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COMMUNICATION

Tuning the conformational flexibility of quinoxaline cavitands for complexation at the gas-solid interface

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Andrea Rozzi[a], Alessandro Pedrini[a], Roberta Pinalli[a], Chiara Massera,[a] Ivan Elmi[b], Stefano Zampolli[b] and Enrico Dalcanale,*[a]

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The selectivity and efficiency of benzene and toluene uptake at the gas-solid interface by quinoxaline cavitands is strongly enhanced by partial rigidification of the receptor cavity and immobilization of the cavitand onto silica gel particles.

Molecular recognition at the gas-solid interface represents a powerful tool for imparting selectivity to analytical devices and chemical sensors.[1] The key requirements for an effective receptor at gas-solid interface are the presence of a preorganized cavity complementary with the guests' shape and size, and the type and number of weak interactions to be implemented in function to the target analytes.[1]

Quinoxaline cavitands[2] are ideally suited for this scope since they present a rigid molecular size cavity, capable of binding neutral guests in the gas phase,[3] in solution,[4] at the gas-solid[5] and gas-liquid interfaces.[6] Furthermore, they have the unique ability to switch between two well defined conformations, a compact one called vase and an extended one named kite.[7] The interconversion between the two relies on the conformational mobility of the quinoxaline walls, which can be controlled in solution by external stimuli like temperature and solvent,[6] metal coordination[8] or pH.[9] Only in the vase form the cavitand exhibits a preorganized cavity capable of binding simple aromatic compounds. In the solid state the interconversion is more difficult: it has been observed only in polymeric matrices by exposing the material to acid vapors.[10] Temperature-driven vase-kite switching in the solid state does not occur, even if temperature determines the amount of fluttering of the cavity,[11] which is amplified at higher temperatures. At the gas-solid interface the driving force for guest uptake is the formation of CH-π interactions among the guest and the aromatic rings delimiting the cavity. These interactions are weakened by the thermal motion of the quinoxaline walls. Therefore, the conformational flexibility of the quinoxaline walls in the solid state is the key molecular parameter to tune the strength of cavitand complexation at the gas-solid interface. An effective way to eliminate the conformational flexibility of the quinoxaline walls is to connect them at the upper rim with suitable bridges. Partial rigidification of the lateral walls in cavitands has been already reported by Diederich[4b] and Rebek,[12] while Gibb[13] reported the preparation of larger, fully blocked deep-cavity cavitands. Following this reasoning, we designed and prepared **MeQxBox**[14] and **EtQxBox**[15] (Chart 1), in which the four quinoxaline walls are connected by four methylenedioxy and ethylenedioxy units, respectively. In the resulting fixed cavities, the CH-π interactions among the guest

[a] Department of Chemistry, Life Science and Environmental Sustainability and INSTM UdR Parma, University of Parma Parco Area delle Scienze 17/A 43124 Parma, Italy.
[b] CNR-IMM Bologna, Via P. Gobetti 101, 40129 Bologna, Italy.

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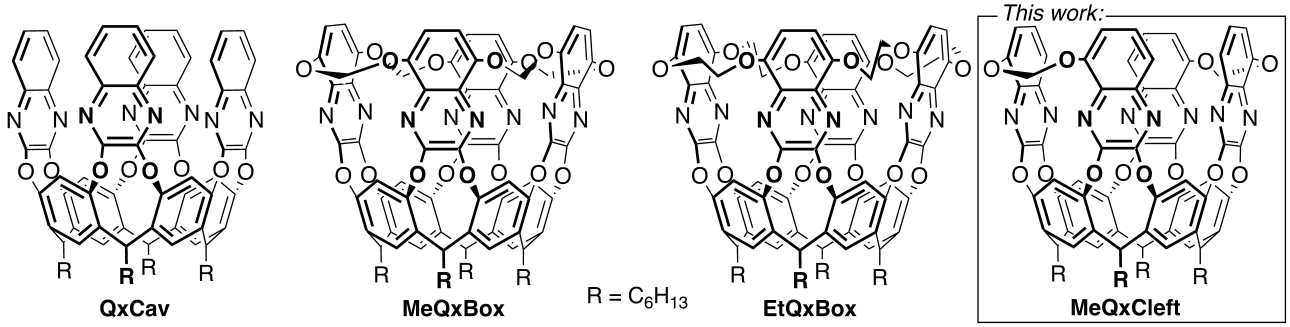

Chart 1. Structure of quinoxaline-based cavitands for BTEX complexation at the gas-solid interface.

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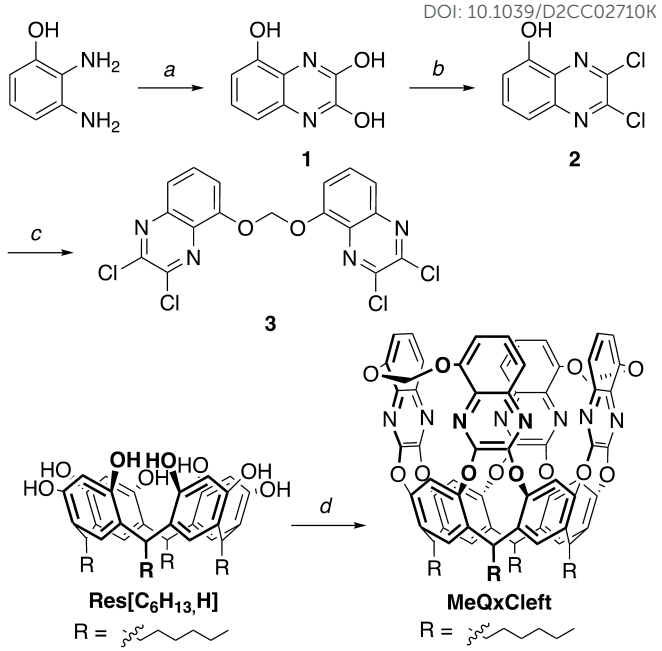
and the cavity walls are strengthened, leading to a very efficient and selective uptake of aromatic volatile organic compounds in air.[5a] The benzene, toluene, ethylbenzene and xylene (BTEX) enrichment properties of the rigid **EtQxBox** have been exploited in environmental sensing by embedding it as preconcentrator in a stand-alone benzene sensor.[15] Alternatively, the even more rigid **MeQxBox** has shown to be an highly selective and sensitive solid-phase microextraction (SPME) coating for BTEX detection.[14] The BTEX inclusion in the two cavitands is so tight in the solid state to permit the complete guests' release only above 220°C, compared to the 100°C needed for the parent **QxCav**.[16] These results prompted us to design and prepare partially bridged cavitand **MeQxCleft** (Chart 1), in which the quinoxaline walls are bridged two by two. Furthermore, a lower rim functionalized version of the cavitand having terminal triethoxysilyl groups was synthetized and grafted on the surface of silica to maximize cavity access by the analytes. Finally, the BTEX desorption curves of the new preconcentrator were tested in comparison with those of **QxCav**.

Cavitand Synthesis. **MeQxCleft** was prepared following a convergent synthetic pathway (Scheme 1). The *ad hoc* designed bis-quinoxaline derivative **3** was synthesized and bridged twice on a proper resorcinarene scaffold to directly introduce the alternate methylene connection motif. A similar approach has been effectively applied to the introduction of intra-walls connection on analogous cavitands starting from the partially bridged AC-tetrol.[17] In particular, tetrachloro-bis-quinoxaline **3** was prepared in three steps starting from commercially available 2,3-diaminophenol. This synthon was then used in the microwave-assisted bridging reaction of hexyl-footed resorcinarene **Res[C_6H_{13}, H]**,[18] under high dilution and basic conditions, to afford cavitand **MeQxCleft** (Figures S12-S15 ESI).

Crystal structures. The crystal structures of complexes **benzene@MeQxCleft** and **toluene@MeQxCleft** were determined *via* X-ray diffraction data on single crystals obtained by slow evaporation of the cavitand from benzene and toluene, respectively. Both guests are fully included in the cavity. The asymmetric unit of **benzene@MeQxCleft** consists of one cavitand and three benzene molecules, one of which is included inside the cavity, one is located among the alkyl legs, and one is found in the lattice (Figure S26). Benzene is stabilized inside the cavity by two C–H···π interactions with the lower aromatic rings of the cavitand and by two bifurcated weak C–H···N interactions involving the nitrogen atoms of non-bridged, adjacent quinoxaline moieties (blue dotted lines Figure 1, see ESI for details).



Scheme 1. Synthesis of **MeQxCleft**: a) oxalic acid, HCl 4 M, 100 °C, 12 h, 96%; b) $POCl_3$, DMF dry, 80 °C, 12 h, 69%; c) diiodomethane, K_2CO_3, CH_3CN, 80 °C, 3 h, 28%; d) **3**, K_2CO_3, DMF dry, 80 °C (MW), 2.5 h, 15%.

The asymmetric unit of **toluene@MeQxCleft** consists of one cavitand and two toluene molecules, one of which is included inside the cavity, while the other is located in the lattice (Figure S27). The toluene solvent inside the cavity is disordered over two positions, which differ for the orientation of the methyl group which is either pointing towards the two non-bridged, adjacent quinoxaline moieties A and D (C7S) or B and C (C7V) (Figure 2 and ESI). As in the case of the benzene complex, the interactions stabilizing the inclusion of toluene inside the cavity comprise two C–H···π interactions with the lower aromatic rings of the cavitand and four C–H···N interactions involving the nitrogen atoms of non-bridged, adjacent quinoxaline moieties. Two weak C–H···π interactions are also present between the methyl group of toluene and the upper aromatic rings of the cavitand (blue dotted lines Figure 2, see ESI for details).

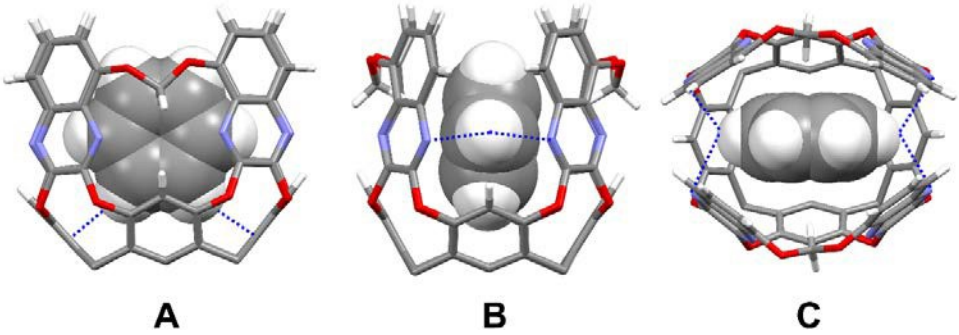


Figure 1. Side (A, B) and top (C) view of the molecular structure of **benzene@MeQxCleft**. The alkyl legs and the lattice solvent molecules have been omitted for clarity. The included guest is shown in space filling mode. The host-guest interactions are represented as blue dotted lines.

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Cavitand grafting on silica. To maximize the amount of cavities accessible to the analytes in the solid phase **MeQxCleft** has been covalently grafted on the surface of silica microspheres (180-250 µm particle size). To this purpose, silylated cavitand **MeQxCleft-Si** was prepared in two steps, adapting a previously reported procedure (Scheme 2).[19] The bridging reaction of decenyl-footed resorcinare **Res[$C_{10}H_{19}$, H]**[20] with synthon **3**, afforded **MeQxCleft-DB** in 27% yield. To introduce triethoxysilyl groups at the lower rim, **MeQxCleft-DB** underwent hydrosilylation[21] using an excess of triethoxysilane in presence of Karstedt's catalyst. Under these conditions internal isomerization of the terminal olefins also occurs as side reaction, and a mixture of partially silylated cavitands was obtained. In particular, mono- di- and tri-triethoxysilyl cavitands were identified, together with a limited amount of the unreacted starting material. An average of 1.2 triethoxysilyl units per cavitand was estimated by ^{1}H NMR signals integration (Figures S20). The surface decoration was performed by reacting the as obtained **MeQxCleft-Si** mixture in boiling toluene with pre-meshed silica (180-250 µm) affording **MeQxCleft@SiO_2**. The weight percentage of organic layer deposited was quantified to be 15.6% by TGA (Figure S27b). The initial 2.3% loss observed in the TGA thermogram is ascribable to the release of cavity included and surface physisorbed toluene, which has been used as solvent in the silica grafting procedure.

BTEX desorption analyses. To evaluate the thermal desorption profiles of the different cavitand preconcentrators, a modified version of the commercial Pyxis-BTEX mini gas-chromatograph[22] was used. The state of the art of the preconcentrator in Pyxis is a MEMS filled with pure **QxCav** with the proper mesh. Each cavitand preparation was packed into a MEMS preconcentration cartridge compatible with the Pyxis-BTEX devices. Compared to the standard fluidic circuit of the mini gas-chromatograph,[16] the MEMS GC separation column was bypassed by a short, heated polyether ether ketone (PEEK) tube, to eliminate the gas-chromatographic retention of the single analytes desorbed from the MEMS pre-concentrator. As opposed to the fast injections performed for the GC analyses, where the preconcentrator is heated to the desorption temperature within less than 10 seconds to provide a possibly sharp injection peak, in this case the preconcentrator is heated with a controlled temperature ramp from 30°C to 170°C in 3 minutes. This allows to determine the temperatures where the maximum desorption for each analyte occurs, together with the absorption efficiency which can be estimated by comparing the area of the desorption peaks. Figure 3 reports the desorption curves of the three following preconcentrators toward BTEX: pure **QxCav**,[16] **QxCav@SiO_2**[22] and **MeQxCleft@SiO_2**. Each analyte was sampled separately. A flow of 250 sccm of the sampled air containing 5 ppb of each analyte was pumped into the preconcentrators for 300 seconds at 30°C. At least 12 measurements were collected for each analysis.

The comparison of the three desorption curves shows the effect of surface grafting and cavity rigidification on the BTEX uptake. The exposure of all cavities to the gas phase enhances the efficiency of the uptake (cfr curves a and b in Figure 3), considering that a larger amount of cavitand is loaded in the pure **QxCav** preconcentrator (50 mg of pure **QxCav** versus ≈ 15 mg of **QxCav** coated on silica, based on TGA analysis Figure S27a). On the contrary, the desorption temperatures are similar in the two cases for all four analytes. The cavity rigidification has a much larger effect on both selectivity and efficiency of BTEX uptake, and on their release temperature. Since the amount of

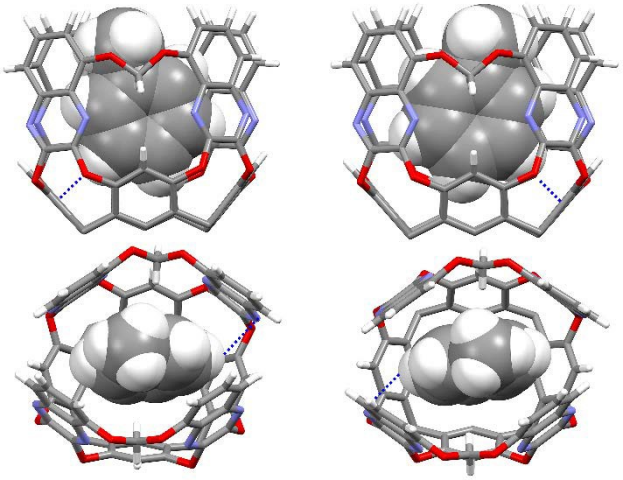
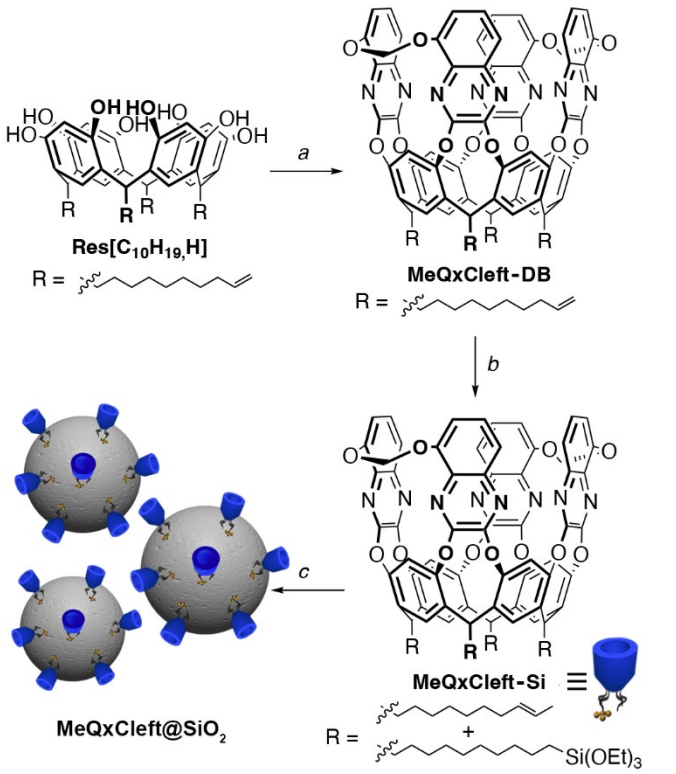


Figure 2. Side and top view of the molecular structure of **toluene@MeQxCleft**, with the two different orientations of the toluene guest displayed in the left and right part of the figure, respectively. The alkyl legs and the lattice solvent molecules have been omitted for clarity. The included guest is shown in space filling mode. The host-guest interactions are represented as blue dotted lines.



Scheme 2. Synthesis of **MeQxCleft@SiO_2**: a) **3**, K_2CO_3, DMF dry, 80 °C, 12 h.; b) triethoxysilane, Karstedt's catalyst, RT, 2 d; c) toluene, 110°C, 24 h.

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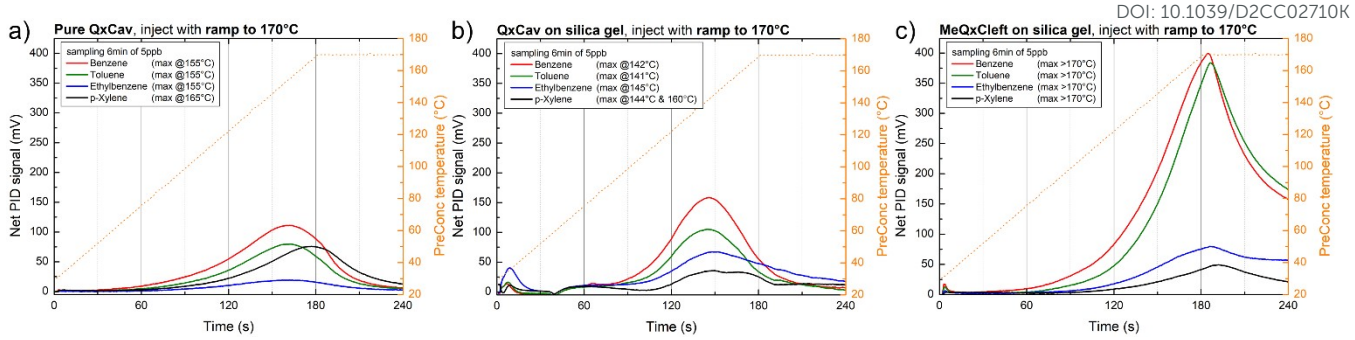

Figure 3. Desorption curves of the three preconcentrators toward 5ppb of BTEX in air: a) pure **QxCav** powder; b) **QxCav@SiO$_2$**; c) **MeQxCleft@SiO$_2$**

cavitand coated on silica in **MeQxCleft@SiO$_2$** and **QxCav@SiO$_2$** is equivalent (cfr the two TGA in Figure S27), the comparison of curves b and c in Figure 3 underline the importance of cavity rigidification on BTEX complexation. The desorption temperature is raised by over 30°C for all analytes (Table S2), as indication of the tighter binding of **MeQxCleft** with respect to **QxCav**. The complexation is strongly enhanced only for benzene and toluene, thus boosting the preconcentrator selectivity. The origin of this bias can be traced in the reduced size of the cavity mouth generated by the presence of the methylendioxy bridges,[14] that facilitates the uptake of the smaller analytes with respect to the larger ones.

In conclusion, the modulation of the conformational flexibility in quinoxaline cavitands coupled with their grafting on silica particles leads to a preconcentrator for BTEX presenting enhanced uptake sensitivity and selectivity as well as higher desorption temperatures. The reported results highlight the importance of preorganization in controlling the complexation properties at the gas-solid interface.

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There are no conflicts to declare.

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