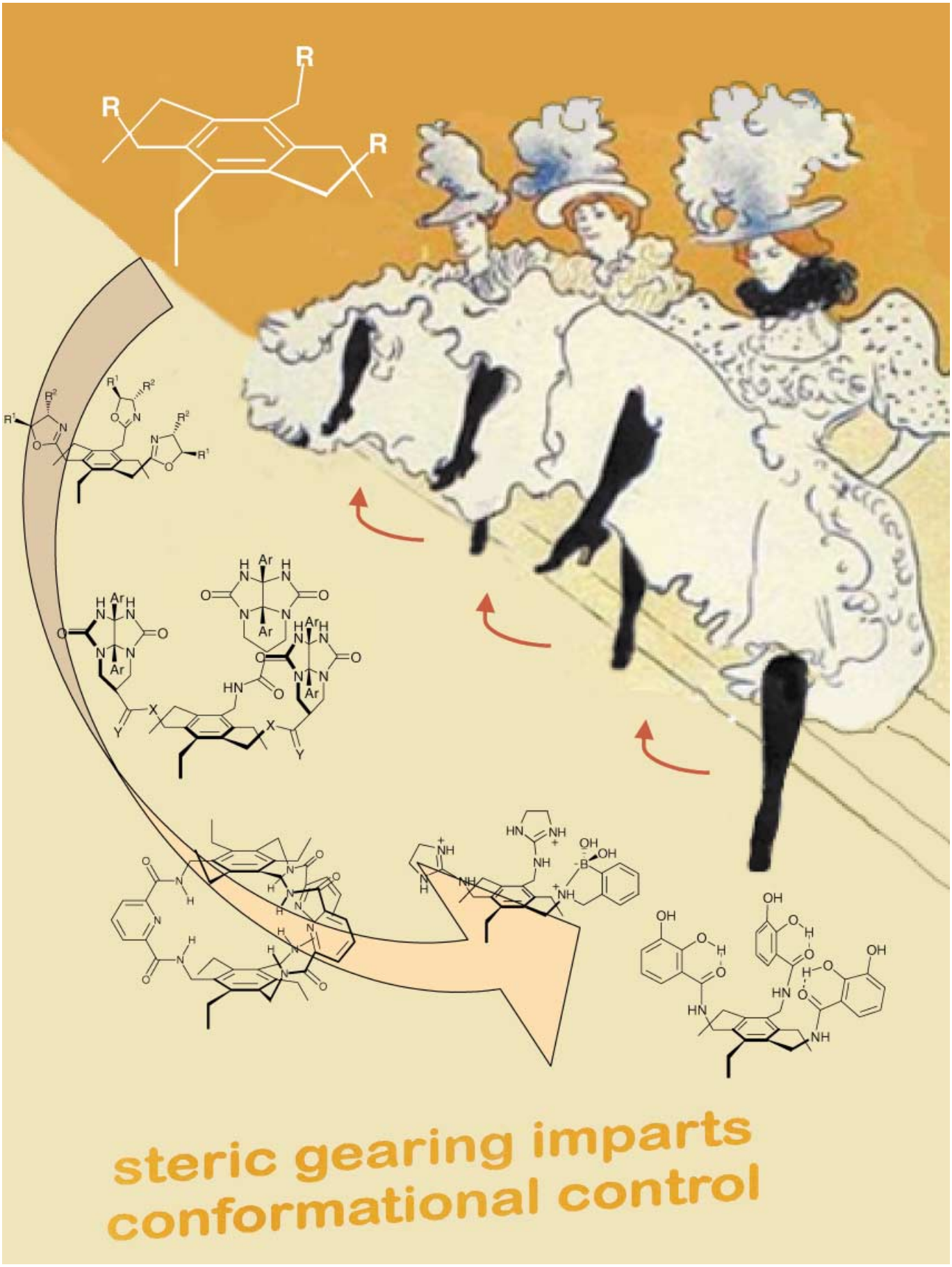

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1,3,5-2,4,6-Functionalized, Facially Segregated Benzenes—Exploitation of Sterically Predisposed Systems in Supramolecular Chemistry

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Abstract: In the present article, we introduce the unique steric features of 1,3,5-substituted triethylbenzenes as a design principle for host molecules and supramolecular systems. Due to steric gearing, all three functional substituents are disposed on the same side of the phenyl plane. The use of this benzene scaffold has lead to the synthesis of various receptor molecules for a wide range of different guest species. Furthermore, the facially segregated systems can be used as building blocks with a controlled conformation in the synthesis of macrocycles or self-assembled supramolecular systems.

Keywords: host–guest systems · ligand design · steric gearing · preorganization · receptors

Introduction

A fundamental design principle in the construction of supramolecular assemblies is the alignment of functional groups on a respective molecular platform to achieve complementarity binding interactions towards a targeted structure.[1] In regard to host–guest chemistry, the chemical and steric features given by a guest molecule have to be matched by a sufficiently predisposed host. In receptor molecules, binding groups are commonly arranged with a distinct conformation controlled by the covalent architecture of the receptor. The most common approach is the use of macrocycles and polyfused rings. In particular, structures that possess a special desired topology, such as calixarenes,[2] fused (aromatic) rings,[3] steroids,[4] or smaller molecules like glycolurils[5] and *cis*,*cis*-1,3,5-substituted cyclohexanes of the Kemp's acid type,[6] are frequently applied as platforms for supramolecular systems. To introduce the required amount of conformational rigidity, some additional covalent synthesis is still often necessary even for these scaffolds.[7] In host molecules based on coordination compounds, the desired conformational control is achieved only upon complexation of an additional component, usually a metal cation.[8]

In order to avoid extensive synthetic effort, that is more or less required for the examples cited above, it would be favorable to exploit "steric gearing". Here, certain subunits within a molecule obtain and retain a preorganized geometry due to adoption of a thermodynamically favored conformation where steric interactions are minimized.[9] The use of spiropyran receptors with defined conformations for metal complexation is a novel example taking advantage of this principle. The tris(spiro) compound **A** turns out to be a highly selective ligand for Li^+ cations in its **A-ax** conformation. This is the thermodynamically preferred conformation due to 1,3-axial interactions, with all three furane oxygens in axial positions (Figure 1).[10] We have designed the sterically geared

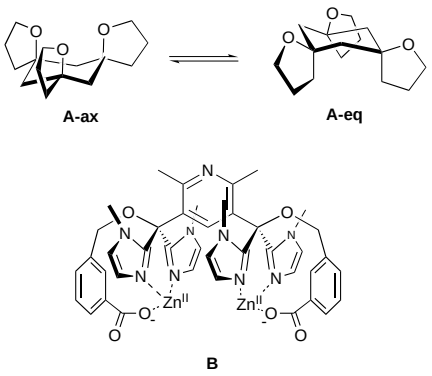

Figure 1. Receptor molecules (**A**, **B**), preorganized due to steric gearing.

bis-zinc receptor **B** for the hydrolysis of phosphoesters. The methyl groups of the pyridine and imidazole rings "mesh" in such a manner to create a rigid preorganized structure without using fused rings.[11]

The Benzene Platform

The benzene ring is useful as a small, rigid platform for receptor systems. However, in the easy accessible 1,3,5-substituted benzene[12] (**C**) or mesitylene-based host molecules (**D**),[13] a conformational control of the binding groups is essentially non-existent (Figure 2).

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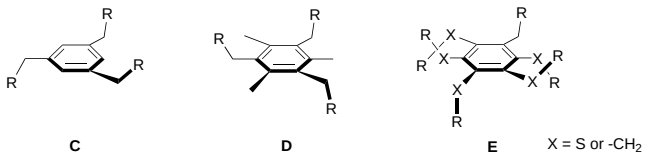


Figure 2. Benzene (**C**), mesitylene (**D**) and hexasubstituted benzene systems (**E**).

In 1976, McNicol discovered the preorganization of the functional groups in hexasubstituted benzene derivatives (**E**).[14] In these systems, six identical substituents are disposed alternatingly above and below the benzene plane. Both McNicol and Vögtle have created a number of ligand systems exploiting the predispose of metal coordinating side arms around the benzene platform.[15] The major limitation for a wider use of these persubstituted benzene systems was the difficulty to synthesize receptors with different functionalities on one phenyl ring, that is the fact that all six substituents had to be the same.

Concept

Starting with the pioneering work of Mislow and co-workers on the structural investigation of metal complexes of hexaethylbenzene,[16] the stereodynamics of 1,3,5-substituted 2,4,6-triethylbenzenes and their metal-arene complexes were examined. The energetic barriers for the rotation of the substituents on the phenyl ring,[17] or the rotation around the metal–arene bond in η^6-arene complexes of transition metals were studied by means of temperature dependent NMR studies.[18] The energy required for the rotation around the C_{aryl}–$C_{methylene}$ bond was determined in several persubstituted benzene derivatives ($\Delta G^{\neq} \sim 11-12$ kcal mol^{-1}).[19] As confirmed by X-ray structures,[20] the 1,3,5-*R*-2,4,6-*R*′-substituted benzenes adopt a preferred conformation (thermodynamically favored by ~ 4 kcal mol^{-1} compared with next stable conformation) with an alternating *ababab* geometrical pattern.[21] They display a 1,3,5- versus 2,4,6-facial segregation of the substituents around the benzene core (Figure 3).[22]

This exceptional stereochemical characteristic is leading many chemists to use such persubstituted systems as platforms for supramolecular systems. In fact, there has been a recent explosion in the literature describing the use of this scaffold, a concept that is being rapidly exploited by many researchers.

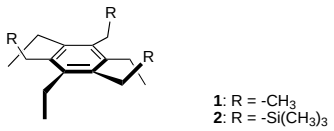


Figure 3. *ababab*-Substituted benzene scaffold displaying facial segregation of the respective substituents around the phenyl plane; as established from the hexaethyl (**1**) or 1,3,5-tris(trimethylsilyl)-derivative (**2**).

Synthesis

Although the excellent aptitude of the 1,3,5-substituted 2,4,6-triethylbenzene scaffold as a building block in supramolecular devices was shown by the early work of Raymond et al. (see below), the poor synthetic accessibility of the basic persubstituted phenyl unit set a limit to a wide application of such systems. 1,3,5-Functionalized triethylbenzene derivatives were usually obtained in low yields by the copper(I) mediated 1,3,5-cyanation of triethylbenzene under harsh conditions with a considerable workup effort being required.[23]

By the independent discovery of an easy synthetic route to 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene by Walsdorff[24] and us,[25] following a different approach outlined by van der Made,[26] the threefold bromomethylation of triethylbenzene lead straightforward to the trisbromomethyl derivative **4** that was converted into the tris-amines **4a** or **4b** as starting materials for different ligand systems (Scheme 1).

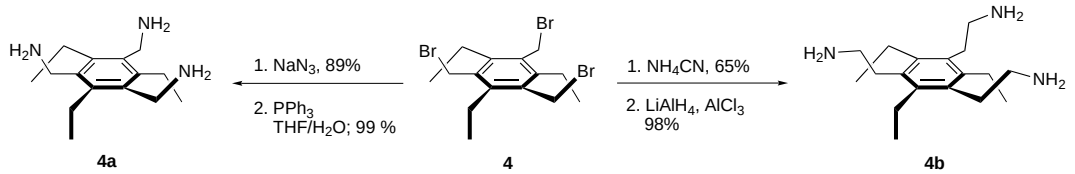
Most recently, Kilway and Siegel reported the synthesis of tris(chloromethyl)benzene **5** as an even more easily available starting material for other alternating persubstituted benzenes by the use of chloromethyl methyl ether and $SnCl_4$,[19] a method that was also under use in our group.[27]

Cation Coordinating Compounds

Having the synthetic tools in hand, the use of the 1,3,5-substituted 2,4,6-triethylbenzene scaffold in supramolecular chemistry has emerged rapidly. Several receptor molecules for cationic (Figure 4) and anionic guests have been designed by placing various binding groups—conformationally controlled in the manner discussed above—around the phenyl platform.

The group of Raymond took advantage of the structural feature of this scaffold to predispose three catechol units around the benzene core to create a tripodal ligand (**3**) for the Fe^{III} cation.[28] After having synthesized the respective 1,3,5-tris(catechol)benzene and mesitylene, the perfectly preorganized receptor **3** exhibited superior complexation properties compared to the previously studied receptors. The binding constant of **3** for Fe^{III} even exceeded that of the natural compound enderobactin, a siderophore with a uniquely strong binding affinity towards Fe^{III}.

Other inorganic complexes have been explored using this benzene motif. By using 1,3,5-tris(pyrazol-1-ylmethyl)-2,4,6-triethylbenzene (**5**) as a ligand for Pd^{II}, Hartshorn and Steel reported the spontaneous formation of the highly symmetric,



Scheme 1. Synthetic pathways to tris(amino)benzenes **4a** and **4b**.

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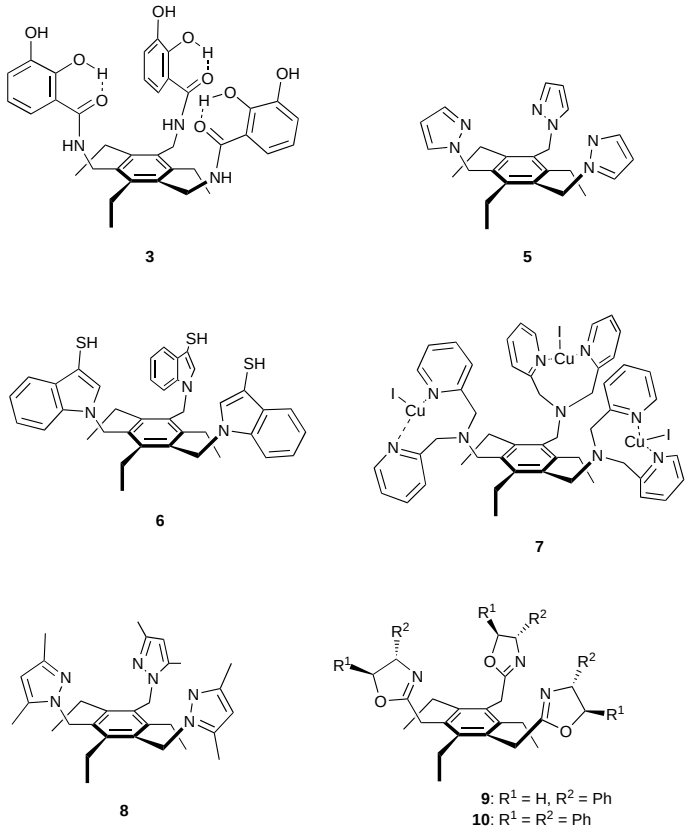


Figure 4. 1,3,5-Tris-substituted 2,4,6-triethylbenzenes (**3**, **5**–**10**) for the complexation of cationic species.

ten-component metallosupramolecular cage.[29] It consists of six *trans*-dichloropalladium units that are arranged in a pseudo-octahedral array and are bridged by four pyrazol ligands. The four central benzene units create a cavity of a 4.7 Å radius. As a model compound for bio-inorganic systems,[30] Saak and co-workers prepared complexes from **6** with Fe_4S_4 clusters. The tristhiol ligand proved to be perfectly preorganised and rigid enough to create isolated, 3:1 subside-differentiated clusters.[31] The tridentate ligand **7** forms trinuclear complexes with Cu^I in which the Cu centers are kept on the same side of the central benzene plane with distances around 7 and 8 Å. Electrochemical studies showed the separate transfer of three electrons from each Cu cation, subsequently.[32]

In the groups of Kim and Ahn the cation coordination properties of these benzene-based ligands were applied for selectively sensing NH_4^+ and alkylammonium cations. Ion selective electrodes (ISE) using the immobilized tris(pyrazole)benzene **8** responded to NH_4^+ over Na^+ and K^+ by a selectivity factor of nearly 5, working in a concentration range between 10^{-4} and 10^{-1} M.[33] Ahn and co-workers also studied the complexation of different alkylammonium cations by trisoxazoline benzenes in chloroform. The ligands **9** and **10** displayed a high selectivity for nBuNH$_3^+$ with association constants of $10^{2.7}$ and 10^4, respectively.[34]

Anion Receptors

In our group, 1,3,5-substituted triethylbenzene derivatives have been extensively explored as receptors for polyfunctional, biorelevant, anionic guest molecules (Figure 5). Hereto, different functional groups are predisposed around the benzene core to match with the functionalities and geometries given by the targeted guest. Initially, we prepared receptors, which possess the same functionalities in the 1,3- and 5-position on the benzene ring.

Receptor **11** binds citrate selectively over other similar carboxylates in D_2O with a binding constant of 6.9×10^3 M^{-1}.[25] By employing a colorimetric competition assay method, a chemosensor was established using **11**, that was able to quantify the amount of citrate in various commercially available beverages.[35] In our competition assays, an indicator

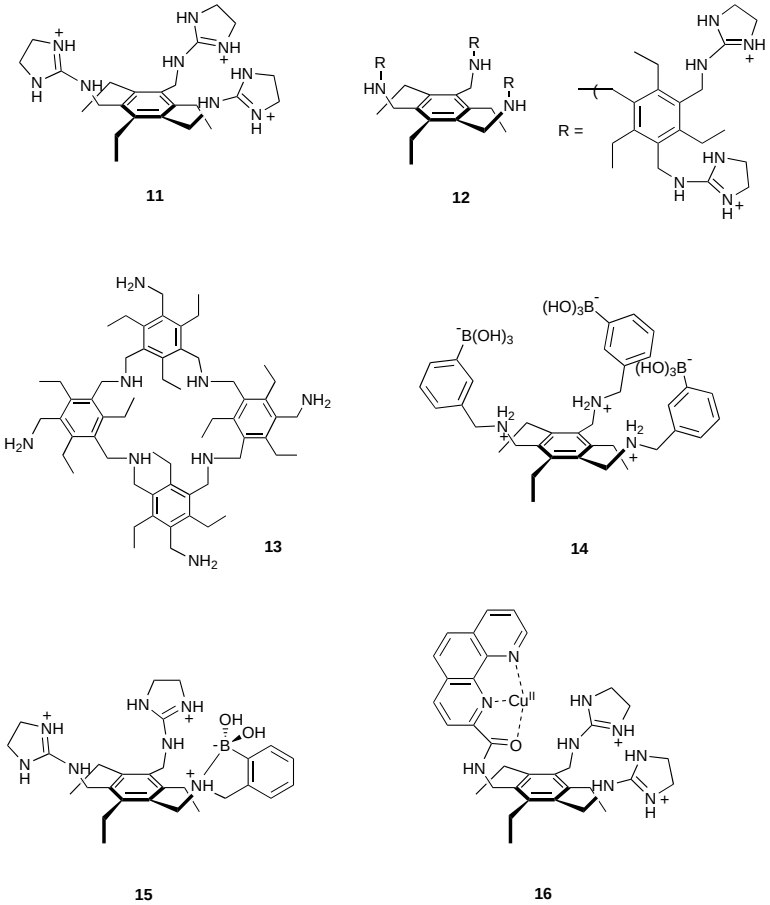


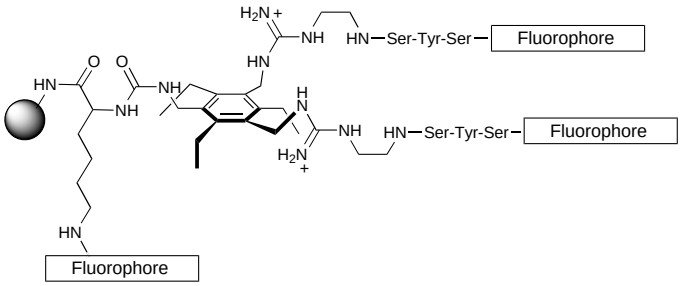
Figure 5. Benzene-based receptors (**11**–**16**) for biorelevant anionic guests.

dye binds to the receptor and is displaced by a stronger binding guest molecule. As a consequence, the indicator's microenvironment is changed as it is released from the host into the solution, which affects its UV/Vis or fluorescence spectroscopic properties. Hence, the choice of the indicator to bind with the respective receptor is crucial in these assays.[36]

The same competition assay method proved that the bowl shaped host **12** bound inositol trisphosphate in buffered water with a binding constant of $2.2 \times 10^4\,\text{M}^{-1}$, while again, conceivably competing substances showed significantly lower binding affinities. In this case, the binding of the different guests was monitored by fluorescence spectroscopy.[37] Addressing the same type of guests, we synthesized aza-calixarene **13** that forms a large cavity. Again, in a fluorimetric competition assay, selective binding of inositol triphosphate ($K_a = 2.4 \times 10^5\,\text{M}^{-1}$) and fructose-1,6-diphosphate ($K_a = 5.0 \times 10^4\,\text{M}^{-1}$) was obtained in aqueous solution.[38] Similarly, the use of a dye displacement assay with the tris-boronic acid receptor **14** revealed selective binding of glucose-6-phosphate over glucose and phosphate in water (30 %)/methanol.[39]

The mono-Boc protection of 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene (**4a**) is being used as a starting material for several receptors we are currently developing. This gives access to triethylbenzenes with different functional groups in the 1,3- versus 5-position. Tartrate and malate bind to the imidazolinium functions of receptor **15** through their carboxy groups and additionally to the boronic acid groups with the hydroxy functions. Receptor **15** was used in a chemosensor ensemble to measure the amount of tartaric and malic acid in wines with high accuracy.[40] The metalloreceptor **16** functions as a fluorescent sensor for citrate which coordinates to both imidazolinium groups and the Cu^{II} center.[41]

A different approach to analyte sensing was taken by attaching two tripeptide side arms onto the benzene scaffold bound to a resin (Figure 6). On the solid support, a library of



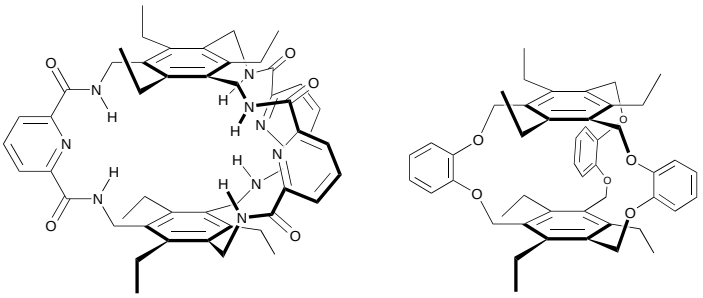
17

Figure 6. ATP-selective resin-bound chemosensor ensemble **17**.

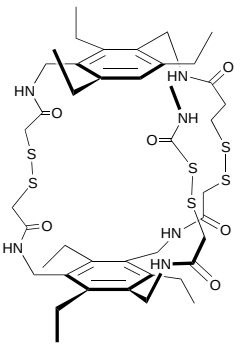
approximately 3600 receptors with different peptide sidearms was scanned by looking for a fluorescence response in the presence of fluorophore-labeled ATP (adenosine triphosphate). ATP was found to bind cooperatively to Ser-Tyr-Ser peptide arms and the guanidinium functions of **17**. The fluorescent receptor system **17** was synthesized by attaching fluorescent end groups to the Ser-Tyr-Ser peptide arms, which displayed the best selectivity and sensitivity among all tripeptides. Hence, a sensor ensemble was obtained that distinguishes between, ATP, AMP and GTP, with only ATP inducing a 1.5-fold fluorescence enhancement upon binding.[42]

Cage Molecules

The preorganization of functional groups around the phenyl ring makes the 1,3,5-substituted triethylbenzene scaffold a valuable building block in the synthesis of macrocycles. The known difficulties in the syntheses of such compounds (Figure 7) can be overcome by arranging the reactive centers in a way that forces the closure of the desired ring system.[43]



18 **19**



20

Figure 7. Macrobicyclic compounds for anion (**18**), and cation sensing (**19**), and for the study of the self-assembled formation of **20**.

Taking advantage of the predisposed NH_2 functionalities in the tris-amine **4a**, compound **18** was obtained in a 40 % yield under mild conditions in a one-step reaction using **4a** and pyridine-2,6-dicarbonyl dichloride. We reported the synthesis of the bicyclic cyclophane **18** and its ability of forming defined inclusion complexes with nitrate and acetate anions.[44] In a dye displacement assay **18** was employed in the optical sensing of inorganic anions.[45] Further, by encapsulation of various enolates into the cavitiy of **18**, we were able to estimate the contibution of NH – π bonding versus hydrogen bonding to the nitrogen lone electron pair in the deprotonation of CH-acidic compounds.[46]

Subsequently to our report of **18**, Kim and co-workers investigated the binding properties of **19** for NH_4^+, Na^+, and K^+. The selective ammonium binding turned out to be partially the result of a cooperative cation – π interaction within the receptor's cavity. In accordance to their previous work, **19** was incorporated into a ISE membrane to build a cation sensing device.[47]

The steric gearing induced by the benzene scaffold also lead to the macrobicycle **20** in good yields. Even though the

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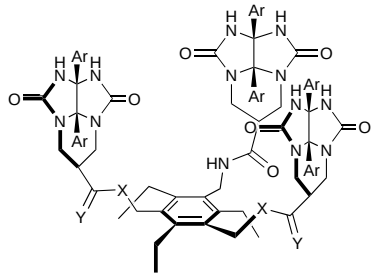
formation of three disulfide bridges in the molecular assembly is disfavored in terms of enthalpy due to the torsion angle strain, the dimeric compound **20** self-assembled from two equal monomers carrying terminal thiol functions. Under equilibrium conditions, **20** was present in solution together with the monomeric tris-thiols and an oligomeric adduct.[48]

Rebek et al. took advantage of the predisposition of three glycoluril groups around 1,3,5-substituted triethylbenzenes to achieve the formation of dimeric, hydrogen-bonded capsules.[49] Analogous to previously described self-assembled capsules,[50] the supramolecular assemblies formed by the "half-bowl" monomers **21** and **22** are capable, according to the size of the cavities and the guest molecules, of encapsulating and re-release the guest reversibly (Figure 8).



21: X = NH, Y = C(O)
22: X = C(O), Y = NH

Figure 8. Monomers **21** and **22** form self-assembled dimeric capsules assisted by the predispose of the two complementary "half-bowls".

Outlook

The facial segregation of the substituents located above or below the phenyl plane, makes 1,3,5-substituted 2,4,6-triethylbenzene an ideal platform for supramolecular systems. By analyzing the examples presented here, it can be seen that its usefulness is being increasingly recognized by chemists working in many different fields, ranging from inorganic to organic, and to analytical applications.[51] We believe that this benzene scaffold will continue to be applied in supramolecular chemistry, and to an even wider extent in the future, as we just have seen its exploitation rapidly increase within only the last few years.

Acknowledgement

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