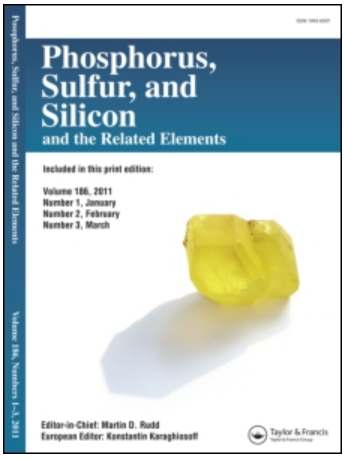

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Conformationally Rigid Hosts Containing Phosphonic Units

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CONFORMATIONALLY RIGID HOSTS CONTAINING PHOSPHONIC UNITS

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We present here a new class of cleft-like receptor molecules containing two or four phosphonates anions, tailored for multipoint binding of their substrates. Depending on the accessibility of the cleft, these hosts are water soluble and selective for short or long α,ω-diammonium compounds. Due to their inherent chirality, we found that only those host-guest combinations which allow a three-point-interaction were effective.

Keywords: Chiral recognition; job-plots; macrocycles; supramolecular chemistry

Small stereochemically rigid cyclophanes are molecules of fundamental relevance in many aspects of macrocyclic and supramolecular chemistry, and therefore research in this fertile field is growing rapidily.[1–3] Despite the large variety of systems synthesized thus far and employed for numerous applications, high interest is still devoted to the synthesis and characterization of geometrically constrained chiral macrocycles for use as specific receptors for selective binding of neutral guests.[3–5]

There exists a need to develop three-dimensional artificial receptors containing selected functional groups in order to introduce suitable binding sites on the cyclophane moiety. Furthermore, if the resulting structures are asymmetric or dissymetric, the system can also be used advantageously for chiral discrimination and separation of a large variety of biologically relevant molecules.

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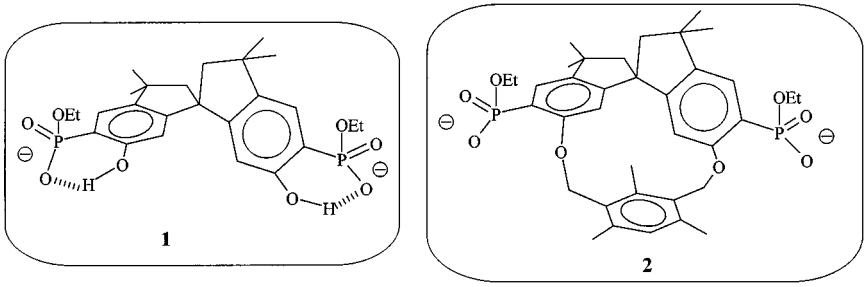


FIGURE 1 Two new host molecules.

Several different strategies have been adopted in which hydrogen bonding groups are held within a macrocyclic or acyclic framework. Our approach to improving the affinity of artificial diammine salts or carbohydrate receptors has been to exploit the strong association of these guests with an anionic functional group, such as phosphonate.[6–7]

We present here a new class of cleft-like receptor molecules, tailored for multipoint binding of their substrates (Figure 1). Depending on the accessibility of the cleft, these hosts are selective for short or long α,ω-diammonium compounds (Figure 2). Due to their inherent chirality, we examined their potential for chiral discrimination and found that only those host-guest combinations which allow a three-point-interaction were effective.

The new host molecules were prepared by careful monodealkylation of the respective cleftlike bisphosphonate esters.[8] A series of NMR binding experiments revealed a remarkably different behavior of the two new host molecules with respect to their chemoselectivity as well as their enantioselectivity. Job plots[9] with **1**, **2**, and several α,ω-diammonium compounds proved that **1** forms 1:1 complexes in all cases, whereas **2** binds two guest molecules as long as they are shorter than

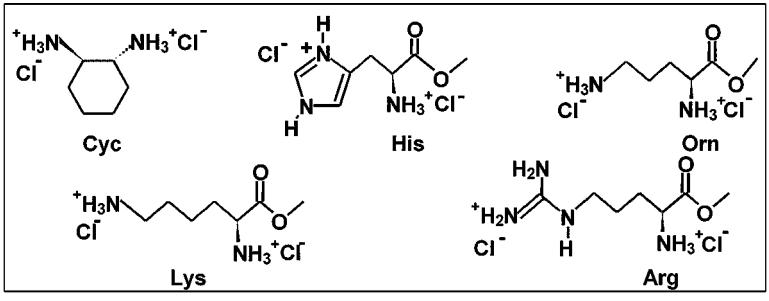
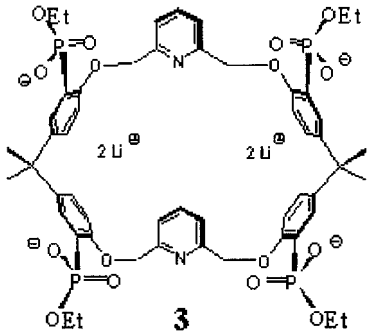


FIGURE 2 Investigated chiral guest-molecules: the distance of the charged amino groups is successively increased by one carbon or nitrogen atom.

lysine and arginine. We performed NMR titrations[10] of various dication guests with a successively increasing distance between their positively charged nitrogen atoms (Figure 2). The resulting binding curves were analyzed by nonlinear regression methods and furnished the association constants. The experimental association constants in DMSO are in the order of 10^2 to 10^4 mol/l.

No enantiodiscrimination is found for the open chain host **1**, and even **2** can only distinguish between enantiomeric guests with an $N^+ \cdots N^+$ distance of more than five bonds. This indicates once again that for an efficient chiral recognition the two binding sites within the C_2-symmetrical open chain host molecule **1** are not sufficient. Only the additional third binding site offered in C_1-symmetrical macrocycle **2** by the chiral surface of the mesitylene bridge leads to a detectable enantiomeric discrimination.

Furthermore, we present the results of host molecule **3**, which binds the basic amino acids listed in Figure 2 in water. It recognizes both positively charged groups of the amino acids by electrostatic and hydrogen bond interactions with its four strategically placed phosphonate anions. Selectivity for lysine is achieved by the correct distance between both bisphosphonate pairs.



By contrast, the smaller amino acids arginine, ornithine, and histidine form 2:1 complexes with **3**. In methanol, a double chelate assembly enforced by π-cation interactions with the imidazolium cation leads to a very high association constant for the **3**:histidine complex of 3×10^4 M^{-1}.

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