed was filtered on a glass filter (G4), obtaining 282 mg of **10** (81% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 11.88 (2s, 4 H), 7.05 (d, J = 8.6 Hz, 2 H), 6.96–6.90 (m, 4 H), 2.56 (t, J = 7.5 Hz, 4 H), 1.87–1.73 (m, 2 H).

MALDI-TOF: m/z 365,1250 calculated for $C_{19}H_{17}N_4O_4$ $[M + H]^+$, found 365,0837.

2.10 Synthesis of 1,3-bis(2,3-dichloroquinoxalin-6-yl)propane (*11*)

To a solution of **10** (280 mg, 768 µmol) in 20 mL of dry dichloroethane thionyl chloride (280 µL, 3.84 mmol) was added together with three drops of dry DMF as catalyst. The temperature was risen to 80°C and the inert atmosphere maintained. The reaction was stirred overnight and then quenched by adding 20 mL of methanol. The solvent was evaporated at reduced pressure, and the crude was suspended in methanol and filtered off. The product was obtained as white solid (252 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.96 (d, J = 8.6 Hz, 2 H), 7.82 (d, J = 1.4 Hz, 2 H), 7.65 (dd, J = 8.6, 1.9 Hz, 2 H), 2.99–2.86 (m, 4 H), 2.19 (t, m, 2 H).

MALDI-TOF, m/z 438,9606 calculated for $C_{19}H_{13}Cl_4N_4$ $[M + H]^+$, found 438,9637.

2.11 Synthesis of baskets B

In a Schlenk flask, **AC-2QxCav** (27.4 mg, 25.4 µmol) was dissolved in 40 mL of dry DMF. After the addiction of K_2CO_3 (10.5 mg, 76.3 µmol) and 3-bis(2,3-dichloroquinoxalin-6-yl)propane (**11**) (12.2 mg, 28 µmol), the reaction was stirred at 80°C for 16 h. The solvent was removed under vacuum and the crude was purified by preparative TLC in DCM as eluent, affording pure **B-C$_s$** (1.7 mg, 5%) followed by **B-C$_2$** (0.7 mg, 2%). The low amount of B-C_2 obtained hampered the possibility of clean ^{1}H-NMR spectrum. However, all the diagnostic peaks were clearly present for the univocal identification of the compound.

B-C$_s$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 8.43 (s, 2 H, ArHup), 8.37 (m, 2 H, QxH), 8.07 (s, 2 H, ArHup), 8.03 (m, 2 H, QxH), 7.97 (m, 2 H, QxH), 7.74 (m, 2 H, QxH), 7.40 (d, 2 H, QxH, J = 8.7 Hz), 7.17 (s, 2 H, ArHdown), 7.06 (s, 2 H, ArHdown), 6.76 (dd, 2 H, QxH, J1 = 8.6 Hz, J2 = 2.0), 6.57 (dd, 2 H, J1 = 11.8, J2 = 1.9 Hz, QxH), 5.86 (t, 1 H, J = 8.2 Hz), 5.69 (t, 1 H, J = 8.2 Hz), 5.57 (d, 2 H, J = 8.4 Hz). 2.40 (m, 2 H), 2.28 (m, 8 H), 2.16 (m, 4 H), 1.35 (m, 32 H), 0.94 (m, 12 H).

MALDI-TOF: m/z 1386.6750 calculated for $C_{87}H_{88}N_9O_8$ $[M+ NH_4]^+$, found 1386.6932 $[M+ NH_4]^+$.

B-C$_2$ ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 8.43 (s, 2 H, ArH_{up}), 8.37z (m, 2 H, QxH), 8.07 (s, 2 H, $QArH_{up}$), 8.04 (m, 2 H, QxH), 7.96 (m, 2 H, QxH), 7.75 (m, 2 H, QxH), 7.47 (s, 2 H, ArH_{down}, J = 9.12 Hz), 7.17 (s, 2 H, QxH), 7.06 (s, 2 H, ArH_{down}), 6.76 (dd, 2 H, QxH, J1 = 8.6, J2 = 2.0 Hz), 6.57 (m, 2 H, QxH), 5.86 (t, 1 H, J = 8.2 Hz), 5.69 (t, 2 H, J = 8.2 Hz), 5.58 (t, 2 H, J = 8.2 Hz), 2.40 (m, 2 H), 2.29 (m, 8 H), 2.16 (m, 4 H), 1.38 (m, 32 H), 1.25 (m, 12 H).

MALDI-TOF: m/z 1386.6750 calculated for $C_{87}H_{88}N_9O_8$ $[M+ NH_4]^+$, found 1386.6876 $[M+ NH_4]^+$.

3 Results and discussion

All cavitand baskets reported so far have a bridging connection between distal walls (AC mode, Figure 2a). We were interested in assessing whether the introduction of the basket bridge in a single step would have been suitable for the vicinal mode connection (AB mode, Figure 2b).

Out of the two synthetic routes to cavitand baskets, namely the introduction of functionalised quinoxaline walls followed by basket bridging (11a) and the single-step introduction of the two connected walls (11b) we opted for the latter. For this purpose, two bis-dichloroquinoxalines were prepared connected *via* ethylenedioxy and propyl chains, respectively (Schemes 1, 2).

Synthesis of bis-quinoxaline bridging moieties

1,2-bis((2,3-dichloroquinoxalin-6-yl)oxy)ethane building block **4** was synthesised *via* a four-step synthesis, with an overall yield of 61% (Scheme 1).

The first step involved the link of two 3-amino-2-nitro phenol moieties with ethylene di(*p*-toluenesulfonate) to give the diamino-dinitro intermediate **1**. The two nitro groups of **1** were reduced in the presence of $SnCl_2$, obtaining the tetraamino compound **2**. Due to the high propensity of the amino groups to undergo oxidation, **2** was directly condensed with oxalic acid to obtain compound **3**. Compound **3** was obtained in pure form directly as precipitate from water. The final step was the chlorination of **3** performed using $POCl_3$ in 1,2-dichloroethane to give the desired synthon **4**.

1,3-bis(2,3-dichloroquinoxalin-6-yl)propane **11** presenting a shorter all hydrocarbon C_3 tether required a longer, more elaborate synthetic sequence (Scheme 2). Both intermediates **5** and **6** were obtained by literature procedure (12).

Compound **5** was obtained in low yields since different isomers were formed during the nitration reaction, and several recrystallisation steps were necessary to isolate the desired isomer. The reduction of the two nitro groups on **5** required Ni Raney as catalyst and hydrazine as reducing agent, to give **6** in high yield. Subsequently, the amino groups of **6** were protected using acetic anhydride, followed by *in situ* nitration using KNO_3 as nitrating agent to give **7** [22]. Removal of the acetyl groups under basic conditions afforded compound **8** in good yield. The subsequent reduction of the two nitro groups was performed following the same conditions used in step b), except for the use of THF as solvent, selected to favour the solubility of **8**. Compound **9** was not isolated but directly converted into **10** *via* condensation with oxalic acid. The desired compound **11** was obtained in the last step by chlorination with $SOCl_2$ in 1,2-dichloroethane followed by precipitation and filtration. The overall yield of the synthetic procedure is 9%.

Synthesis of baskets A and B

AB and AC dibridged quinoxaline cavitands were prepared following a known procedure (21). All attempts to form the AB connected basket with compounds **4** and **11** failed. These reactions led to the exclusive formation of oligomeric material. A reasonable explanation of this failure can be attributed to the conformational flexibility of both di-bridging units, which disfavours the vicinal connection.

In contrast, bridging AC di-quinoxaline cavitand **AC-2QxCav** with **4** and **11** to give the corresponding baskets **A** and **B** turned out to be successful under the same conditions, as reported in Scheme 3. In both cases, the reaction leads to two different isomers, one characterised by a C_2 symmetry (**A-C_2** and **B-C_2**), and the other one by a C_s symmetry (**A-C_s** and **B-C_s**). Baskets **A-**

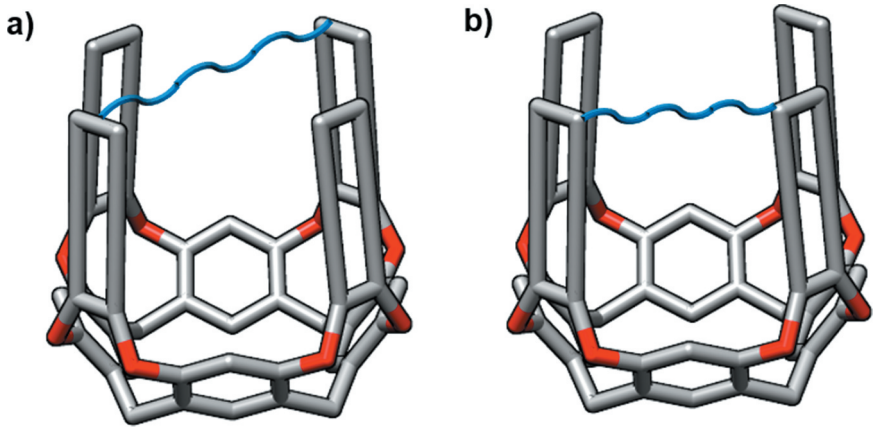
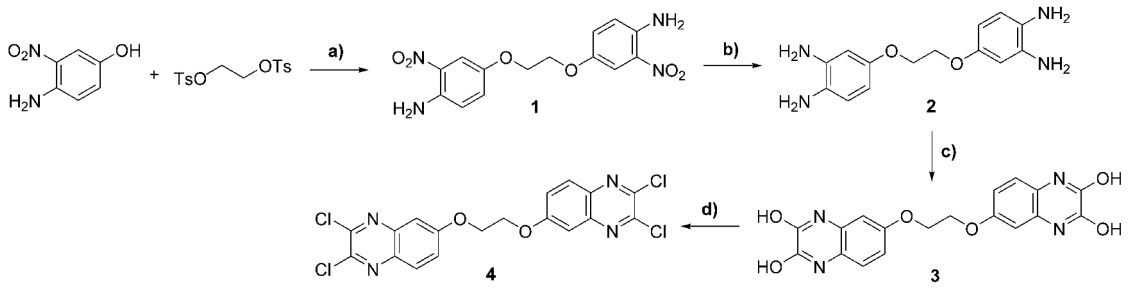
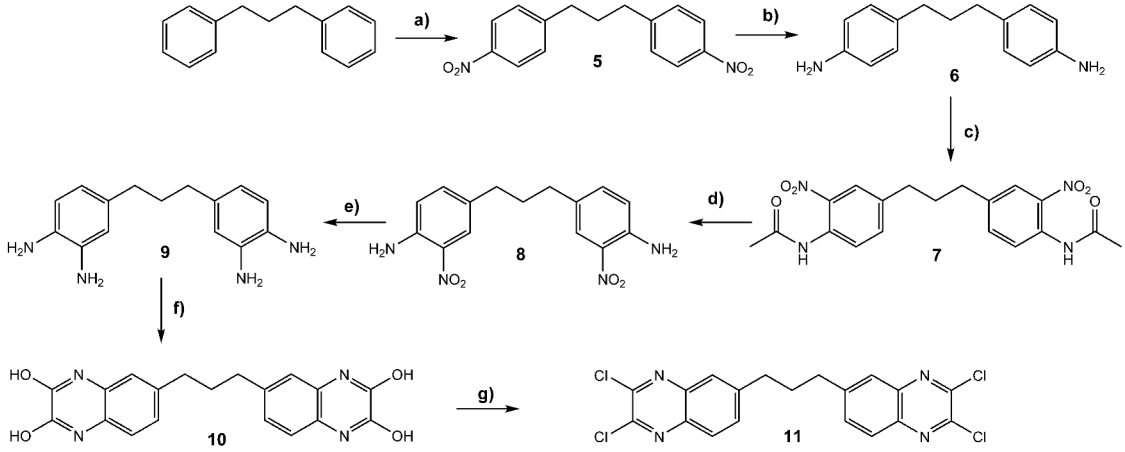


Figure 2. (a) AC mode and (b) AB mode bridging connection.



Scheme 1. Synthetic pathway to obtain the bridging moiety **4**. Conditions: a) ACN, K_2CO_3, 80°C, o.n., 69%; b) $SnCl_2$*H_2O, EtOH, 80°C, o.n., quantitative; c) oxalic acid, HCl 4 N, reflux, o.n., 92%; d) $POCl_3$, DCE, DMF, 80°C, o.n., 96%.



Scheme 2. Synthetic pathway to obtain bridging moiety **11**. Conditions: a) HNO_3/H_2SO_4 in acetic anhydride, 95°C, 1 h, 23%; b) Dioxane, hydrazine hydrated 80%, Ni Raney, 60°C, 1 h, 93%; c) Acetic anhydride, R. T., 1 h; *p*-Toluenesulfonic acid, KNO_3, R. T., o.n., 74%; d) EtOH, H_2O, NaOH, 80°C, 5 h, 90%; e) THF, hydrazine hydrated 80%, Ni Raney, 60°C, 30 min, not isolated; f) Oxalic acid, 100°C, o.n., 81%; g) DCE, DMF, $SOCl_2$, 80°C, o.n., 75%.

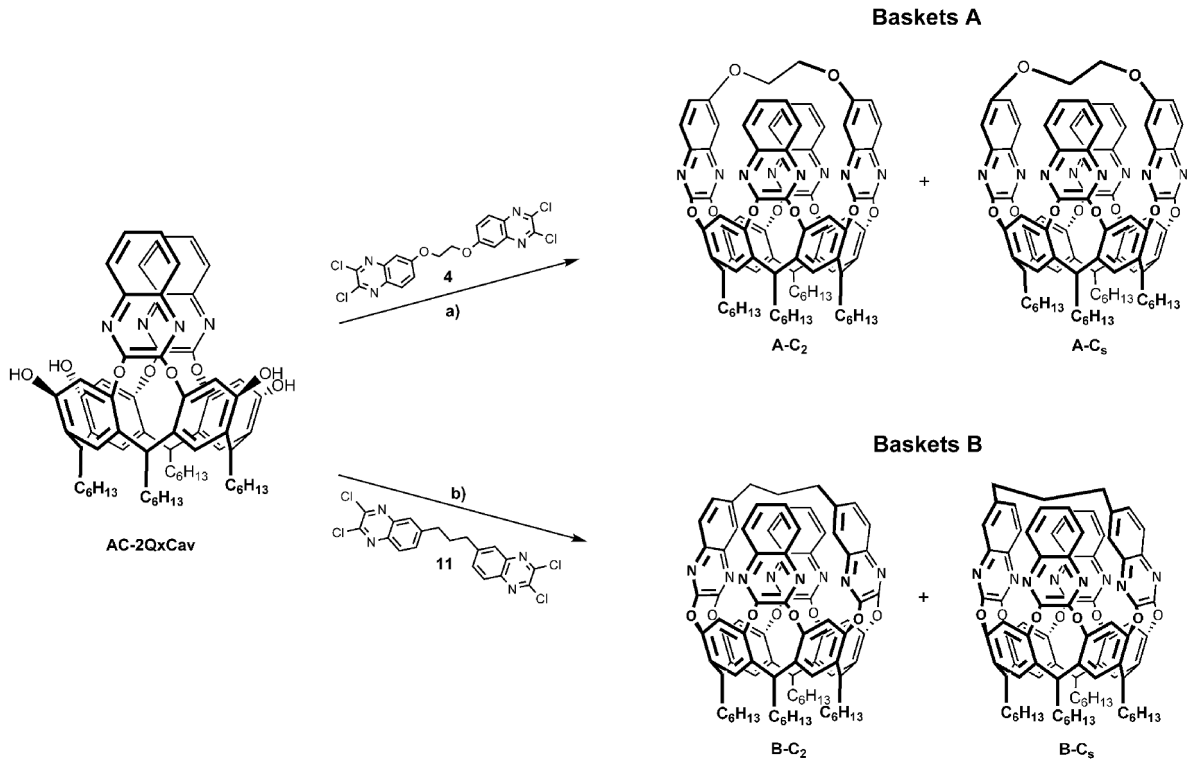
C_2 and **B-C_2** present one C_2 axis, with the quinoxaline linker crossing the cavity. Instead, baskets **A-C_s** and **B-C_s** present only a σ plane, since the linker moiety is on the same side of the scaffold. In both cases, the two isomers form in a ratio of **C_s/C_2** ≈ 2.5:1, highlighting that the C_s symmetry is favoured. In all cases, the yields are quite low, being oligomers the major components of the crude. Isolation of the baskets required in both cases extensive column chromatography and several preparative TLCs.

The different symmetry of the two isomers allowed their identification through ^{1}H NMR. In the case of basket **A-C_s**, the NMR assignment was confirmed by single-crystal X-ray diffraction analysis.

^{1}H NMR analyses

The different symmetry of the two cavitands is reflected in the number of resonances of the methine protons of the resorcinarene skeleton in the ^{1}H NMR spectrum. Cavitand **A-C_2** presents two methine resonances at 5.6–5.7 ppm (pink dot – Figure 1 upper part) in 1:1 ratio, in agreement with the symmetry of its structure, while **A-C_s** shows three resonances in 1:1:2 ratio (pink dot – Figure 3 lower part) in the same ppm range. The chemical shift of these resonances is diagnostic of the vase conformation for both cavitands in solution, as confirmed in the solid state for **A-C_s** by its crystal structure.

In both isomers, the ethylenedioxy bridge, indicated by light blue dots, appears as a pair of multiplets between 3.3 and 3.6 ppm (Figure 3). Its multiplicity and broadening are caused by the protons slow motion on the NMR timescale, which allows distinguishing between proton pointing inward or outward to the cavity. The quinoxaline resonances are between 6.0 and 7.5 ppm for the linked ones, and 7.5–8.0 ppm for the others. The resorcinarene aromatic protons are split into four



Scheme 3. Synthesis of the four basket cavitands. Conditions: a) DMF, K_2CO_3, 80°C, o.n., **A-C$_2$** 5%, **A-C$_s$** 12%. b) DMF, K_2CO_3, 80°C, o.n., **B-C$_2$** 2%, **B-C$_s$** 5%.

singlets, as expected by symmetry considerations. Both isomers are the result of a first attack of the dimeric compound **4** on **AC-2QxCav**, followed by reaction of the remaining portion either in a parallel or antiparallel mode on the remaining OHs. The formation of the C_s isomer is more favoured, as testified by the reaction yield.

Crystal structure of A-C$_s$

In the case of cavitand **A-C$_s$**, suitable crystals for X-Ray diffraction analysis were grown from DMSO. The obtained molecular structure is shown in Figure 4. Isomer **A-C$_s$** crystallises in the space group *C2/c* and the asymmetric unit comprises half of the molecule of the cavitand and two half molecules of DMSO. The whole molecules are generated by rotation around a 2-fold axis. As a result, the ethylenedioxy bridge is disordered over two equivalent positions, as are the two DMSO molecules which are located in the cavity and among the four alkyl feet. The quinoxaline walls bridged by the ethylenedioxy moiety are bent towards the inside of the cavity. This is evidenced by the C19B···C20B^i (and the equivalent C20B···C19B^i) distances of 4.714(5) Å (i = 1-x, y, 1/2-z) and by an inclination angle of 67.60(8)°. This is the angle between the mean planes passing through the walls and the mean plane passing through the eight O1/O2 oxygen atoms. By comparison, the corresponding values for the other pair of quinoxaline walls are 10.377(4) Å for the C19A···C20A^i distance and 89.49(7)° for the inclination angle. Due to the geometry of the ethylenedioxy bridge which leans more towards one of the two lateral walls, the opening of the cavity is asymmetric, as clearly shown by the space filling view in Figure 2C,D.

Synthesis of baskets B-C$_s$ and B-C$_2$

The formation of basket **B** was performed similarly to basket **A**, through a bridging reaction on **AC-2QxCav** in presence of bis-dichloroquinoxaline **11**. Also, in this case, two isomers **B-C$_s$** and **B-C$_2$** were formed and separated via preparative TLC. As in the previous case, the distinction between the two isomers was performed through ^{1}H NMR. In the case of basket B, the presence of a shorter link between the two quinoxaline moieties led to a reduction of the yield reaction compared to basket A. The main products are oligomeric species, present in the final crude and insoluble residue. It is interesting to note that, like basket A, the major product is the C_s isomer. Working under high dilution conditions did not affect the final yields.

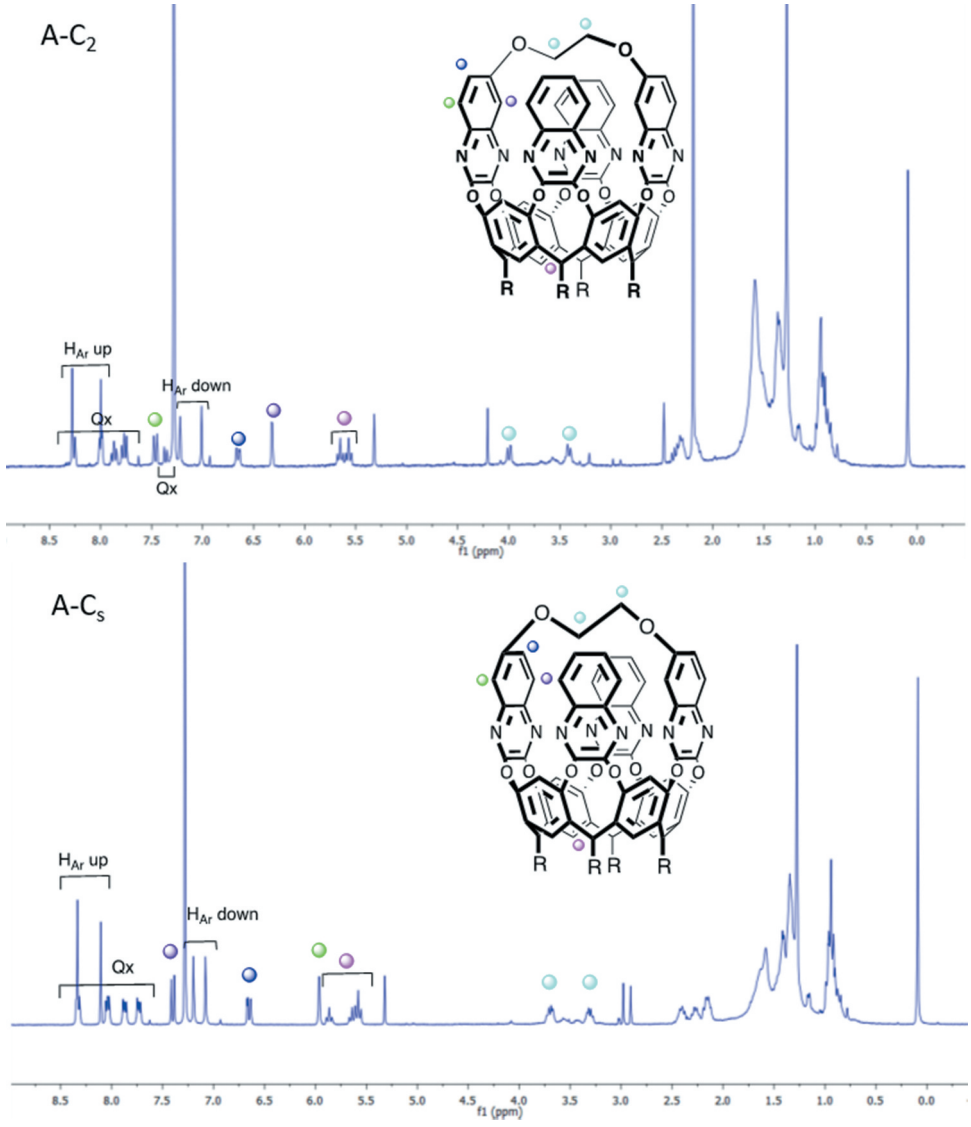


Figure 3. ^{1}H NMR spectra of compounds **A-C$_2$** and **A-C$_s$** in $CDCl_3$, 25°C, 400 MHz. Diagnostic peaks are highlighted with coloured dots.

^{1}H NMR analyses

Similar considerations for cavitands A can be applied to cavitands B, namely the different symmetry of the two isomers is reflected in the number of resonances of the methine protons of the resorcinarene skeleton in the ^{1}H NMR spectrum. Basket **B-C$_2$** was obtained in only 2% yield (0.7 mg) so the low S/N ratio of the ^{1}H NMR spectrum (Supplemental material, Figure S1 upper part), made the aromatic peak assignment difficult. In the spectrum reported in Figure S1 – upper part, it is possible to clearly distinguish two methine resonances in the 5.6–5.7 ppm range (green dots) in about 1:1 ratio, in agreement with the symmetry of the structure. The low field shift of the methine protons confirms that the cavitand is in a vase conformation. The quinoxaline resonances can be seen between 6.5 and 8.3 ppm, while the bridging unit resonances are between 2.0 and 2.5 ppm, together with the protons of the cavitand chain.

As for isomer **B-C$_s$**, the ^{1}H NMR shows for the methine protons three resonances around 5.9, 5.7 and 5.6 ppm in about 1:1:2 ratio (green dot – Supplemental material, Figure S1 lower part), respectively. In this case, the chemical shift of these resonances is also diagnostic of the vase conformation of the cavitand in solution. The quinoxaline resonances can be seen between 7.7 and 8.3 ppm, while the bridging unit resonances are between 2.0 and 2.5 ppm, together with some protons of the cavitand chain.

Conclusions

Four new quinoxaline-based cavitands, namely **A-C$_2$**, **A-C$_s$**, **B-C$_2$**, and **B-C$_s$**, possessing a narrow and partially rigid cavity have been designed and synthesised. The cavitands

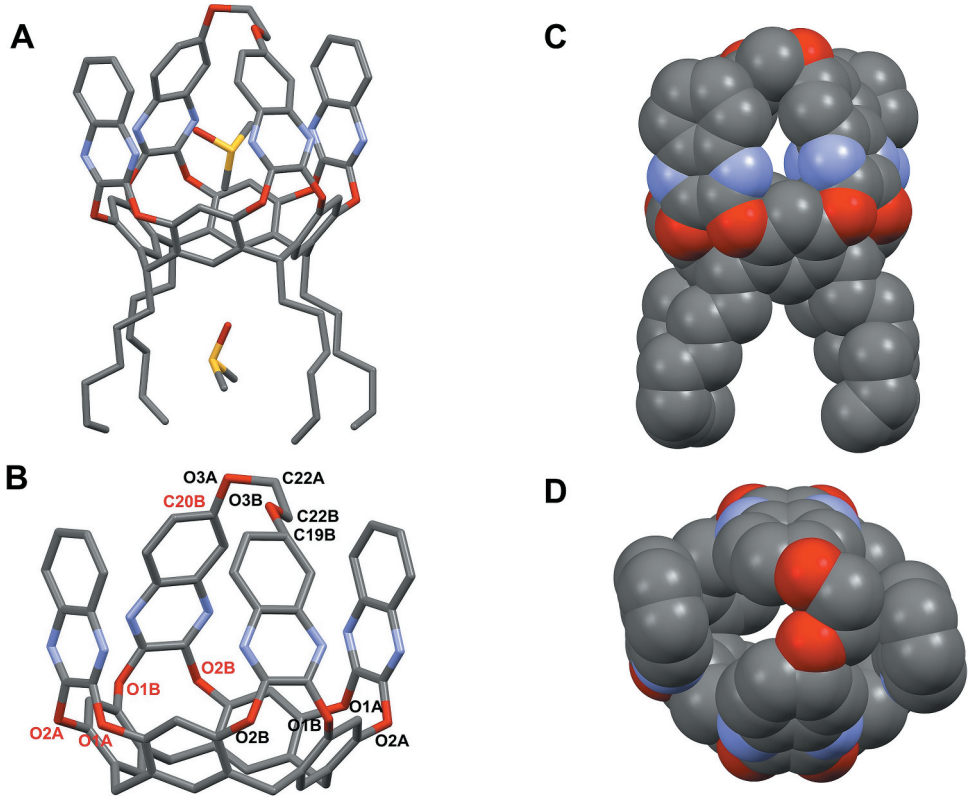


Figure 4. Molecular structure of cavitand **A-C$_s$** (A). Detail of the cavity with partial labelling scheme (B). H atoms and disorder have been omitted for clarity. Labels coloured in red refers to atoms generated by symmetry (1-x, y, 1/2-z). (C) Side and (D) top view of the cavity in space filling mode. H atoms, disorder and solvent molecules have been omitted for clarity. Colour code: Gray: carbon; red: oxygen; blue: nitrogen.

were obtained through a bridging reaction on an AC diquinoxaline bridged cavitand, **AC-2QxCav**. Two different bridging units were used, an ethylenedioxy bis-dichloroquinoxaline synthon, obtaining baskets **A**, and a propane bis-dichloroquinoxaline unit, presenting a smaller linker between the two quinoxaline moieties, that led to basket **B**. In both cases, two isomers were obtained, differing in the symmetry of the cavity. In the isomers **A-C$_2$** and **B-C$_2$**, the linker unit crosses the cavity providing a C_2 symmetry, while in the isomers **A-C$_s$** and **B-C$_s$**, the linker is on the same side of the resorcinarene scaffold affording a C_s symmetry. The structure of the isomers was assigned *via* ^{1}H NMR and, in the case of **A-C$_s$**, it was confirmed through X-Ray diffraction analysis. Both reactions showed a preference for the formation of the C_s isomer, probably due to the preferred orientation of the linker in solution. The slightly higher yields obtained for basket **A** with respect to basket **B** highlight that the longer linker between the two quinoxaline units allows a better insertion of the bridging unit. However, reduction of the length of the linker does not lead to AB bridging. These baskets will be tested as selective preconcentration units to investigate the role of partial cavity rigidification on the uptake/release of VOCs in air.

Acknowledgments

This work has benefitted from the equipment and framework of the COMP-HUB Initiative, funded by the 'Departments of Excellence' program of the Italian Ministry for Education, University and Research (MIUR, 2018-2022). The authors acknowledge MIUR through the PRIN project 20179BJNA2 for financial support. The authors acknowledge the Centro Interdipartimentale di Misure "G. Casnati" of the University of Parma for the use of NMR facilities and Prof. D. Bonifazi of the University of Vienna for MALDI-TOF analyses. Chiesi Farmaceutici SpA is acknowledged for its support with the D8Venture X-ray equipment.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Ministero dell'Istruzione, dell'Università e della Ricerca [PRIN project 20179BJNA2].

ORCID

Alessia Favero http://orcid.org/0000-0002-1106-9818
Andrea Rozzi http://orcid.org/0000-0001-7674-264X
Chiara Massera http://orcid.org/0000-0003-0230-1707
Alessandro Pedrini http://orcid.org/0000-0003-3949-7563
Roberta Pinalli http://orcid.org/0000-0002-0000-8980
Enrico Dalcanale http://orcid.org/0000-0001-6964-788X

References

[1] Moran JR, Ericson JL, Dalcanale E, et al. Vases and kites as cavitands. J. Am. Chem. Soc. **1991**;113(15):5707.
[2] Pinalli R, Pedrini A, Dalcanale E. Chapter 5. In: George W. Gokel, Jerry L.A, editors. Comprehensive supramol. Chem. II. Vol. 3. Oxford: Elsevier; 2017. p. 87.
[3] Gropp C, Quigley BL, Diederich F. Molecular recognition with resorcin[4]arene cavitands: switching, halogen-bonded capsules, and enantioselective complexation. J. Am. Chem. Soc. **2018**;140(8):2705.
[4] Hooley RJ, Rebek Jr J. Chemistry and catalysis in functional cavitands. Chem & Biol. **2009**;16(3):255.
[5] Milic JV, Diederich F. The quest for molecular grippers: photo-electric control of molecular gripping machinery. Chem. Eur. J. **2019**;25(36):8440.
[6] Vincenti M, Pelizzetti E, Dalcanale E, et al. Molecular recognition in the gas phase. Pure Appl. Chem. **1993**;65(7):1507.
[7] Vincenti M, Dalcanale E. Host–guest complexation in the gas phase. Investigation of the mechanism of interaction between cavitands and neutral guest molecules. J Chem Soc Perkin Trans 2. **1995**;6:1069. DOI:10.1039/P29950001069
[8] Soncini P, Bonsignore S, Dalcanale E, et al. Cavitands as versatile molecular receptors. J. Org. Chem. **1992**;57(17):4608.
[9] Giannetto M, Pedrini A, Fortunati S, et al. Sensing of halogenated aromatic hydrocarbons in water with a cavitand coated piezoelectric device. Sensors and Actuators B: Chemical. **2018**;276:340.
[10] Condorelli GG, Motta A, Favazza M, et al. Grafting cavitands on the Si(100) surface. Langmuir. **2006**;22(26):11126.
[11] Condorelli GG, Motta M, Favazza M, et al. Molecular recognition of halogen-tagged aromatic VOCs at the air–silicon interface. Chem Commun. **2010**;46(2):288.
[12] Dalcanale E, Hartmann J. Selective detection of organic compounds by means of cavitand-coated QCM transducers. Sens Actuators B. **1995**;24(1–3):39.
[13] Zampolli S, Betti P, Elmi I, et al. A supramolecular approach to sub-ppb aromatic VOC detection in air. Chem. Commun. **2007**;27:2790. DOI:10.1039/b703747c
[14] Clement P, Korom S, Struzzi C, et al. Deep cavitand self-assembled on Au NPs-MWCNT as highly sensitive benzene sensing interface. Adv. Funct. Mater. **2015**;25(26):4011.
[15] Rudkevich D, Hilmersson G, Rebek J Jr. Intramolecular hydrogen bonding controls the exchange rates of guests in a cavitand. J Am Chem Soc. **1997**;119(41):9911.
[16] Rahman F-U, Li YS, Petsalakis ID, et al. Recognition with metallo cavitands. Proc Natl Acad Sci USA. **2019**;116(36):17648.
[17] Trzcinski JW, Pinalli R, Riboni N, et al. In search of the ultimate benzene sensor: the EtQxBox solution. ACS Sens. **2017**;2(4):590.
[18] Hornung J, Fankhaser D, Shirtcliff LD, et al. Cycloalkane and alicyclic heterocycle complexation by new switchable resorcin[4]arene-based container molecules: NMR and ITC binding studies. Chem. Eur. J. **2011**;17(44):12362.
[19] Fankhauser D, Kolarski D, Gruning WR, et al. Resorcin[4]arene-based molecular baskets and water-soluble container molecules: synthesis and 1 H NMR host-guest complexation studies. Eur. J. Org. Chem. **2014**;2014(17):3575.
[20] Nagasawa HT, Gutmann HR. Notes—preparation and properties of S-acetyl-N-benzoylcysteamine. J. Org. Chem. **1958**;23(3):487.
[21] Castro PP, Zhao G, Masangkay GA, et al. Quinoxaline excision: a novel approach to tri- and diquinoxaline cavitands. Org. Lett. **2004**;6(3):333.
[22] Chong JH, MacLachlan MJ. Robust non-interpenetrating coordination frameworks from new shape-persistent building blocks. Inorg. Chem. **2006**;45(4):1442.