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Molecular recognition and stereotopic group recognition

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Abstract: Crown ethers modified by arylboronic acid ester moieties are unique host molecules in several respects, including the ability to bind two different guests simultaneously. The combination of crown ethers and arylboronic acids constitutes the currently most efficient carriers for the transport of amino acids through organic membranes. The first direct evidence for enantiotopic group recognition involves a meso-configurated bis-ammonium salt and a chiral crown ether, the latter acting as a host which binds one of the two enantiotopic H_3N^+-groups selectively.

INTRODUCTION

One of the important motivations for designing, synthesizing and testing novel host molecules concerns enzyme models (1). Mimicking natural biological systems on the basis synthetic receptors allows one to study the factors involved in host/guest interactions on a molecular level. It is thus an exercise in physical organic chemistry. Furthermore, those synthetic receptors capable of molecular recognition and catalysis are attractive goals in organic chemistry. Most workers in the field have relied on non-covalent interactions known in supramolecular chemistry, namely hydrogen bonds, van-der-Waals forces, π-π interactions, etc., whereas donor-acceptor bonds involving metals have not been exploited in depth (1).
We envisioned a long-term goal based on host molecules containing σ-bonded metal centers (2). Accordingly, the host binds a specific guest selectively from a collection of different molecules in a synergistic way involving the traditional interactions as well as dative bonds at the metal center (Fig. 1). In the ideal case, the system is catalytic, i. e., an enzyme mimic, allowing for substrate-selective chemical conversion. Although we have not reached this goal, interesting observations have been made which are summarized in this progress report, including serendipitous findings.

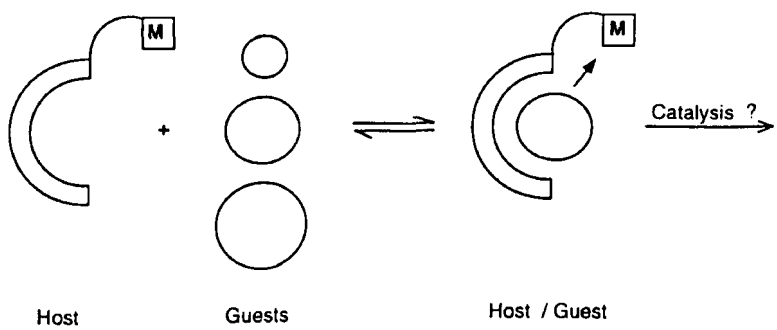


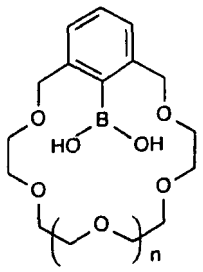
Fig. 1. Combination of molecular recognition and catalysis

Boron-containing Host Molecules

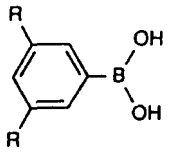
We initially chose boron as the metal and prepared a series of boronic acid esters derived from the boronic acids **1** (3).

The boronic acid esters are receptors which possess a number of highly unusual features in a variety of host/guest interactions: 1) They bind KF, KCN and $KOCH_3$ ditopically, while KJ and KSCN bind monotopically (3). 2) They bind primary amines selectively (4). 3) They are capable of hosting two different guests simultaneously, specifically amines and alcohols (5), such supramolecular species of three different molecules being mimics of biological systems (many enzymes bind two or molecules selectively before inducing molecular transformation).

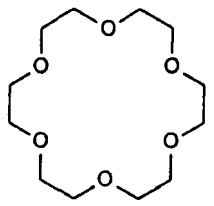
The transport of biomolecules such as amino acids or carbohydrates through organic membranes using synthetic receptors as carriers is an important area of research (1). We envisioned that boronic acids **1** might function as carriers of amino acids across organic membranes, because lipophilization of the betain form $H_3N^+(R)CH\text{-}CO_2^-$ could occur by complexation at two sites: The H_3N^+-group at the crown ether moiety and the carboxylate at boron as an ate-complex.



1 a) n = 0
b) n = 1
c) n = 2
d) n = 3



2 a) R = H
b) R = CF_3



3

Using a "glass cylinder" apparatus, the transport rate of phenylalanine through chloroform in the presence of various crown ether-modified arylboronic acids was measured. Indeed, relative transport rates of 2 to 350 with respect to a "blank" experiment in the absence of a carrier were observed (6). However, since the receptors are geometrically not ideally suited for the ditopic interaction, we also tested two-component carrier systems composed of arylboronic acids and crown ethers. Indeed, the combination of phenylboronic acid (**2a**) and 18-crown-6 (**3**) led to a relative transport rate of 720. In the case of bis(3,5-trifluoromethyl)phenylboronic acid (**2b**) and 18-crown-6 (**3**), an even higher value was recorded, namely 1270 (6)!

Since it is difficult to compare our results directly with literature values of other carrier systems, we checked several known carriers under identical conditions. The recent carrier systems based on a derivative of Kempf's acid (7) and phenylboronic acid/$nOct_4N^+Br^-$ (8), which were reported to be highly efficient for the transport of amino acids through organic phases, turned out to have relative transport rates amounting to 360 and 15, respectively. Thus, the combination of bis(trifluoromethyl)phenylboronic acid and 18-crown-6 appears to be the most efficient abiotic pH-neutral transport system currently known. In a detailed study the nature of the boronic acid, crown ether component and amino acid was varied systematically (6). On the basis of the data, ate-complex formation as originally conceived seemed unlikely. Rather a model was postulated in which the H_3N^+-function of the amino acid binds to the donor positions of the crown ether and the boronic acid portion forms unique hydrogen bonds to the carboxylate moiety. It should be noted that in the literature alkyl- and arylboronic acids are traditionally viewed as Lewis acids undergoing ate-complex formation, and not as Brönsted acids.

Upon mixing phenylalanine, boronic acid (**2b**) and 18-crown-6 (**3**) in ethanol/toluene, crystals were obtained which were studied by X-ray crystallography. The results clearly show that the proposed model is in fact correct (Fig. 2).

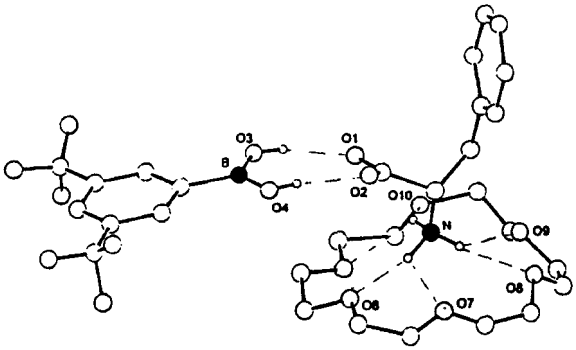
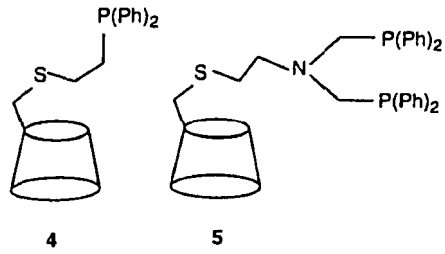


Fig. 2. Crystal structure of the supramolecular ternary complex composed of phenylalanine, **2b** and **3** (6).



Stereotopic Group Recognition

Our first attempt at putting the scheme shown in Fig. 1 into practice involved the synthesis of the phosphine-modified β-cyclodextrin **4** (9). Unfortunately, the corresponding Rh-complex failed to show reasonable catalytic activity in hydrogenation reactions. We therefore turned to bidentate phosphine ligands of the type **5**, the synthesis of which was recently completed (10). However, work with compound **4** was not completely abandoned because crystals were serendipitously obtained. The X-ray structural analysis shows a unique feature (11): One of the two diastereotopic phenyl groups dips into the cyclodextrin cavity, namely the pro-S group. Thus, phosphorus has the S-configuration, assuming a convention in which the complexed phenyl group has the higher priority within the Cahn-Ingold-Prelog nomenclature.

This structure intruiged us because an interesting effect may be involved, namely "diastereotopic group recognition". Whereas traditional molecular recognition is based on the ability of a host to select between two (or more) guest molecules, the present phenomenon appears to involve selective binding of one diastereotopic group within one molecule. Fig. 3 shows "enantiotopic group recognition" in the case of meso-compounds by a chiral host. The extension to other prochiral guests is obvious (11).

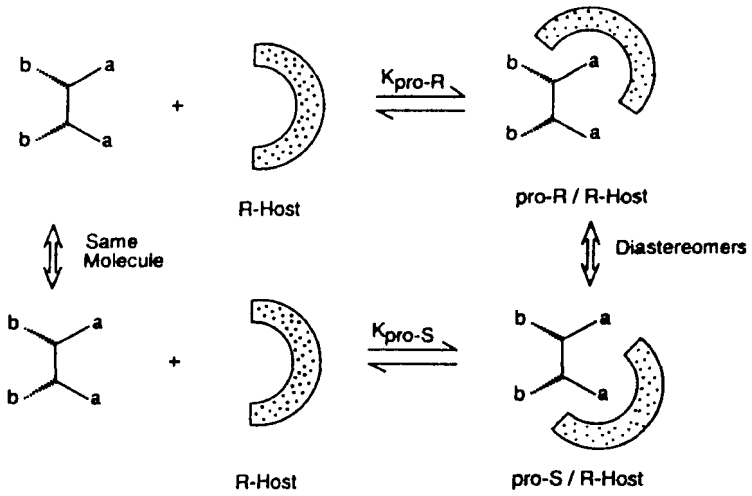
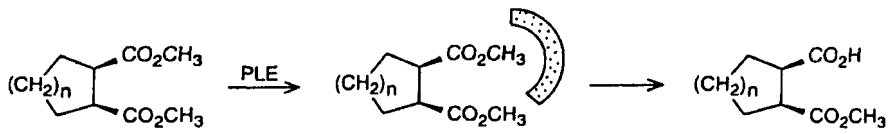


Fig. 3. Enantiotopic group recognition

In organic synthesis a number of reactions have been described in which stereotopic groups react selectively. However, direct evidence for selective complexation of a stereotopic group in a given compound prior to reaction has never been presented. The same applies to many enzyme-catalyzed reactions. For example, in the stereoselective hydrolysis of meso-diesters such as **6** catalyzed by pig liver esterase (PLE) (12), it is likely that the enantiotopic group which is hydrolyzed is selectively complexed by the enzyme (cf. **7**) prior to the actual hydrolysis step (cf. **8**), but no direct evidence for **7** exists.

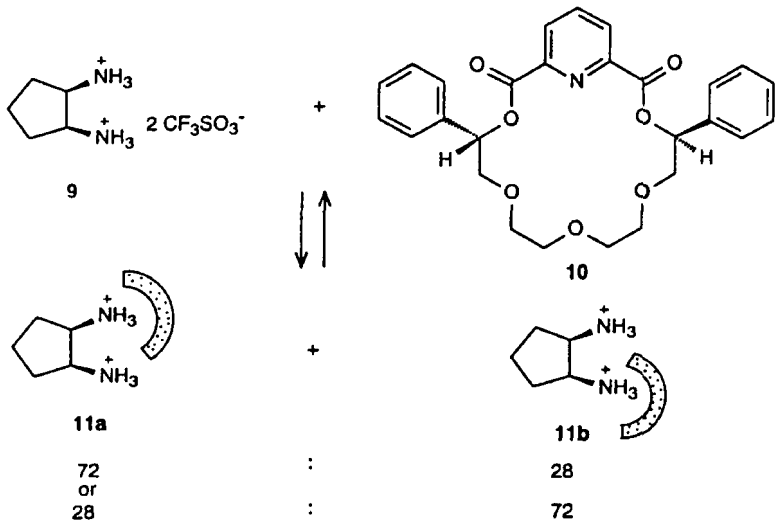


6 **7**

8 a) n = 1; ee 17%
b) n = 2; ee 97%

We therefore embarked on a research program directed toward finding model systems in which enantiotopic group recognition becomes "visible". Since NMR spectroscopy provides the only means for direct spectroscopic evidence (in the absence of suitable crystals for X-ray analyses), dynamic effects need to be excluded. It should be noted that complexation alone is not stereotopic group recognition; rather, it involves selective complexation.

Our first successful attempt relates to the interaction of the meso-configurated guest **9** with the chiral host **10** first prepared by Izatt (13). Using NMR spectroscopy, we could unambiguously prove that one of the two enantiotopic H_3N^+-groups binds selectively to the chiral host, the ratio of the two respective diastereomeric complexes **11a/11b** being 72:28 (7,11). Thus, this is the first case of direct evidence for enantiotopic group recognition. Although a catalytic transformation is not involved, the relationship to the PLE-catalyzed reaction of **6** is evident.



9 **10**

11a **11b**

72 : 28
or
28 : 72

Conclusions

Crown ethers modified by or in combination with boronic acids or boronic acid esters are interesting host systems capable of a variety of unique recognition phenomena, including the ability to function as carriers for amino acid transport through organic membranes. In several situations unique ternary supramolecular species are involved which can be viewed as mimics of biological systems. The first

example of direct observation of enantiotopic group recognition (involving a meso-configurated bis-ammonium salt and a chiral host) has to do with a phenomenon prevalent in certain enzyme-catalyzed reactions. More work is necessary in this fascinating new area of supramolecular chemistry.

Acknowledgement

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