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Selective molecular hosts for anions

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Abstract - The ideas fundamental to the design of cation complexing host molecules can also be applied in the construction of molecular hosts for anions. Following the basic concept the macrotricyclic ammonium hosts 1a and 1b were prepared. They were shown to bind anions by encapsulation into their molecular cavities in aqueous solution. This inclusion process causes guest discrimination according to integral properties like charge, hydrophobicity and size. Besides this equilibrium selectivity differential rate effects (kinetic selectivity) are observed favouring reactions, which run through delocalized anionic transition states. In order to improve the selectivity, accessability and applicability the concept of linearly connected locular molecular hosts was developed. A selectivity advantage exclusively attributable to this design can be demonstrated even with the simplest member of the series, the ditopic host 2. A better definition of orientational and distance relations than attainable in the anion inclusion hosts can be expected from bicyclic guanidinium host structures (Fig. 3). The binding mode of oxoanionic guests to symmetrical molecular hosts of this type resembles the interaction pattern found in natural receptors. The synthesis of chiral guanidines via three different approaches opens the way to predetermined enantioselective anion recognition. An initial step in this direction is achieved by linear combination of two guanidinium units to produce the ditopic host 29.

INTRODUCTION

One of the most successful concepts to introduce selectivity into chemically reacting systems is the binding of the educt(s) to a host molecule in the ground state prior to any conversion event. This principle is the basis of specifity in biology but it has been adapted in a great variety of ways in artificial systems as well. Even very primitive molecules or molecular assemblies can enhance the reaction rate between two reaction partners, if the latter can be bound simultaneously, i.e. if they can act as molecular guests. The rate accelerations originate - at least in part- in the entropic gathering phenomenon, which increases the proximity of the reactants and thereby their encounter frequency. The selectivity in these cases in terms of the capability of one educt to discriminate among a selection of second reactants is primarily governed by their groundstate binding constants to the hosts. Since the absolute rate augmentations, and even more so the specificity characteristics of these artificial hosts are by far inferior to natural examples, the conclusion was obvious that guest binding may be a mandatory but not a sufficient prerequisite for selective molecular hosts.

Instead accumulating evidence from biological and totally abiotic receptors produced the hypothesis that it is the optimal alignment of reacting groups in the educts interacting with complementary functions of the host that causes high selectivity. This optimal arrangement of binding substructures

in the host requires their utmost preorganization (ref. 1) Before any attempt to the rational design of an optimal abiotic receptor can be made, three pertinent points must be clarified (ref. 2):

- Which guests are to be selected by binding to the molecular host?
- In which solvent is the host-guest-complexation to take place?
- Does the complexation serve a peculiar purpose?

In answering the first question the recognition pattern between host and guest must be defined. This ultimately addresses the structural integrity and the peculiarities of the guest structure, the type, number and topology of functional groups to be bound by the host. Clearly this point has attracted major attention and surely constitutes the foundation of the host-guest interrelationship.

The second point must not be neglected though: Apart from complexation in the gasphase the direct interaction of host and guest is subject to the influence of the solvent. The solvent shell around the binding partners will be altered on complexation and this can either be a very costly process in terms of the interaction free energy obtainable in binding, or restructuring the solvent may rather favour complex formation. In any case the very nature of the solvent largely determins host-guest complex stability and the incorporation of some consideration of the change in the solvation characteristics into rational host design will pay off greatly, although solid data on the contributions of individual substructures to the overall solvation energy are very scarce at present.

The analysis of the third question seems trivial at first sight. However, in host compounds serving a particular function (catalysis of a chemical reaction, transport of guests accross a membrane etc.) it is vital that the best complementarity of host and guest and therefore maximum binding is <u>not</u> realized at the ground state level (ref. 3). Rather some unfavourable influences e.g. at nonreacting sites in the guests must be abolished on approaching the rate determining step of the overall process in order to lower the limiting energy of activation. Selectivity in this sense is a kinetic phenomenon which requires nonequilibrium conditions for expression. However, this is the relevant term to optimize, if one wants to influence chemical conversions.

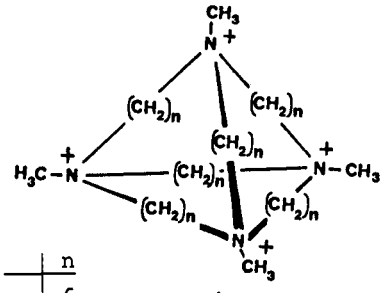
Selectivity thus refers to the differences in free energy $\Delta\Delta G$ of host--guest complexes of one host compound interacting with various guests either in the ground state (equilibrium binding) or in the transition state with the highest activation energy along the reaction coordinate of a chemical conversion relative to the uncomplexed state (kinetic selectivity).

Obviously $\Delta\Delta G$ can only become large, if the interaction free energies themselves are high, i.e. if stable host-guest complexes are formed. Since most components contributing to host-guest interaction are additive to a first approximation the overall attractive energy in general will increase with guest size. This in turn will ease attempts to maximize $\Delta\Delta G$, so that one can state a conceptual advantage in the design of selective host compounds aiming to complex large guest molecules.

On the contrary selective binding of small guests is limited by low levels of the maximum available interaction energy. Thus, it is a stringent necessity to preorganize the anchor groups in a very precise fashion in order to achieve an optimal complementarity to the guest to be selectively complexed. This is the basic reason why the placement of binding functions on more or less rigid macrocyclic frameworks is the method of choice to construct artificial receptors for small species like the metal cations.

ANION BINDING BY MACROTRICYCLIC INCLUSION HOSTS

This concept, however, holds for simple anionic guests as well. Our basic idea was (ref. 4,5) to design a host molecule that could bind negatively charged species in aqueous solution, that is under highly competitive conditions. Even superficial inspection of the guest properties rapidly discloses that anions are more heavily hydrated than cations of the same size (ref. 6); binding of anions therefore required strong and far reaching attractive forces essentially electrostatic in nature, which had to be installed on a rigid molecular framework to assure maximum charge density at a fixed position. The attractive interaction must not be so intense as to inhibit rapid host-guest exchange reactions. Because even the simplest anions are much larger than cations but should be amenable to a complete scanning of their surfaces, a potential anion host must be considerably larger than a cation complexing analogue. It is thus advisable to lend it a symmetrical structure in order to ease monitoring of its synthesis.



	n
a	6
b	8

1

Table 1: Binding constants K_{ass} for the association of the tetrahedral hosts 1a and 1b with representative anions in water [T = 298 k]

entry	K_{ass} [M^{-1}] 1a	anion	1b
1	1020	Br^-	106
2	500	I^-	286
3	125	$H_2PO_4^-$	-
4	345	HPO_4^{2-}	~2
5	285	ATP^{4-}	83
6	< 5	p-nitro-phenolate	178

These boundary conditions have been incorporated into the construction of the macrotricyclic quaternary ammoniumsalts 1 (ref. 4,7). By virtue of the electrostatic repulsion of the permanent positive charges at the corners of a tetrahedron a molecular cavity of well defined size is formed. The high positive potential inside should be suitable for the encapsulation of negatively charged species, which have to undergo a check of their sizes on penetration, because it follows from geometric considerations that the radius of the tetrahedral faces is smaller than the cavity radius. Two different tetrahedral tricyclic compounds have been prepared following a strategy that involves three successive macrocyclization steps under high dilution conditions, which severely limit the yield and even more the scale of these syntheses. The compounds 1a and 1b do not differ in chemical nature but only in size, the smaller one offering a cage with ~ 4.5 Å, the larger one with 7.5 Å in diameter as measured by CPK-models. The similarity of these quaternary ammonium salts to certain cationic surfactants mandated the proof that 1a and 1b do not aggregate in aqueous solution, which could obscure molecular host-guest binding. As was inferred from the high ratio of hydrophilic (cationic) to hydrophobic groups and from the symmetrical architecture, quite a number of methods including NMR- and conductivity measurements clearly indicated that these compounds formed molecularly dispersed solutions in water.

Anion complexation with 1:1 host-guest stoichiometries in aqueous solution proved that the tetrahedral macrocycles indeed served the purpose they had been designed for (ref. 8). Some representative binding constants are given in Table 1. An overview shows that the smaller tetrahedral host 1a displays better binding of very hydrophilic anions, which reflects its higher charge density. The larger host prefers the more polarizable "soft" anions with low charge density, which probably indicates the enhanced participation of hydrophobic and dispersion forces in complexation. Steric strain in the host

guest complex should be the reason for the unexpected inversion of the stabilities for the iodide vs the bromide complex of 1a, because the monotonous decrease of the hydration enthalpies of the halides with their size (ref. 6) should lead to better binding of iodide ion as is found with the bigger host 1b. Doubling the charge increases the binding constant by a factor of 3; reasonably strong binding of biologically relevant anions like ATP^{4-} occurs (entry 5) if only the anionic moiety, but not the entire molecule can be encapsulated by the host. If even this is not possible as in the case of p-nitrophenolate interacting with 1a one observes complete steric discrimination.

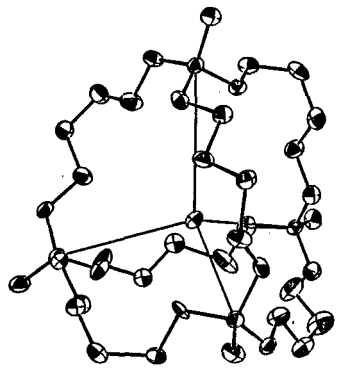


Fig. 1. X-ray crystal structure of the iodide inclusion complex of 1a

The mode of host-guest interaction can be deduced from NMR- spectroscopy and from the strict adherance to 1:1 complex stoichiometries even on addition of a large excess of the guests. Even more convincing is the isolation of a crystalline iodide salt of 1a, the structure of which was elucidated by X-ray crystallography (Fig. 1, ref. 9). One out of four iodide counterions occupies the central cavity. A very snug fit is indicated from a slight outward bending of the alkylene chains, giving the complex a more spherical shape. There can persist no doubt that the tetrahedral quaternary ammonium salts function as true inclusion hosts for anions in water.

The equilibrium selectivity, however, does not exceed a factor of 1000. Since the tetrahedral hosts 1a and 1b are chemically almost inert, it was tempting to see whether they could influence the energy of transition states (TS) in the same way as had been found for the stabilization of ground states (equilibrium binding). The kinetic selectivity was evaluated by measuring the rate effects in organic reactions running through negatively charged TS on addition of 1a or 1b. A selection of reactions is depicted in Fig. 2 (ref. 10, 11, 12, 13). While all reactions tried are inhibited in the presence of 1a, the larger host 1b shows subtle differences: Monomolecular and bimolecular reactions may be accelerated provided the rate determining step involves a highly delocalized anionic TS.

In nucleophilic aromatic and aliphatic substitutions (entry 1 and 2) acceleration factors in excess of 1000 fold can be observed in favourable cases. The decarboxylation of the 1-diastereomer of 2,3-dibromo-3-phenylpropionic acid gives a particularly informative example of the directing influence of host 1b: The uncatalyzed decarboxylation follows two parallel mechanistic paths, one involving a concerted fragmentation ultimately yields the Z-bromostyrene exclusively. The other starts with rate determining heterolysis of the benzylic carbon-bromine bond and finally leads to a mixture of E- and Z isomers in the thermodynamic ratio, with the E-bromostyrene strongly predominating. In the presence of 1b the latter pathway is suppressed completely, while the former is enhanced in rate, so that this host shows reaction selectivity. If a reaction follows a mechanism that involves the localization of charge in the rate determining step, inhibition will be found (entry 4). These and other observations emerging from the quantitative analysis of the rate effects lead to the view that the reactions take place within the cavity of 1b. Catalysis of a reaction will be observed if the stabilizing effect on the TS exceeds the stabilization of the educts at the ground state level, i.e. on host-guest complex formation. The favourable interaction of host 1b with the softer delocalized TS rather than with TS-structures having sites of localized charge density is in accord with the trend already seen in host-guest binding with 1b.

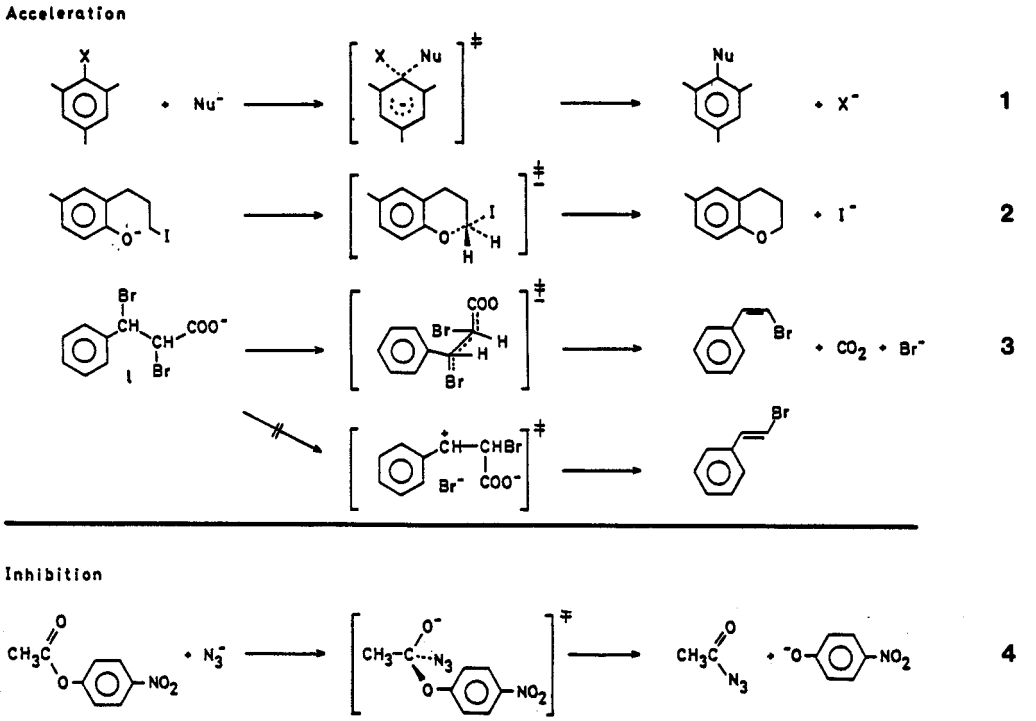


Fig. 2. Reactions, the rate of which is affected by the presence of host 1b

Though the quaternary ammonium hosts exhibited many of the characteristics peculiar to natural anion receptors, it became clear that they could only scan integral properties of the guest, like the overall charge, the hydrophobicity or the size of the anionic moiety. They could not serve to make subtle distinctions between structural guest variants, primarily because of their symmetrical design.

THE CONCEPT OF LINEAR LOCULAR ANION RECEPTORS

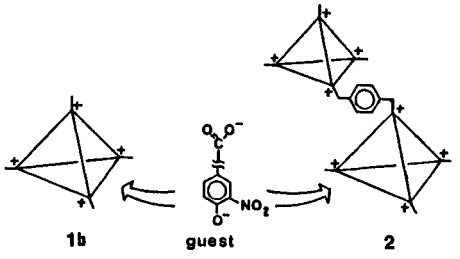
Most anionic species with interest to organic chemistry and biochemistry (carboxylates, sugar phosphates, nucleotides, coenzymes) are much larger and structurally more complicated than their positively charged counterparts, the metal cations. In general, the anionic moiety constitutes only one out of several substructures, which might function as independently recognizable determinants. One could, of course, envisage the construction of a molecular host compound that contains an anchor group for each single determinant embedded in just the right topology within a rigid molecular framework. Following this approach up to 4 functional units have been joined so far to produce rigid macrocyclic skeletons (ref. 14). The synthetic expenditure on this route to selective anion hosts is considerable, and it is at least doubtful whether it can be elaborated to produce receptors for multifunctional biologically relevant guests. This strategy on the other hand suffers from inherent conceptual drawbacks: The accumulation of anchor groups in rigid molecular structures inevitably increases the risk of slow guest exchange kinetics, which would impair most practical applications. Furthermore, this approach does not lend itself to the easy modifiability of hosts, if guests of closely related structures are to be bound selectively.

A very practical alternative strategy towards selective molecular hosts would be the linear - branched or unbranched - covalent attachment of anchor modules. Different recognition loculi may be lined up with the help of various spacer groups in any desired sequence. It is left up to the guest to arrange these binding functions in space within the restrictions given by their type, number and distances that in turn are imposed by the primary sequence. This strategy is not at all novel; it basically is the approach nature uses to produce highly selective receptors from linear copolymers of

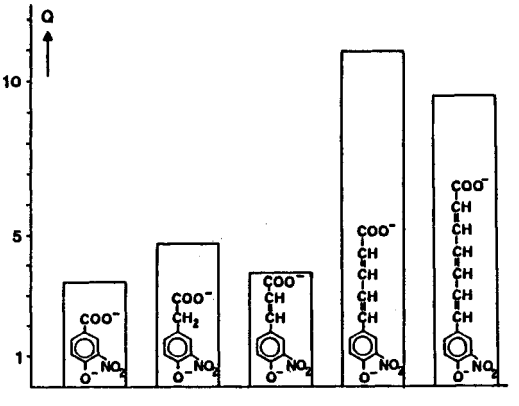
amino acids. Given a set of anchor groups the selectivity attainable is expected to be inferior to that of a completely preorganized arrangement. But there is well founded hope that this loss in selectivity can be easily compensated by increasing the number of binding functions in the host, provided the guest possesses a sufficient number of recognizable determinants. Besides the much more ready synthesizability of linear locular arrays of anchor groups compared to macrocyclisation procedures which pays off in the easy modifiability, too, this host design guarantees high motional flexibility. Therefore, the host-guest exchange kinetics should be fast and need not suffer from a counteracting selectivity increase.

We may intuitively feel that there must be an interplay between the number of binding modules necessary for selectivity and the strength of their individual interactions with the guest substructures. Increasing the number, binding strength and the barriers between different binding epitopes, all should lead to improved selectivity. Inversely, the same selectivity might be reached using several binding modules of low interaction capacity or fewer anchor groups of high individual binding strength.

An important question to answer is whether the linear polytopic host design is subject to a selectivity threshold, beyond which alterations in the number of binding modules do not surface in the selectivity parameters. This problem was addressed (ref. 15) with the help of a set of dimensional probes and a ditopic anion receptor (scheme 1). This anion host represents the initial step on the route to polytopic linear receptors. It consists of two anchor groups, one small (1a) and one large (1b) tetrahedral host substructure interconnected by a freely rotatabe p-xylene bridge. The probes contain two anionic sites in a fixed but adjustable distance. Binding can be monitored and quantified as association constants K_{ass} by the solvatochromic shift in the UV-spectrum of the o-nitrophenolate moiety interacting only with the large host structure. The appropriate reference to which any selectivity advantage of the ditopic receptor must be related is thus the monotopic host 1b. The analysis of the host-guest complexation reveals that binding of all



$$Q = \frac{K_{ass}(\text{guest} \subset 2)}{K_{ass}(\text{guest} \subset 1b)}$$



probes to the ditopic host 2 invariably exceeds ($Q > 1$) that to 1b by at least a factor of 3. This is attributable to the electrostatic attraction, because 2 bears double the positive charge of 1b. The sensitivity to structural peculiarities becomes obvious on inspection of the ratio of binding constants depending on the fixed distance of the anionic moieties. There is not much change with the smaller members of this set of probes, indicative of very similar binding modes. But lengthening the distance of negative poles in the cinnamic acid salt by another increment of ~ 2.8 Å suddenly boosts the Q-value by a factor of 3 and this level is almost maintained in the next step. The spacing of the anionic sites in the two most extended probes must be just sufficient to span the gap between the anion binding subsites of the host, which are held apart owing to the electrostatic repulsion. It is the extra interaction of the carboxylate with the smaller tetrahedral subsite that is not available to the smaller probes, but shows up as an increase in binding with the two larger ones. The anion host 2 is sensitive to the structure rather than chemical nature of the probes. We find a definite selectivity advantage by a factor of 3 exclusively due to the linear ditopic receptor design, although rotation of the host binding modules around the connection axis would prevent simultaneous recognition of the guest functions.

ANION HOSTS BEARING GUANIDINIUM ANCHOR GROUPS

The general capacity of the linear locular host strategy had been verified using the macrotricyclic ammonium hosts. However, it seemed advisable to continue on this road with a different anchor group design, which exhibits directionality and a better definition of the distance relationship of host and guest. Inspired by the unique rôle that the guanidinium side chain function of arginine plays in binding a variety of oxoanions in the proteins (ref. 16), we devised a bicyclic guanidine that incorporates the essential features of enzyme-oxoanion binding and the requirements of artificial polytopic anion hosts (Fig. 3). The central feature of the oxoanion- (carboxylate, phosphate) guanidinium interaction is an electrostatic ion pairing assisted by two parallel ionic hydrogen bonds. Protein engineering studies with Lactate Dehydrogenase replacing the substrate binding guanidinium (Arg) by a primary ammonium (Lys) moiety led to the notion that this particular binding pattern is more stable than the ammonium-carboxylate couple by some 25 KJ/mol (ref. 17). The incorporation of the guanidinium structure into a bicycle leaves only one site open for noncovalent interaction with e.g. carboxylates in the energetically favourable mode just described. So the relative position, orientation and distance of host and guest are precisely defined. Elaboration of various substituents in the α,α' position may serve to conjunct this binding unit to other anchor modules in the sense to produce a polytopic receptor. Or it may be attached to solid or polymeric supports for certain application purposes. If one succeeds to introduce chirality in these positions, enantiotopic guest recognition with predetermined enantioselectivity via attractive rather than repulsive host-guest interactions may be envisaged.

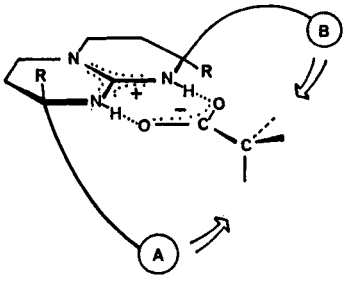
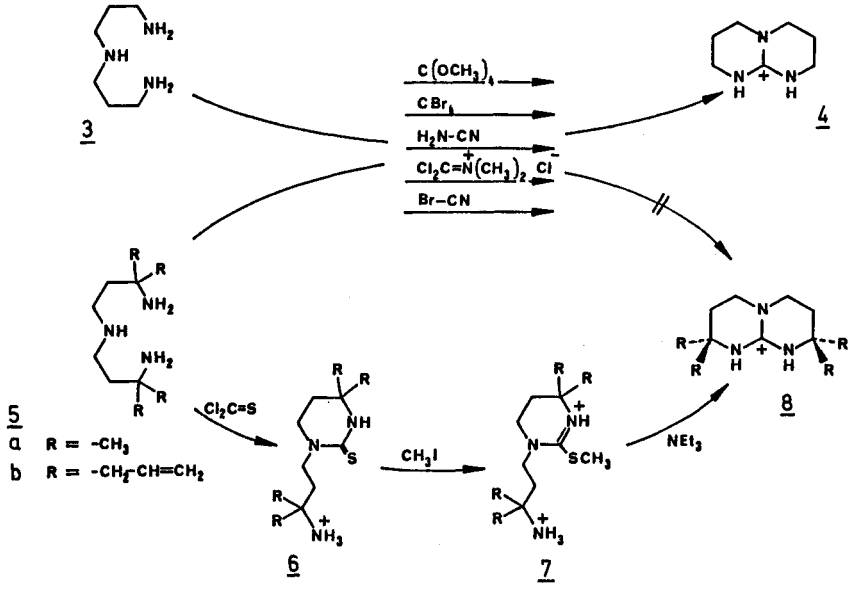


Fig. 3.
Proposed mode of binding of carboxylic anions to a polytopic bicyclic guanidinium receptor

The synthesis of the bicyclic skeleton seemed straight foreward by cyclization of an open chain triamine with a C_1-unit of the appropriate oxidation state, since the resulting heterocycle should be almost tensionless. Though this proved to be the case starting with unsubstituted triamine 3, neither of these condensation reactions with a variety of C_1-reagents gave the desired tetrasubstituted guanidine 8 starting from the corresponding α,α'-tetrasubstituted triamines 5. Instead a stepwise procedure was developed furnishing first the monocyclic thiourea 6, followed by specific S-alkylation. Deprotonation then triggered the smooth ring closure to the bicyclic guanidine.



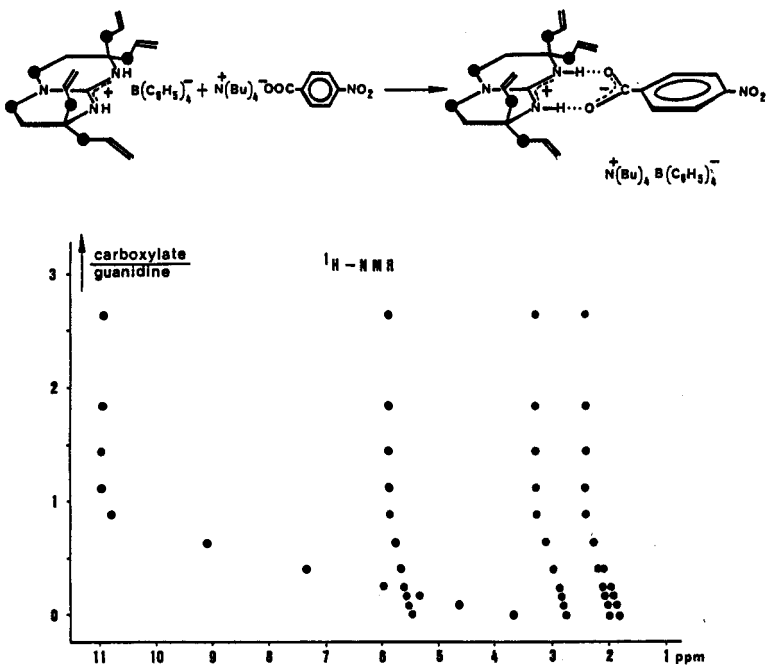
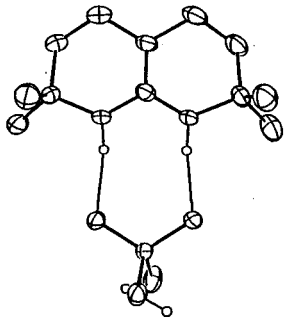


Fig. 4. ^{1}H-NMR-Titration of the complexation of p-nitrobenzoate by the bicyclic guanidinium receptor 8b

Evidence for guest complexation in the expected manner emerged from NMR-titrations (Fig. 4, ref. 18). On addition of tetrabutylammonium p-nitrobenzoate to the guanidinium tetraphenyloborate salt in $CDCl_3$ most ^{1}H-NMR-signals of the host are shifted downfield. The strongest shift, however, is seen for the guanidinium N-H peak, which moves over 7 ppm across. The plot of shift-change vs. guest/host ratio unambiguously indicates a 1:1 host-guest complex formation with rapid guest exchange kinetics, since concentration weighted signals are observed. Thermodynamically this complex is too stable in $CDCl_3$ to be measured directly by NMR. The slight hypsochromic shift of the UV-absorption band of the guest can be exploited to determine the dissociation constant. This is found to be in the micromolar range and thereby underlines the preculiar mode of ion pairing between single charged ions. We succeeded to grow crystals of some completely symmetrical guanidines as salts with a variety of oxoanions, which were suitable for X-ray examination (Dr. G. Müller, Garching). Figures 5 and 6 illustrate two complexes. The phosphate as well as the carboxylate bind to the guanidinium unit by means of the anticipated array of interactions. All of the acidic hydrogen atoms have been localized, so that there remains no doubt about the unsymmetrical nature of the N^+-H···O hydrogen bond. An amazing feature of the crystal structure of the acetate complex (Fig. 6) is the bridging function of the guest: while the more basic electron pairs (syn-lone-pairs) (ref. 19) at the carboxylate oxygen atoms are engaged in the expected pattern of the hydrogen bonds with one guanidinium receptor unit a second unit interacts by virtue of the hydroxypropyl substituents with the less basic anti-lone pairs. This binding motif continues throughout the lattice and since the remaining hydroxy groups in the sidechains of one bicycle are hydrogen bonded to their neighbouring units, too, a network of hydrogen bonds stabilizes the whole crystal.

With the proof of a well defined host-guest relationship in the series of completely symmetrical guanidinium bicycles at hand, it would be attractive to see how guests would arrange in a chiral environment. The requisite chiral hosts in principle can be prepared by either of three routes (Fig. 7): Functionalization of the symmetrical parent compound 8b may give a mixture of products, each of which after appropriate separation and enantiomeric resolution might yield an attractive candidate for chiral recognition studies. Alternatively, one may start from cheap building blocks of the chiral pool. α-Amino acids would be first choice here, because many of them are available



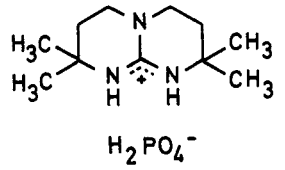
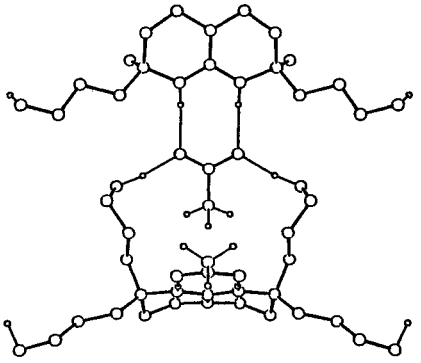


Fig. 5. X-ray crystal structure of the 8a$^+$ · $H_2PO_4^-$ salt



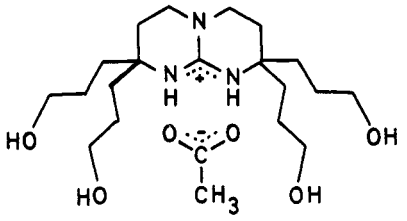


Fig. 6. X-ray crystal structure of acetate complexed by the guanidinium host 11

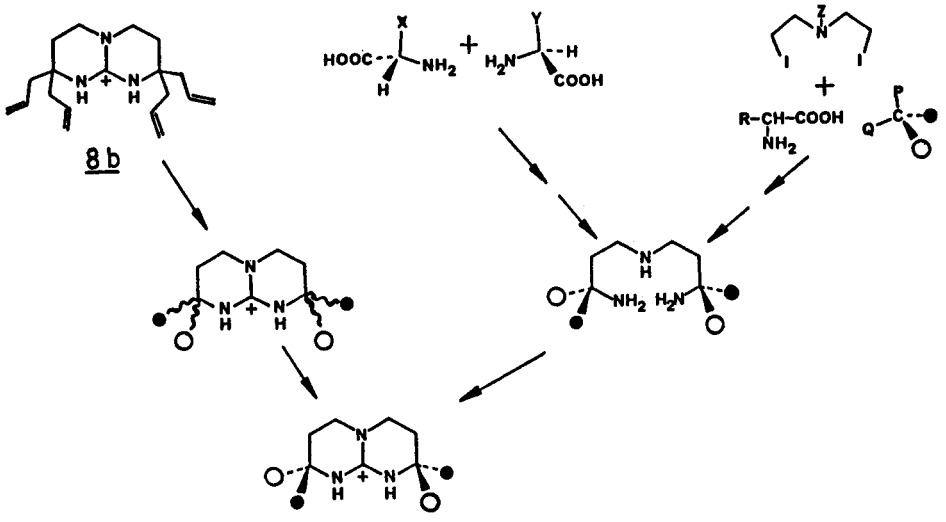
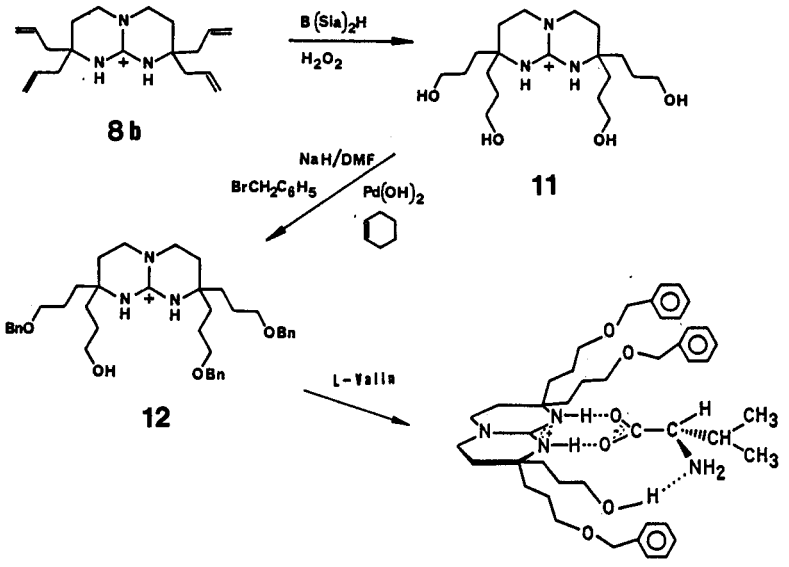


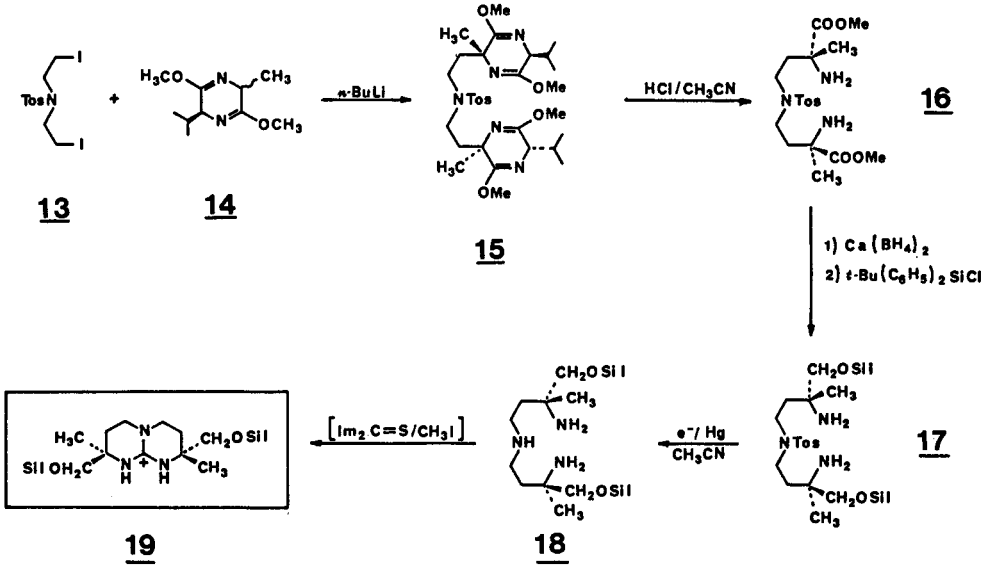
Fig. 7. Three conceptually different approaches to chiral guanidinium receptors

in either configuration and their chemistry is highly developed, so that their conversion to open chain triamines necessary for the guanidine ring-closure process can be readily planed. A third possibility is presented by the multitude of asymmetric induction syntheses starting e.g. from racemic amino acids, an alkylating agent and some chiral auxiliary, which may lead to a chiral triamine as well. To reach a founded decision between these various approaches which to follow on a large scale synthesis, each of them was investigated.

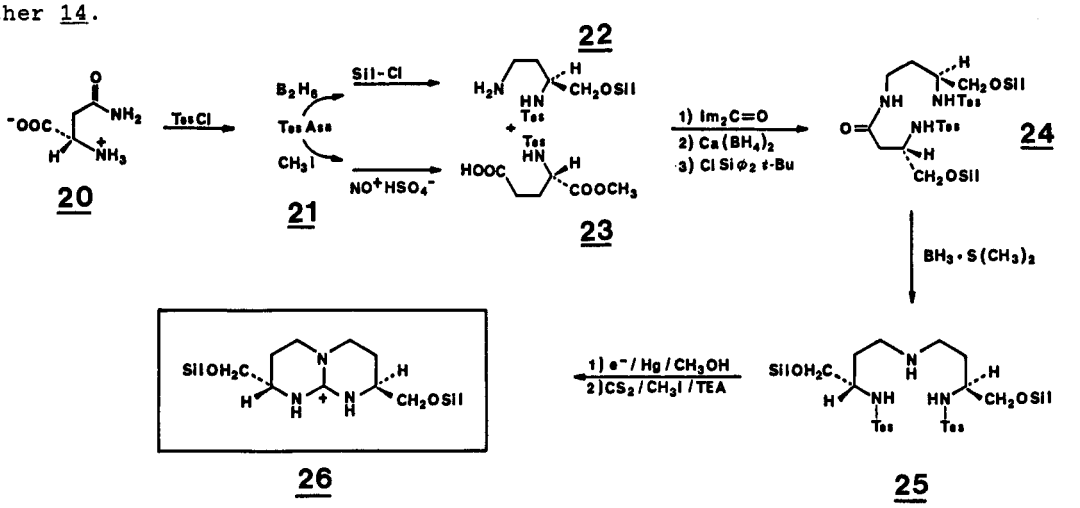
The hydroboration of 8b and subsequent oxidation of the intermediate organoboranes produced the tetrahydroxy compound 11 in good yield. To convert this still symmetrical alcohol into a chiral derivative, a monofunctionalization was planed that should give a racemic mixture of a monohydroxy bicyclic unit. The best recipe involved perbenzylation followed by partial benzylether cleavage, to give a mixture of tetra- and tribenzylether only, which was easily separated. Our initial hope to resolve the racemate of 12 by crystallization of the diastereomeric salts with optically active carboxylic acids, could not be substantiated. However, it was shown by NOE measurements, that the extending sidechains of 12 wrap around the guest on complexation with L-valin. The amino acid in its anionic form thereby is readily extracted from aqueous solution into chloroform, but the formation of diastereomeric complexes could not be detected in this case.



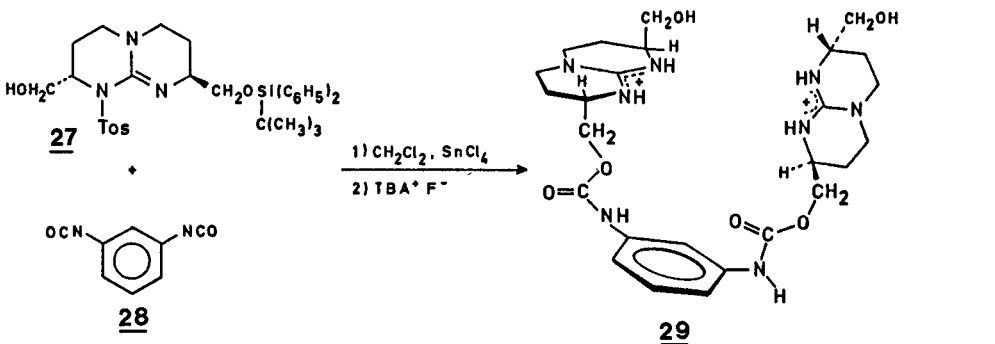
A more rational way to chiral guanidinium receptors consists in the asymmetric alkylation of α-amino acid derivatives. One particularly successful methodology was introduced by Schöllkopf (ref. 21): The alkylation of bislactim ethers derived from L-valin and alanin proceeds with very high enantioselection. In fact on reaction of 14 with the mustard derivative 13 only one stereoisomer (ee > 98 %) 15 was obtained. The hydrolysis of the bislactim ether moieties was followed by reduction of the amino acid ester 16 to the amino alcohol, which was protected as a silyl ether. Deprotection of the sec. aminofunction of 17 could be achieved by a variety of methods, cathodic



reduction being the method of choice, to furnish the chiral open chain triamine 18. An improved one pot version of the cyclization sequence finally yielded the chiral tetrasubstituted bicyclic guanidine 19. Though this route reliably gives the desired target compounds, it does not lend itself to large scale synthesis, because of the high costs of the starting bislactim ether 14.



Costs can be cut making use of readily available trifunctional α-amino acids as chiral building blocks. Asparagine 20 is one of these being available in both enantiomeric configurations and being adaptable to a synthetic scheme that in principle allows for the distinction of the rings in the bicycle. The Tos-protected L-asparagine 21 may either be reduced and protected at the alcoholic function by a silyl group. Alternatively 21 can be esterified and selectively hydrolyzed at the prim. amido group according to published procedures. The connection of 22 and 23 via an isopeptide link preceeds the reduction of the ester function and the protection of the newly formed alcohol. At this stage the introduction of a blocking group different from that in 22 would allow the differentiation of the "eastern" vs the "western" half of the final guanidine 26. The reduction of the amido group in 24 gave the partially protected triamine 25, the deblocking of which presented the major obstacle of the whole route. Only electrolytic cleavage under carefully controlled conditions afforded the deprotected triamine suitable for the conventional two step ring closure to the chiral receptor 26. This guanidinium compound has a C_2-axis, so both faces are identical, but it bears very bulky sidechains adjacent to the anion binding site. That is why complexation with racemic N-acetyl-amino acids or α-hydroxy-carboxylic acids gives diastereomeric complexes, which are readily distinguishable by NMR and may serve to determine the enantiomeric purity of these classes of substances.



Tosylation and partial cleavage of the silyl protecting groups yields the alcohol 27, which can add to the bisisocyanate 28 under Lewis acid catalysis. Treatment with fluoride removes the tosyl as well as the silyl protecting groups and furnishes a linear ditopic guanidinium host 29. The urethane functions are preferentially coplanar with the benzene ring causing the guanidiniums to arrange perpendicularly with respect to each other, if they are to act simultaneously in guest binding. We expect this to constitute a favourable geometry for the selective binding of tetrahedral anions.

At present the utility of linear polytopic hosts to boost selectivity still needs fortification. Nevertheless, we strive for it with the conviction:

Though encapsulation of ions
in cages was first to rely on,
the better perspective
for being selective
have locular hosts for anions

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