

Role of preorganization in host-guest-chemistry

D.N. Reinhoudt* and P.J. Dijkstra

Laboratory of Organic Chemistry, University of Twente, 7500 AE, Enschede, The Netherlands

Abstract - The concept of preorganization in the complexation of alkali cations is illustrated by a systematic variation of the structure of molecular cavities. The parent hemispherand 2 has been compared with novel hemispherands that contain a nitrogen (pyrido) or oxygen (4H-pyran) atom. These two types of hemispherands have been synthesized using pyrylium building blocks. A novel approach to the parent hemispherands that have a functional group at the outer sphere, involves the macrocyclization of a flexible precursor to give 5 and subsequent reaction of 5 with nitromalondialdehyde. Finally, modification at the inner sphere of hemispherands has been achieved via pyrylium hemispherands (13). These compounds have been attained by reaction of the corresponding 4H-pyran hemispherand (12) with the triphenylmethyl carbenium ion. Comparison of the X-ray structures of two hemispherands (2 and 9) with the corresponding sodium picrate complexes shows the degree of preorganization. This is also reflected in the free energies of complexation with different picrates.

INTRODUCTION

The design and synthesis of macrocyclic receptor molecules can be based on two major principles (ref. 1). Firstly, the receptor can be designed for an optimal complementarity between the structures of the host and the guest. Secondly, the molecular cavity of a receptor can be preorganized which means that for complexation of a matching guest species only minor conformational changes of the host are necessary.

The first principle has been widely applied for the synthesis of macrocyclic polyethers that complex alkali and alkaline earth metal cations, the so-called "hole-size relationship" (ref. 2). In our group we have extended this approach for the development of receptor molecules that selectively complex polyfunctional cations and neutral molecules. Highly flexible macrocycles with ring sizes of 27 or more can encapsulate guanidinium and uronium cations (ref. 3-5). Even urea, providing there is an electrophilic site present in the molecular cavity can be encapsulated by such macrocycles (ref. 6,7).

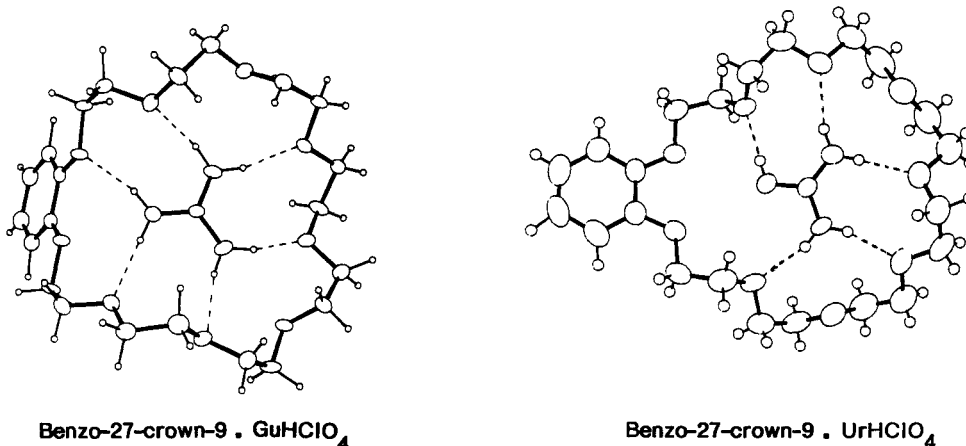


Fig. 1. Encapsulated guanidinium and uronium (urea) complexes.

These encapsulated complexes are highly hydrophobic which renders them very useful as carriers in the transport of guanidinium salts through liquid membranes (ref. 8). However, as we have recently reported, the disadvantage of highly flexible receptor molecules is that they undergo "self complexation" which means that in the uncomplexed state the molecular cavity is filled by parts of the molecular framework e.g. benzo, pyrido, or 1,3-xyleno moieties (ref. 9).

In a similar fashion strong intramolecular hydrogen bonds may be formed (ref. 10,11). All these factors will lower the thermodynamic stability of complexes because these stabilizing interactions are lost in the process of inclusion of a guest species. Although most evidence for these interactions in the receptor molecules is obtained from X-ray data of the solid state, and consequently be attributed to crystal packing forces, our recent studies on the conformations of large flexible macrocycles have provided evidence for similar interactions in solution. In particular ^{13}C T_1 -relaxation time studies (ref. 12) and determination of accurate pK_a -values of intra-annular acidic groups (ref. 13) provide qualitative and quantitative evidence for these interactions in solution. Moreover, structures of large ($n \geq 24$) 2,6-pyrido and 1,3-xylyl crown ethers, generated by molecular mechanics (MM-2) calculations, support the assumption that the energy of the macrocycle is lowered by "self complexation" (ref. 9).

In the complexation of cations these contributions to the "ground state" energy of the hosts can easily be compensated for by the desolvation of the guest and the electrostatic forces between the host and the positively charged guest.

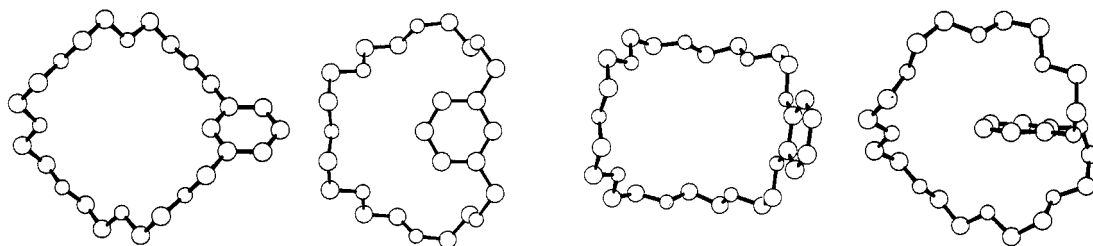


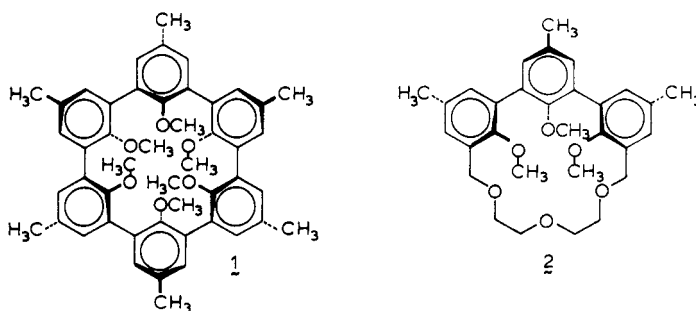
Fig. 2. "Self complexation" of larger macrocyclic polyethers.

However, the free energies of complexation of neutral guests are much smaller (ref. 13) and as a consequence even small stabilizing contributions of intra-annular hydrogen bonds or "self complexation" to the "ground state energy" of the host become very important. The energy that can be gained, at least in principle, by preorganization of the receptor stimulated our interest in preorganized receptor molecules.

The potential of the concept of preorganization was originally formulated by D.J. Cram. Experimentally Cram et al approached the design of preorganized hosts by making the molecular framework, in which the ligating sites are incorporated, more rigid (ref. 14). This not only reduced the mobility of the host but simultaneously introduced severe repulsion between the free electrons of the donor sites. In the complexation the relieve of repulsion may contribute substantially.

The extremely high thermodynamic stability of the Li^+ and Na^+ complexes of the hexa-anisyl spherand (1) is probably the best illustration how this principle of preorganization can be used to enhance both stability and selectivity of complexation.

In addition to an enhanced thermodynamic stability, the kinetic stability of these complexes is so high that decomplexation becomes slow ($t_{1/2} \geq 1\text{h}$) (ref. 15).



RESULTS AND DISCUSSION

The reported high kinetic stability of these complexes is a major reason why we became actively interested in this field, because we realized that several problems in our work might only be solved if we are able to increase the kinetic stability, the selectivity e.g. K^+/Na^+ and the lipophilicity of complexes with cations but also with neutral guests. Firstly, in relation to our work on organ imaging (ref. 16) we were interested in complexes of $^{81}\text{Rb}^+$ that are kinetically "stable" ($t_{1/2}$ of decomplexation $\geq 1\text{h}$) and that can be linked covalently to biological systems (proteins, antibodies).

Secondly, for our work on a K^+ selective biosensor on the basis of ISFET technology (ref. 17,18) we needed a highly hydrophobic ligand that has a high ($\geq 10^3$) K^+/Na^+ -selectivity. Thirdly, in order to increase the stability of complexes of neutral species, reduced flexibility of the ligands was required. Since for none of these objectives the 18-membered spherands can be used because the molecular cavity in such ligands is only accessible for

small electrophilic cations (Li^+ and Na^+) we have concentrated our synthetic efforts on the modification of the rigid moiety as found in partially preorganized host molecules. These so-called hemispherands (e.g. 2) have been investigated in great detail by Cram et al (ref. 14), but compounds specifically designed for the above mentioned purposes had not been published.

Our objectives were in the first place to modify the outer sphere of (hemi)spherands which would allow us to link the receptors to biological species and the chemically modified ISFET surface. In view of the synthetic methodologies applied by Cram this was not a trivial problem. Secondly, large rigid cavities are required for K^+ or Rb^+ complexation and therefore we have studied the modification of the inner sphere by replacing one methoxy donor site of the parent hemispherand 2 by a nitrogen (pyrido) or an oxygen (pyran) atom. The objectives required synthetic pathways different from those employed by Cram et al. Moreover, we realized that the synthesis of rigid ligands in which repulsion between donor sites contributes largely to the complex stability will be difficult.

In the macrocyclization of a linear precursor molecule, this repulsion will strongly increase, thus lowering the yield. Although the presence of a template cation may reduce this effect we felt that an alternative would be the macrocyclization of a flexible molecule followed by rigidification of the relatively flexible macrocycle, by constructing an additional aromatic ring.

The aromatization reaction would provide the energy to compensate for the increased O-O repulsion.

SYNTHESIS OF HEMISPHERANDS VIA AROMATIZATION

As a consequence of the above approach we have synthesized ketone 3 in 4 steps from 2-hydroxy-5-methylbenzeneacetic acid in an overall yield of 58%. Subsequently the carbonyl group in 3 was protected through the cyclic ethylene ketal, and converted into 4 via bromo to lithium exchange, reaction with dimethylformamide, and reduction of the formyl groups thus introduced.

Macrocyclization to the 18-membered macrocycle 5 proceeds in 65%. The good yield is indicative for a flexible macrocycle, which is confirmed by the X-ray crystal structure (Fig. 3), showing no organization of methoxy and ketal oxygens prior to complexation. The

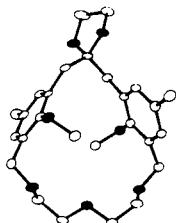
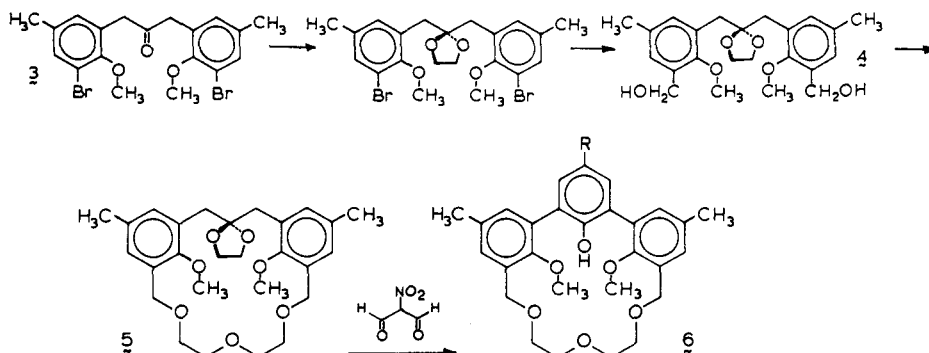


FIG. 3: X-Ray of 5

outer sphere functionalized hemispherand 6, which contains a central hydroxy group, was obtained from 5 by deprotection and reaction of the resulting propanone moiety with nitromalondialdehyde in 89% overall yield (Scheme 1). The aromatization energy involved in the final reaction is large enough to overcome the rigidification of the macrocycle. The hydroxyl group may be alkylated in high yield.

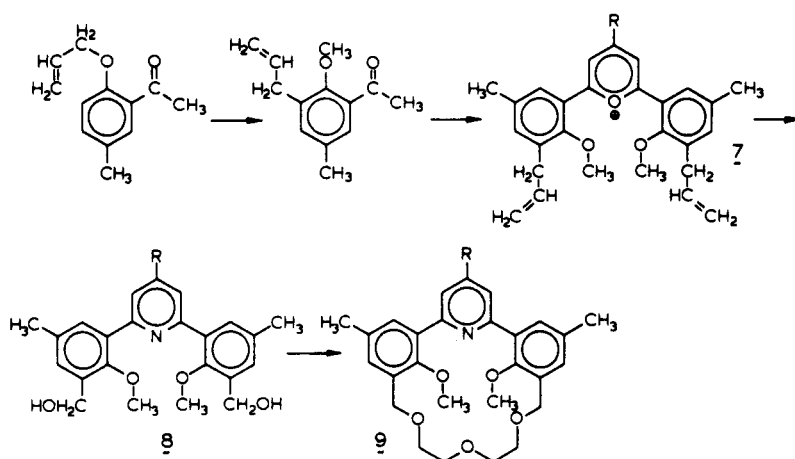
Scheme 1



VARIATION OF THE DONOR SITES IN HEMISPHERAND CAVITIES

Since our major interests required relatively large molecular cavities we have investigated the effect of substitution of the "central" methoxy group in the parent hemispherand 2. However, this required a different strategy for the synthesis of the rigid building block. We have taken advantage of the mirror plane of symmetry in hemispherands. Pyrylium salts proved to be excellent starting materials for the synthesis of building blocks containing a

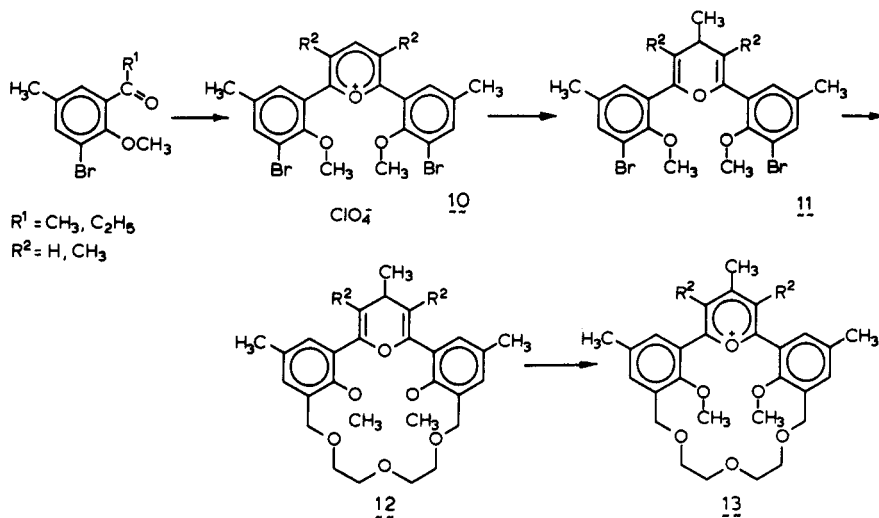
Scheme 2



pyridine or 4H-pyran moiety. Different aryl substituted pyrylium salts were required to synthesize the building blocks with suitable functional groups ortho to the methoxy groups. The introduction of an allyl substituent in 7 solved the problem of low yields obtained by introducing formyl groups in building blocks containing a pyridine ring through lithiation and reaction with DMF or electrophilic aromatic substitution. The allyl groups were isomerized followed by oxidation to give 8. Reduction and conversion to the bromomethyl derivative was followed by macrocyclization to give 9 (Scheme 2).

Pyrylium salts that are unsubstituted at the 4-position react with strong nucleophiles to give 4H-pyrans (ref. 19). Thus, the 4H-pyran 11 was obtained from 10 upon reaction with methylmagnesium iodide in 93% yield. The 4H-pyran hemispherand 12 was prepared by the same method as described for 5, the macrocyclization reaction proceeding in 65% yield (Scheme 3).

Scheme 3

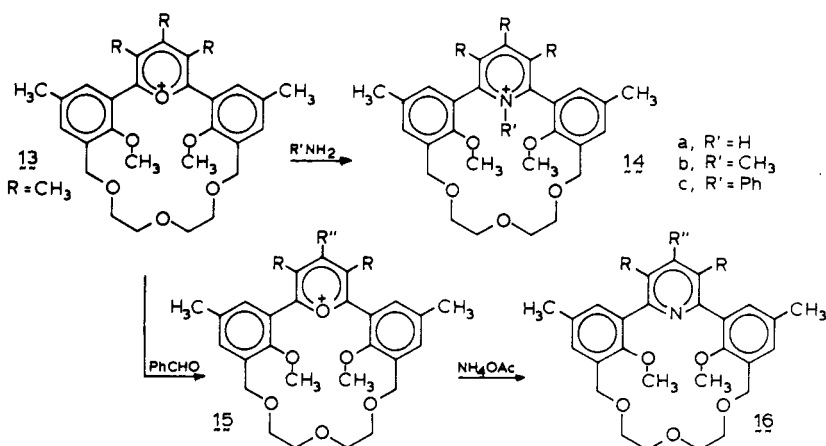


PYRYLIUM HEMISPHERANDS

It is obvious from the above synthesis of 6 and 9 that such a diverging approach requires long routes to individual hemispherands. Consequently we have developed a converging synthesis via pyrylium hemispherands.

The 4H-pyran hemispherand (12) obtained as described above was reacted with the triphenylmethyl carbenium ion. Hydride abstraction facilitated by the formation of the 6 π -pyrylium nucleus proceeded almost quantitatively to give 13. This hemispherand has two reactive sites *viz* the carbon atoms at the 2- and 6-positions and at the 4-position. Reaction of a nucleophile at the 2- or 6-carbon atom of the pyrylium ring leads to ring transformation. We have investigated reactions with ammonia and primary amines to give the pyridine and N-methyl and N-phenyl pyridinium hemispherands 14a and 14b,c. The aromatization energy involved in these reactions appears to be large enough to introduce large steric barriers as illustrated for 14c. CPK molecular models of 14c show that ring inversion is impossible and the NMR spectra of this compound also show that the N-phenyl ring is out of the plane of the pyridinium ring.

Scheme 4



The pyrylium 4-methyl protons are acidic and reaction of **13** with a base gives the 4-methylenepyran (anhydrobase). This compound also is an intermediate in the condensation with carbonyl compounds. This was illustrated by the reaction of **13** with benzaldehyde to give **15**, which subsequently can be converted into the pyridine hemispherand **16** (Scheme 4). Because reactions of anhydrobases are numerous and well documented in the literature, the 4-methyl group in **13** provides a method for the synthesis of various outer sphere functionalized hemispherands.

SINGLE CRYSTAL X-RAY ANALYSIS OF FREE LIGANDS AND THEIR SODIUM PICRATE COMPLEXES

Whereas the conformation of the *m*-teranisyl moiety in **2** is hardly changed upon complexation as seen in **2**.NaPic, the hemispherand **9** shows that conformational change of an anisyl unit is necessary to give **9**.NaPic. The resulting conformation has also been found in **12**.NaPic. The changes observed in the crystal structure of **9** and **9**.NaPic are consistent with the ¹H NMR spectral changes observed. The free ligand shows a singlet for the benzylic hydrogen atoms indicating that ring inversion is fast on the ¹H NMR time scale. Upon complexation with sodium picrate the spectrum of **9**.NaPic resembles that of **2**.NaPic with analogous chemical shifts and the benzylic protons appear as an AB system. The spectral changes observed for **9** upon complexation are also found for **12** showing that this hemispherand is conformationally more mobile than **2**.

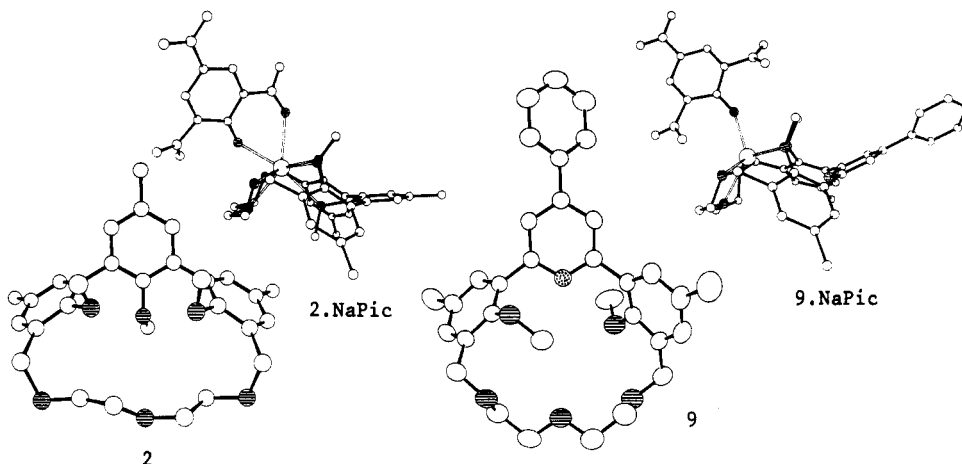


FIG. 4

COMPLEXATION OF HEMISPHERANDS WITH ALKALI CATIONS

The complexation of the hemispherands was studied by the picrate extraction method of Cram et al (ref. 20). In Fig. 4 the results are summarized and it is clearly shown that relatively small variations in the structure are reflected in significant differences in stability and selectivity.

It is self-evident that extending the ethyleneoxy bridge in **2** by one unit to give **17**, shifts the selectivity to the larger alkali cations K⁺ and Rb⁺. However, compared to the hemispherand **18** which contains four self-organizing anisyl units in a 21-membered ring, no enhancement in association is observed and **17** also appears to have a larger K⁺/Na⁺ selectivity as found for **18**.

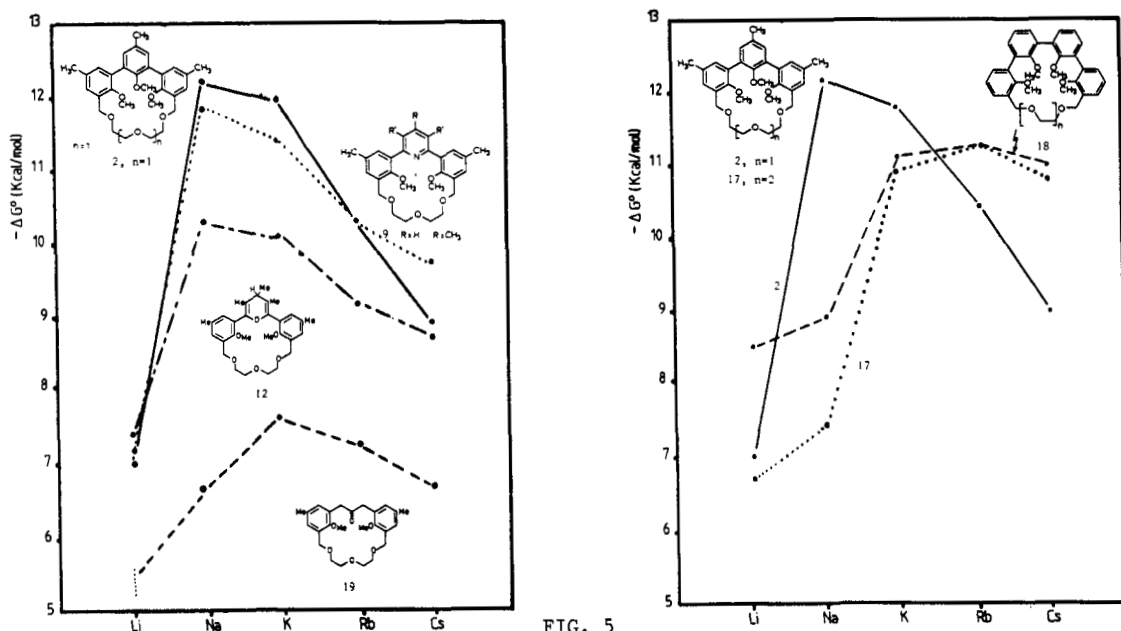


FIG. 5

The binding free energies of the 4H-pyran and pyridine hemispherands 12 and 9 show the concept used in the synthesis of inner sphere modified hemispherand via the pyrylium hemispherand. The relatively flexible 4H-pyran hemispherand 12 shows low $-\Delta G^\circ$ values caused by the conformationally mobile macroring and the weak ligating divinyl ether oxygen. Converting the 4H-pyran ring to a pyrido ring shows the increase in $-\Delta G^\circ$ values, which are almost equal to those found for 2 (Fig. 5). This concept is once more illustrated in the $-\Delta G^\circ$ values determined for 19, the starting compound to synthesize an outer sphere functionalized hemispherand of type 2.

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