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Review Article

Chelate Complexes with the P=O Double Bond – a New Concept for Molecular Recognition

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Abstract. Compounds capable of forming chelate complexes with their P=O double bond systems represent excellent host molecules for most of the biologically important classes of organic cations in polar media. Additional cooperative hydrogen bonds render even simple bisphosphonates highly selective: mono- and disaccharides, 1,2- and 1,3-amino alcohols, arginine derivatives in peptidic environment and aromatic guanidines can now be recognized with high efficiency and high selectivity. The Review Article presents this relatively new concept for molecular recognition which imitates in many cases the recognition motifs found in nature itself

Key words: phosphonates, chelate complexes, cation recognition, cooperative binding, receptor molecules, P=O double bond

1. Introduction and General Remarks

Phosphinoxide groups are strong hydrogen bond acceptors but weak Brønsted bases. The high dipole moment of these functionalities make them excellent binding sites for molecular recognition of cations. However, synthetic receptors containing multiple P=O groups are rare in the literature, probably because phosphorus is usually a stereogenic center and the synthesis of new host molecules gives rise to complex isomeric mixtures. This problem can be circumvented with the achiral charged phosphonate or phosphate anions, in which an even more pronounced polarization is present; these also offer the great advantage that even at physiological pH they are fully dissociated due to their much lower pK_a values compared to carboxylates (1.8 vs. 4.8). Another convenient feature of a phosphonate or phosphate is the additional ester functionality which can at a later stage serve to introduce substituents for lateral and possibly chiral recognition of the substrate. Nature uses the phosphate anion extensively for many critical molecular recognition processes: in chromosomes the DNA is wound in a highly ordered manner around compact protein bundles consisting mainly of basic (i.e., cationic) amino acids such as arginine and lysine which are acting as counterions for the phosphodiester-backbone (Fig-

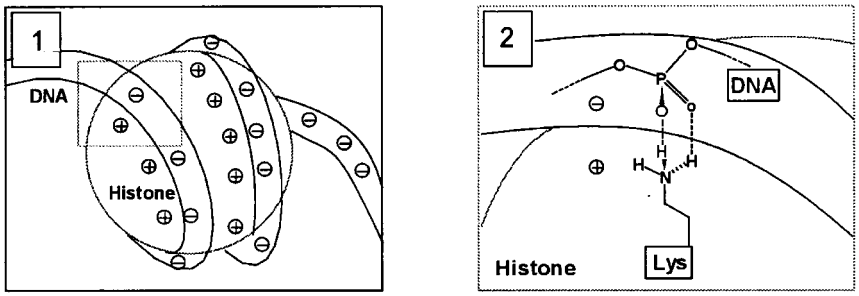


Figure 1. P=O$^{\delta-}\cdots$H$^{\delta+}$—N interactions in Nature: self-organization of DNA and histone in chromosomes.

ure 1). The reason for this self-organization is evident: it permits storage of huge amounts of data on a very confined area and at the same time guarantees fast access and safe data-handling [1]. Binding of the allosteric effector diphosphoglycerate to the histidine- and lysine-rich central region of human desoxyhemoglobin changes the conformation of the protein and thereby drastically decreases its affinity towards oxygen altitude adaptation [2]. (*For many other natural examples vide infra*). In view of the key role of P=O$^{\delta-}\cdots$H$^{\delta+}$—N interactions in Nature it is surprising how little attention has been paid to phosphonates and phosphates in the design of artificial receptor molecules and enzyme models. This paper summarizes the efforts of others and ourselves in this biomimetic field of supramolecular chemistry. It cannot be exhaustive and will necessarily omit several excellent contributions to the topic because of the inevitable selection process. Metal complexation by bisphosphonates or tripods [3] and the development of phosphonates or phosphonamidates as receptor agonists or antagonists [4] are explicitly excluded. The focus of this article will be the efficient and selective binding of biomolecules by synthetic receptors via chelate complexes with the P=O double bond.

2. Sugar Recognition

Hamilton et al. incorporated the anionic, bidentate motif found in sugar binding proteins into synthetic phosphonate-based receptors, which were able to bind to all four hydroxyls of an alkyl glycoside in acetonitrile [5]. Diederich et al. used a rigid cyclophane host with a preorganized central cavity lined with four anionic phosphodiester groups and observed 1 : 1-host-guest inclusion of alkyl pyranosides in the same solvent [6]. By modifications of the above mentioned basic structures enantioselective and size-selective molecular recognition of pyranosides and disaccharides could be achieved (Figure 2) [7].

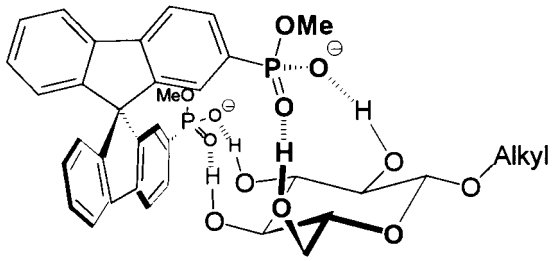


Figure 2. Enantioselective complexation of alkylpyranosides with a chiral bisphosphonate cleft.

3. Ammonium Receptors

Calixresorcinolarenes represent an easily accessible family of preorganized host compounds which can be tuned with a wide range of functional groups to achieve selective binding of the desired guest molecule. Dutasta et al. and others have introduced phosphorus bridges around their upper rim [8, 9]. These cone shaped compounds are exceptionally good hosts for simple ammonium ions in nonpolar organic media, if all P=O groups are oriented towards the center of the upper rim of the cavitand, as it is the case with all *iiii*-isomers [9]. Recently, calix[4]arene based α-aminophosphonates have been used as carriers for the membrane transport of zwitterionic amino acids; their neutral dialkylphosphonate group is assumed to bind the ammonium functionality [10]. Gellman et al. reported on a macrocyclic phosphinoxide disulfoxide array, which he could synthesize as a single *meso*-isomer. The crystal structure shows all S=O and P=O groups in proper alignment for a three point hydrogen bonding interaction with alkylammonium ions [11]. In fact, the positive termini of the three strong local dipoles appear to be suitably arranged for simultaneous interaction with the respective halide counteranion [12].

3.1. AMINO ALCOHOLS

We recently embarked on a program for the development of synthetic adrenaline receptor molecules and envisioned that the double electrostatic attraction between a *p*-xylylene bisphosphonate and an alkylammonium ion should be accompanied by formation of an almost ideal network of linear hydrogen bonds. Job-Plots confirmed the expected 1 : 1-stoichiometry of the complexes and NMR-titrations in DMSO resulted in high binding constants for various primary *and* secondary alkylammonium ions [13]. Surprisingly, these simple host molecules are able to form strong cooperative hydrogen bonds with 1,2- and 1,3-amino alcohols; in these cases the association constants increase by another order of magnitude to reach about 50,000–100,000 M^{-1} (in DMSO). The xylylene bisphosphonate moiety represents indeed a simple structural motif for the selective biomimetic 1,2- and 1,3-amino alcohol recognition (Table I) [14].

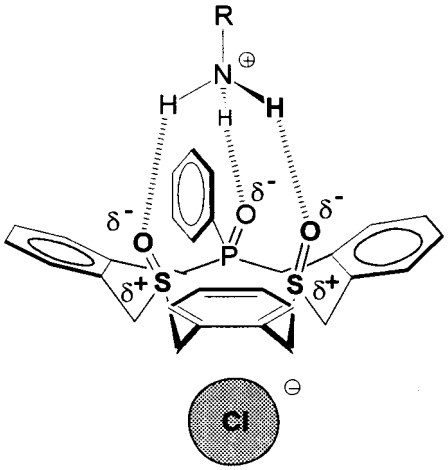
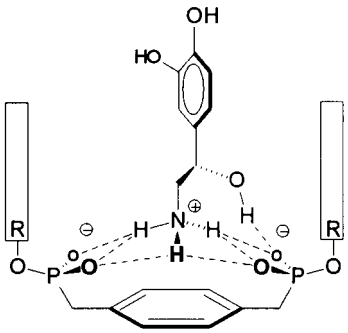


Figure 3. Simultaneous recognition of alkylammonium and halide ion by a highly polarized P=O-/S=O-macrocycle.

Table I. Association constants for amines vs. amino alcohols ($K_{1:1}$)[M^{-1}] from NMR titrations with **3** in DMSO at 20°C

Amines	10^3 [M^{-1}]	Amino alcohols	10^3 [M^{-1}]
Benzylamine	7	(±)-**4**	55
(*L*)-Alanine methyl ester	10	α-D-Glucosamine	59
2-Phenylethylamine	12	(1*S*, 2*R*)-Norephedrine	62
N-Benzyl-*N*-methylamine	19	(*R*)-Propranolol	66



We are currently refining in a stepwise manner the structure of this artificial receptor molecule by including an increasing number of the interactions used by the natural β-adrenergic receptor. If the phosphonate groups are attached to the periphery of a macrocycle, the catechol ring may be inserted into the interior of

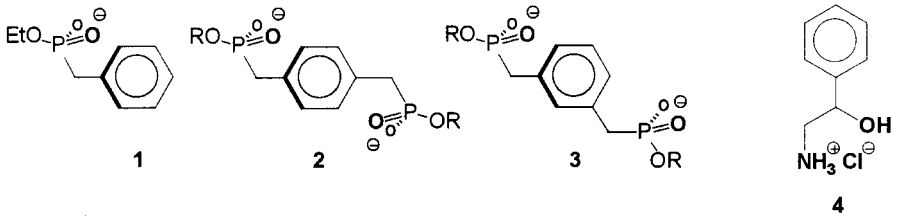


Figure 4. Simple phosphonate receptor molecules **1–3**.

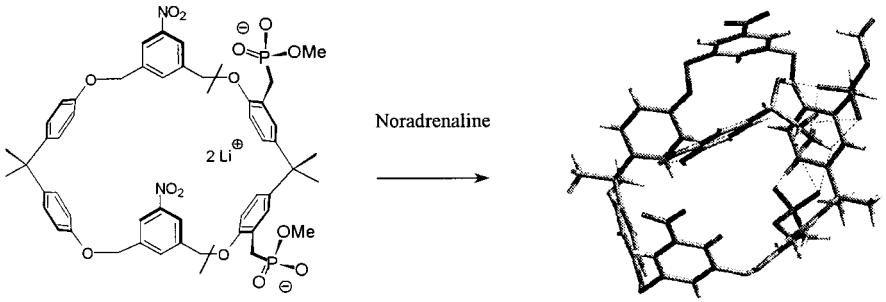


Figure 5. Macrocyclic host **5** with peripheral phosphonates – energy minimized inclusion complex with noradrenaline; strategic bonds for the macrocyclization step are marked with /.

the macrocycle; in addition to π-stacking interactions the stability of the developing complexes should, especially in water, be markedly enhanced by hydrophobic interactions [15]. Figure 5 shows our first example of such a host molecule: in a convergent synthesis the macrocycle is formed in the penultimate step by template-assisted reaction of the U-type predecessor with the phosphonate-functionalized bisphenol A. NMR-titrations with **5** in methanol give indeed the highest association constants for noradrenaline and propranolol ever measured by us in that solvent. By incorporating the xylylene bisphosphonate unit into larger, chiral macrocycles with several properly positioned functional groups we are currently trying to realize the biomimetic multipoint recognition of adrenaline derivatives. These artificial hosts may serve as adrenaline sensors, as new stationary phases for the racemic resolution of catecholamine pharmaceuticals or – after thorough tests of their drug transport and toxicology properties – even as new therapeutic agents to cure *phaeochromocytomes*.

3.2. AMINO SUGARS

Gellman's P=O/S=O bowl (vide supra) with additional peripheral hydroxymethyl groups is also capable of binding protonated amino sugars via interaction with both ammonium and hydroxyl groups. It even shows some selectivity for certain 2- and 4-epimers, but binding studies with this neutral host molecule have to be restricted to organic solvents. Also for solubility reasons, only lipophilic *p-tert*-butylbenzyl thioglycosides have been investigated [16].

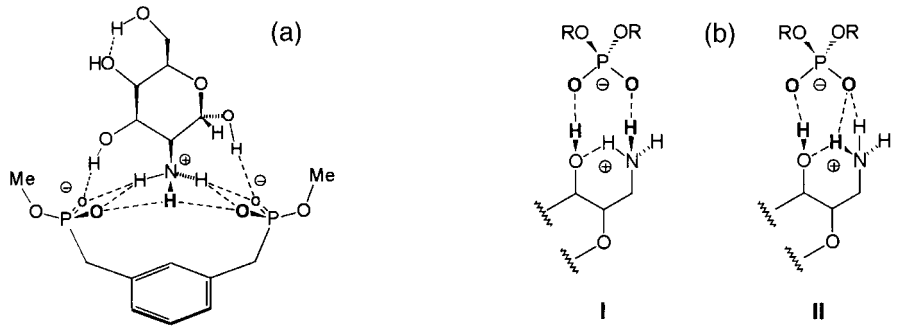


Figure 6. (a) Complex between **3** and glucosamine according to force-field calculations; (b) Two possible conformations of the 1,3-amino alcohol recognition by the RNA phosphodiester groups.

Contrary to most artificial sugar receptors, it is possible with bisphosphonate anions to bind free amino sugars in very polar media such as DMSO, methanol or even water [17]. The complex geometry is precisely defined: preorientation through the chelate of bisphosphonate and the ammonium group induces the formation of two cooperative hydrogen bonds between each phosphonate and both hydroxyls adjacent to the NH_3^+-functionality (Figure 6a). This binding motif is also used by nature itself, as Wong et al. could recently demonstrate for the RNA-recognition of aminoglycoside antibiotics [18]: the phosphodiester groups of the RNA are involved in strong electrostatic as well as directed hydrogen bond interactions with the 1,2- and 1,3-amino alcohol moiety (Figure 6b).

The high degree of molecular order generated in complexes of xylylene bisphosphonates with amino sugars can be used for anomer-selective recognition: this could be demonstrated for four aminopyranoses and a synthetic open chain amino sugar alcohol. None of these carried any protective groups which could have created differences in steric demand of epimeric OH-groups. We performed NMR-titrations in [d_6]DMSO with anomeric mixtures of varying α, β-content. The binding curves obtained had a distinct sigmoidal character for one binding partner, while a relatively normal curve was found for the other. Diastereomeric excesses of up to 90% were found in these competitive binding experiments [19]. All stability constants are well above 10^4 M^{-1}, confirming the above discussed binding mode. This means that the degree of epimeric discrimination is determined by the different strength of a single cooperative hydrogen bond between the phosphonate and the relatively acidic anomeric hydroxyl group. We are currently synthesizing chiral macrocyclic bisphosphonates and hope to achieve stereoselective inclusion of free amino sugars in water.

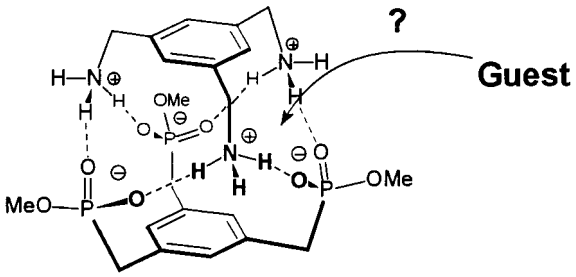


Figure 7. Molecular table tennisball from **6** and its triammonium pendant – self assembling capsules as new host systems?

4. Di- and Trications – Self Organization

α,ω-Dicationic structures are found in many natural compounds, e.g., the basic amino acids. Force-field calculations suggest that the α,ω-bisphosphonate moiety present in our simple receptor molecules is able to form highly symmetrical 1 : 1-complexes with diammonium ions. The resulting network of alternating positive and negative charges and multiple hydrogen bonds should lead to strong binding – possibly even in water. Job-Plots and NMR-titrations proved the postulated 1 : 1-stoichiometry and confirmed the existence of distinct momomeric species in solution – a simple system of self-organization was found [20]! A wide range of different aliphatic and aromatic α,ω-diamines unanimously forms these electrically neutral complexes, including the amino acids lysine, arginine and even histidine. In order to improve the moderate association constants (in the 10^3 M^{-1} range in DMSO), the C_{3v}-symmetrical trisphosphonate **6** was synthesized and titrated with various C_{3v}-symmetrical organic trications: Again discrete 1 : 1-complexes are formed, which topologically resemble table tennis balls (Figure 7) [21]. In some cases the complexes formed of achiral components become inherently chiral because a propeller conformation is induced for stereoelectronic reasons. Force-field calculations also suggest that larger complementary structures of this type form capsules which can accommodate guest molecules.

5. Guanidinium Receptors

To the best of our knowledge no artificial receptor molecule has been developed for the second class of biologically important organic cations, i.e. alkyl or aryl guanidinium ions [22]. A synthetic host for this planar cation must place both phosphonate groups in the same plane as the guanidinium ion, at a greater distance than for the ammonium cation. This array can be realized with bisphosphonate tweezer molecules.

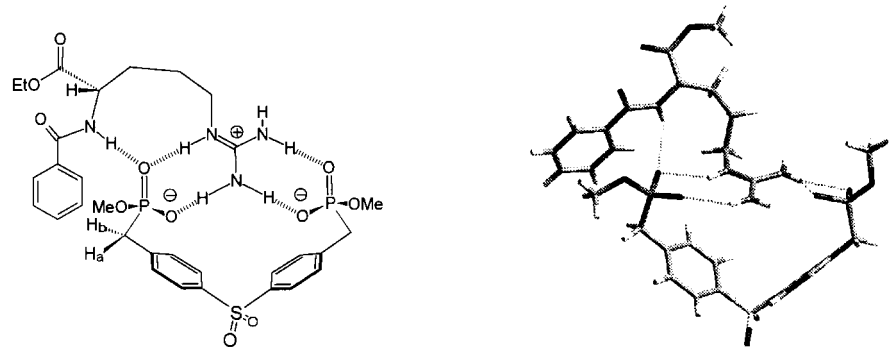
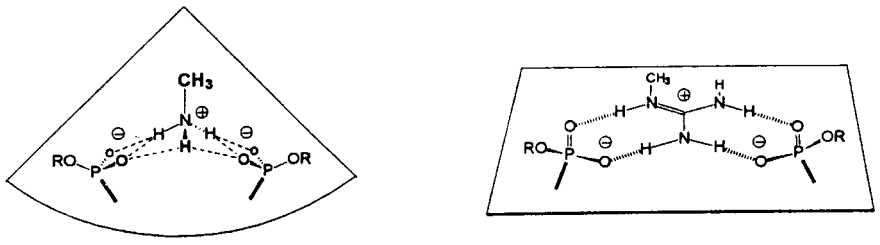


Figure 8. Conformational lock of α-*N*-benzyolarginine ethyl ester in its complex with **7** according to force-field calculations.



5.1. ALKYL GUANIDINES

Bisphosphonate **7** represents the first artificial receptor for alkyl guanidines [23]. It binds to the guanidinium moiety by forming a 1 : 1-chelate-complex, stabilized by a planar network of electrostatic interactions and hydrogen bonds. Although binding of monosubstituted alkyl guanidines is generally strong ($K_a \geq$ 10,000 in DMSO), this molecular tweezer recognizes *N*- and *C*-amide protected arginine derivatives especially well ($K_a \sim$ 300,000 in DMSO), because an additional hydrogen bond is formed between the amide and the phosphonate (Figure 8). Since **7** does not bind amines effectively, it is highly selective for arginine, even in the presence of lysine or other amino acids. For di-, tri- and tetrasubstituted guanidines the association constant remains low ($K_a \leq$ 1000 in DMSO) reflecting the increase in the guest's steric bulk. We intend to use the high selectivity of the artificial arginine receptor **7** to design enzyme mimics which are able to cleave proteins after arginine like thrombine and trypsine. To this end the phosphonic acid ester groups may be modified by appropriate nucleophiles.

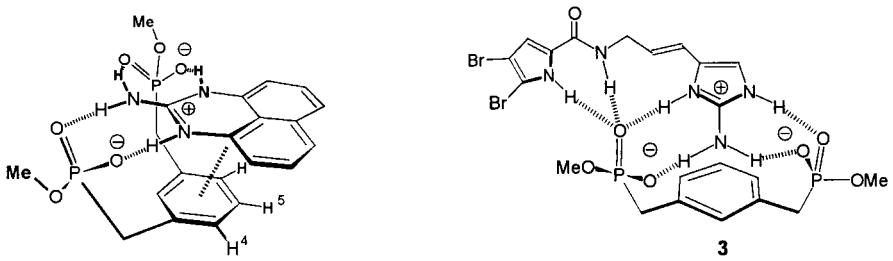


Figure 9. Left: Complex of **3** with 2-aminoperimidine according to force-field calculations. Right: Molecular recognition of oroidin by multiple hydrogen bonding.

5.2. AROMATIC GUANIDINES

We discovered that certain benzylic bisphosphonates also bind very strongly to guanidinium cations, but that these hosts are selective for aromatic guanidines [24]. Force-field calculations predict preferential formation of an "endo"-arrangement, which places the guanidinium cation directly on top of the receptor's benzene ring, leading to solvophobic and π-cation-stabilization (Figure 9). The calculated distance between the cation and the arene (3.4 Å) is ideal for such interactions [25]. If the guanidine is incorporated in a benzofused heterocycle, as in 2-aminobenzimidazole or in 2-aminoperimidine, binding constants reach values of up to 1,600,000 M^{-1}. In methanol binding constants of up to 34,000 M^{-1} are produced, even in water these guanidines are complexed strongly with K_a's of up to 2000 M^{-1}. The reason for this remarkable increase in binding strength is indicated by the large highfield shifts of the aromatic receptor protons H^{4-6} (0.3–1.0 ppm): the extended aromatic guanidinium system lies exactly on top of the *m*-substituted phenyl ring of the receptor molecule and is engaged in strong π,π-interactions. This is supported by force-field-calculations and illustrated in Figure 9.

In DMSO, receptor molecule **3** forms a 1 : 1-complex with oroidin hydrochloride, an important natural compound found in marine sponges [26]. It recognizes simultaneously the aminoimidazole nucleus as well as both the amide- and pyrrole-NH groups by formation of a network of cooperative hydrogen bonds. The high selectivity of our artificial receptor molecule **3** for aromatic guanidines can be used to develop a method for the selective extraction of oroidin and other naturally occurring guanidine derivatives. This is especially valuable, because many of the antiviral natural compounds which are currently tested against HIV-infections, are guanidines [27].

6. Amidinium Recognition

NMR-titrations with *m*-xylylene bisphosphonate **3** produced surprisingly high binding constants for several *N*,*N*-dialkylguanidines. This can only be explained if the complex adopts an alternative chelate conformation with kinked hydrogen bonds

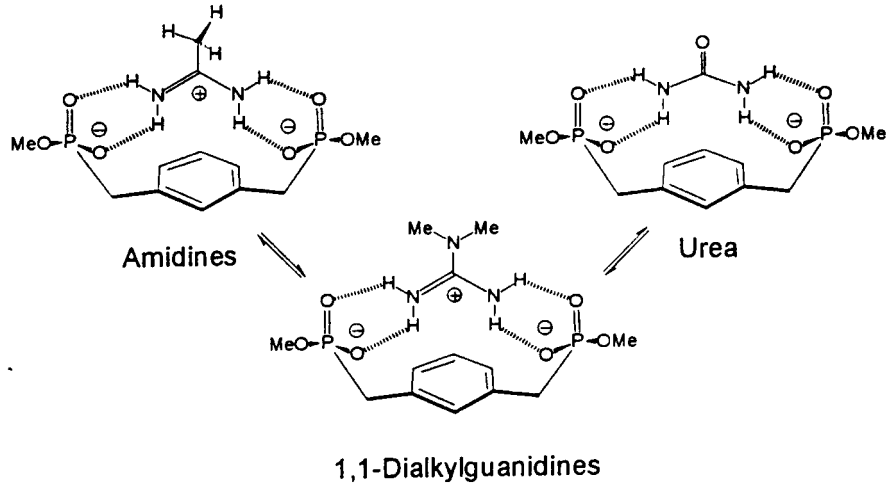


Figure 10. Molecular recognition of amidines and urea according to the same binding pattern as *N*,*N*-dialkyl guanidines.

(Figure 10). In this array, however, only two nitrogen atoms are bound to the phosphonate via four hydrogen bonds. Exchange of the third N-atom in the complex against C or O suggests that this receptor substructure can also bind amidines and even urea. On addition of **3** to DMSO-solutions of amidines in an NMR tube, both amidine protons shift downfield until 1 equivalent is reached, indicating the postulated chelate binding mode. Dilution titrations furnished high association constants about two orders of magnitude higher than those obtained with the classical carboxylate-amidinium interaction (10^5 M^{-1} vs. 10^3 M^{-1}); these amidinium-bisphosphonate complexes belong to the strongest associates of amidines with an artificial receptor [28]. (Bell et al. developed a concave polypyridine receptor molecule which also binds benzamidine efficiently, but requires a multistep synthesis [29].)

Bisamidines play an important role in AIDS therapy: 80% of all AIDS-patients suffer from a severe pneumonia caused by the pathogen *pneumocystis carinii*. Bisamidines bind to AT-rich sequences in its genome and thus prevent replication [30]. We are currently trying to imitate the DNA binding site in the minor groove with stilbenetetrakisphosphonates **8** with suitable spacers to achieve a size-selective recognition (Figure 11). Attraction of the bisamidines is based on electrostatic and hydrogen bond interactions, assisted by the hydrophobic effect of a rigid aromatic wall. With these modified phosponate hosts we hope to achieve strong and selective binding of these pharmaceuticals in water.

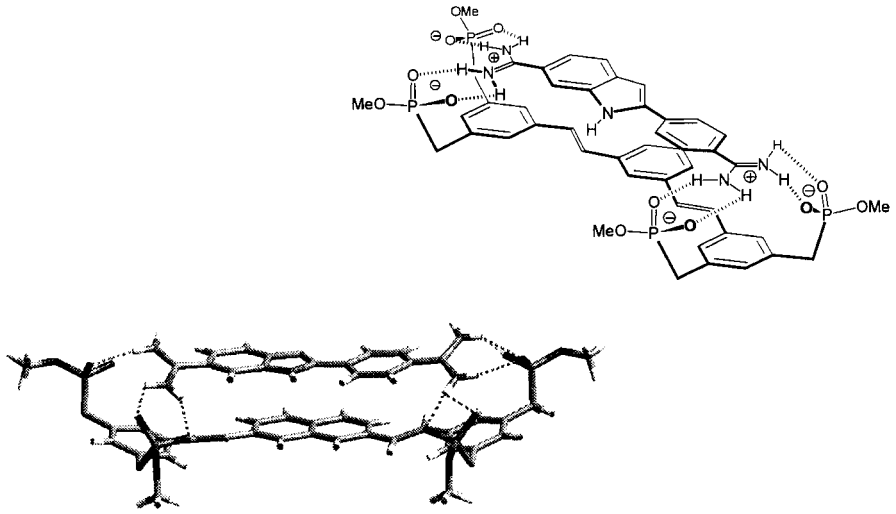


Figure 11. Force-field optimized complex between tetrakisphosphonates **8** and the bisamidinium salt DAPI (Diamidiniumphenylindole).

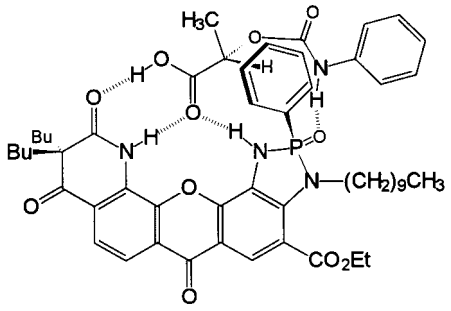


Figure 12. Chiral recognition of carbamoyl-α-hydroxy acids with a cleft-like receptor.

7. Miscellaneous

Several groups designed phosphoryl-containing macrocycles – the first X-ray structure of such a potential host molecule dates back to 1974 [31]; however, only a few of them recognized the enormous potential of binding cationic and neutral organic molecules [32]. Morán, Caballero et al. found that even a freely rotating phosphonamide group can compete with a rigid *cis*-carboxamide with regard to their complexing ability for carboxylic acids [33].

They incorporated a l,3,2-diazaphosphorinane ring into dibutylmalonic acid receptors which catalyzed their decarboxylation by way of stabilizing the transition state [34]. In an elegant approach Morán et al. recently achieved the efficient molecular recognition of chiral carbamoyl-α-hydroxy acids with a cleft-like receptor [35]. The chiral discrimination depends on the critical hydrogen bond between the

receptor's P=O double bond on a stereogenic phosphorus atom and the guest's carbamoyl amide proton (Figure 12).

8. Summary and Conclusions

Di- and tridentate compounds capable of forming chelate complexes with their P=O double bond systems represent excellent host molecules for most of the biologically important classes of organic cations in polar media. Additional cooperative hydrogen bonds render even simple bisphosphonates highly selective: mono- and disaccharides, 1,2- and l,3-amino alcohols, arginine derivatives in peptidic environment and aromatic guanidines can now be recognized with high efficiency and high selectivity. This opens the door for a wide range of applications: sugar and adrenaline sensors, catalytically active thrombine-models, new stationary phases for the extraction and chromatographic separation of naturally occurring guanidines are only a few examples among the possible future developments of this emerging new class of artificial receptor molecules.

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