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A NON-MACROCYCLIC HOST FOR BINDING ORGANIC PHOSPHATES IN PROTIC SOLVENTS

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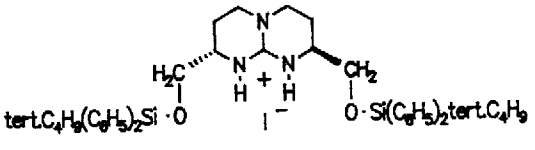
Abstract: The novel linear ditopic anion host compounds 8 and 2 bind dicarboxylic and organophosphate guest species in chloroform and in water, respectively. NMR studies indicate the formation of a host-guest complex between 2 and thymidine-5'-phosphate^{2-} in water possessing a defined molecular structure.

The complexation of apolar or polar charged substrates from aqueous solution has been studied by a variety of artificial host compounds which feature either hydrophobic or highly charged binding sites [1]. In general the main objective of the host design was to maximize the binding constant. Application of host-guest binding in the selectivity enhancement of organic chemical reactions, however, requires instead the optimization of a well defined host-guest complex structure. Shining examples in this respect are the natural enzymes and receptors, which preferentially act on oxoanionic substrates like phosphate esters. Though successful attempts [2] to bind organic phosphates to artificial macrocyclic host compounds have been reported, no structural characterization of the complexes had been possible.



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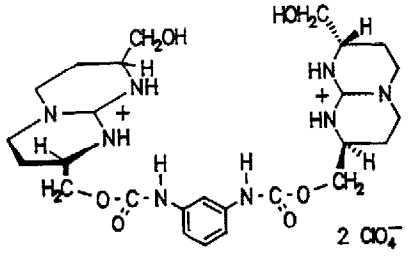


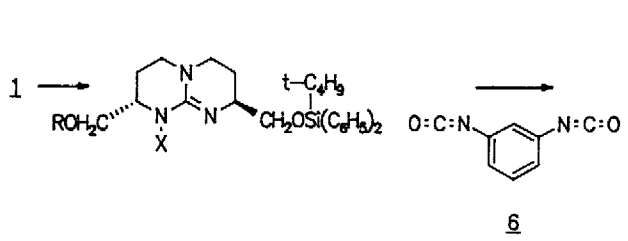
2

Since the guanidinium moiety appears to be well suited for binding oxoanions [3] as evidenced by its abundant use for this purpose in proteins [4] we constructed bicyclic guanidines and demonstrated their ability to bind and orient oxoanionic organic substrates in aprotic solution as well as in the solid state [5]. The chiral guanidinium salt 1 [6] forms diastereomeric complexes with rac. α-substituted carboxylates in acetonitrile [7], but fails to do so

in the more competitive protic solvents. A fortification of binding interactions with polyanionic phosphates was expected from an artificial host consisting of two covalently connected bicyclic guanidines 1. The resulting linear ditopic host ⊕ ⊕ could serve to complex suitable phosphates even from aqueous solution while a defined structural integrity of the host-guest complex is still conserved. We chose the urethane 2 as the prime synthetic target, because CPK model inspection led to the conclusion that molecular dimensions and hydrogen bonding features are well suited for binding tetrahedral oxoanions and the synthetic strategy seemed straightforward.

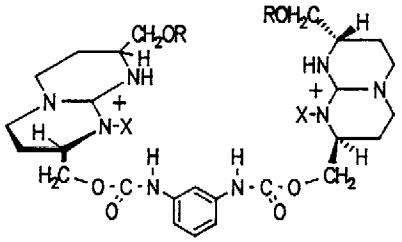
Addition of the partially protected alcohol 3 to the commercial 1,3-phenylenediisocyanate 6 and subsequent cleavage of the remaining silyloxy functions was believed to give the ditopic artificial receptor 2. However, the acid hydrolysis of 1 under controlled conditions invariably yielded a mixture of cleavage products in which the desired compound 3 amounted to about 40%. In order to enhance the yield of a monohydroxy compound and at the same time protect the guanidinium function the starting chiral guanidine 2 was tosylated to 4. Acid solvolysis (CH_3OH/HCl) of 4 now produced a 6:1 mixture of monoalcohols. Reverse phase chromatography gave the major isomer 5 ⊕ ⊕ in 70% yield.

The formation of the urethane proceeded in CH_2Cl_2 employing $SnCl_4$ as a catalyst. A mono- and the bisadduct 7 formed which were isolated by prep. HPLC. The deprotection of the guanidino function in 7 was cleanly achieved by electrochemical reduction (0.1M $NaClO_4/CH_3OH$; Hg cathode, -2.5V vs 0.1N $AgNO_3/CH_3CN/Ag$). Finally cleavage of the silylether functions furnished the target compound 2, which crystallized as the perchlorate salt from water.



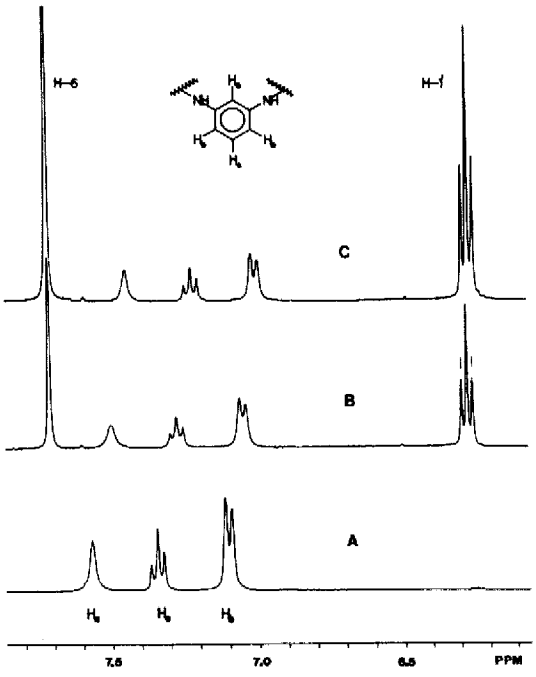
6

	R	X
3	H	H
4	$Si(C_6H_5)_2t-C_4H_9$	Tos
5	H	Tos



	R	X
7	$Si(C_6H_5)_2t-C_4H_9$	Tos
8	$Si(C_6H_5)_2t-C_4H_9$	H
2	H	H

First indications that these bis-guanidinium compounds indeed qualify as ditopic hosts came from extraction experiments with the protected precursor 8·2ClO_4^- : Dicarboxylates like succinate, fumarate, folate and N-acetylaspartate but no monocarboxylates were extracted from an aqueous phase into chloroform in the presence of 8.



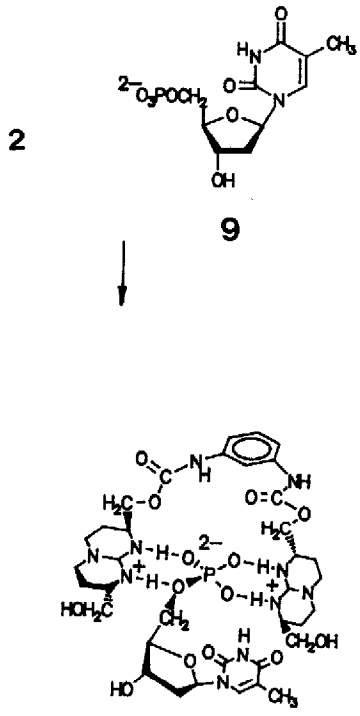


Fig.1:
Low field region of the ^{1}H-NMR titration (360 MHz) of 2 with thymidine-5'-phosphate in D_2O; A: host 2·2F$^-$ at 0.025M; B: host/guest = 0.37; C: host/guest = 0.16

Fig.2:
Tentative host-guest complex structure of thymidine-5'-phosphate 9 with 2

Well defined host-guest complex structures apparently exist in the organic phase, since e.g. the succinate protons become diastereotopic in this system. If the two guanidinium moieties converge for binding an anionic guest a perpendicular arrangement of their main planes exists, due to the chirality and the planar layout of the phenylenebisurethane spacer unit. The guanidinium N-H bonds thereby point to the corners of a distorted tetrahedron and may favor the complexation of tetrahedral anions. Simple and biologically relevant phosphates like p-nitrophenylphosphate or cytidin-5'-phosphate were shown by NMR to form 1:1 complexes with 8 even in methanol solution. The solubility of 2·fluoride (prepared by anion exchange using Serdolit AS 6 F$^-$ in CH_3OH/CH_3CN) in water allowed to follow host-guest complexation with hydrophilic phosphates by NMR. Fig 1 shows the changes of chemical shift of the aromatic signals of 2

shifts but not quite as pronounced are seen for several other signals of host and guest and they all can easily be fitted to a 1:1 binding model. The calculated association constant [10] of 10.6 M^{-1} in water may be interpreted in terms of simultaneous binding of both guanidinium units to the phosphate moiety of the guest enabled by the peculiar host design. Since simpler linear bisguanidinium compounds - even with narrower spacing of the positive charges and higher charge density - display no binding of HPO_4^{2-} in water at all [3b], the ditopic host 2 appears to be the first example of specific complexation of a mononucleotide to an artificial receptor in water, the precise interaction mode being under current investigation.

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