Pergamon

Tetrahedron Letters 39 (1998) 517–520

TETRAHEDRON LETTERS

Strong Binding of Arylguanidinium Ions by Benzylic Bisphosphonates – Evidence for π-cation and π,π-interactions

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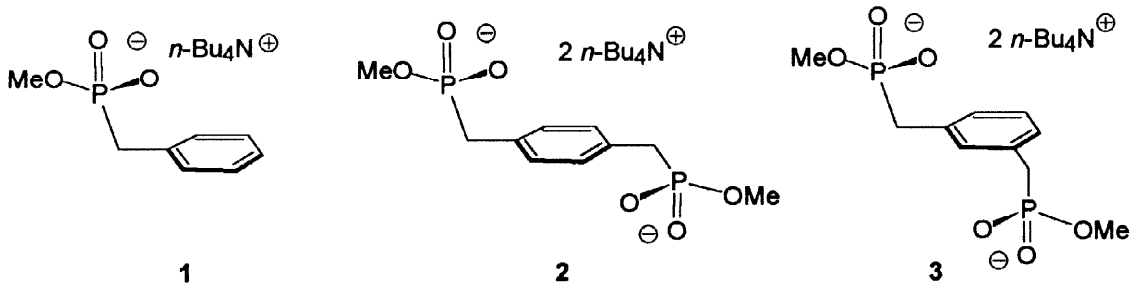
Received 29 July 1997; revised 4 November 1997; accepted 13 November 1997

Abstract: Benzylic bisphosphonate **3** represents a highly selective host for aromatic guanidinium cations. It binds to the guanidinium moiety by forming a 1:1 chelate-complex, stabilized by a planar network of electrostatic interactions and hydrogen bonds. π-Cation-attraction of the guanidium moiety as well as π-stacking of the arene rings complement the repertoire of multiple noncovalent interactions resulting in association constants of up to 1,600,000 M^{-1} in DMSO. Thus, the pharmacologically active natural compound oroidin is recognized with high structure sensitivity by formation of a network of cooperative hydrogen bonds.

In form of the amino acid arginine guanidinium cations often bind to anionic biomolecules, for which they constitute important binding sites in enzymes and antibodies.[1] Guanidines are also present in many of the antiviral natural compounds which are currently tested against HIV-infections.[2] Strong and selective binding of guanidines by artificial receptor molecules is of great medicinal interest, because it is hoped that such a receptor molecule will also be able to remove isoelectronic urea from the dialysis liquid.[3]

We have recently introduced bisphosphonate molecular tweezers as the first artificial hosts that strongly and selectively bind to monoalkylguanidines, and found high selectivity for arginine in a peptidic environment, even in the presence of lysine or other amino acids.[4] Now we discovered, that certain benzylic bisphosphonates also bind very strongly to guanidinium cations, but that these hosts are selective for aromatic guanidines. The specific recognition pattern of these molecules includes additional π,π-interactions, which were absent in the arginine-selective molecular tweezer.



1 2 3

Fig. 1. Synthetic phosphonate receptor molecules.

To check their relative binding strength we compared the benzylic mono- and bisphosphonates **1-3**. Addition of equimolar amounts of any of these phosphonates to methylguanidinium chloride **4** in [D_6]DMSO

0040-4039/98/$19.00
PII: S0040-4039(97)10672-4

results in strong complexation-induced shifts (CIS) of host- and guest signals in the ^{1}H NMR as well as the ^{31}P NMR spectrum. A Job plot confirmed the assumed 1:1-stoichiometry for all cases.[5] We performed NMR titrations of various guanidines with the receptor molecules **1-3** and calculated the association constants from the obtained titration curves with nonlinear regression methods (Fig. 4).[6] The bisphosphonates **2** and **3** complexate methylguanidine **4** 53 and 153 times stronger than monophosphonate **1**, and thus prove the postulated chelate-type binding mode (Table 1).

Table 1. Association constants $(K_{1:1})[M^{-1}]$ from NMR titrations in DMSO at 20°C.[a]

Methylguanidine **4** + Receptor molecule:	$(K_{1:1})/10^3$ $[M^{-1}]$	ΔG^{293} [kcal mol^{-1}]	Receptor molecule **3** + Arylguanidine:	$(K_{1:1})/10^3$ $[M^{-1}]$	ΔG^{293} [kcal mol^{-1}]
1	0.2	(2.9)	4-Guanidinobenzoate **5**	50	(6.3)
2	8	(5.2)	4-Guanidinobenzoate **6**	130	(6.8)
3	23	(5.8)	2-Aminobenzimidazole **7**	700	(7.8)
			2-Aminoperimidine **8**	1600	(8.3)

[a] Because of the strongly hygroscopic character of both titration partners the $[D_6]$DMSO solution contained about 0.1% of water. Errors in K_a are estimated at ± 3-50%.

However, *m*-xylylene bisphosphonate **3** adopts a geometry more favorable for a complete hydrogen bond network than **2** (Fig. 2). In addition, 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.[7] The calculated distance between the cation and the arene (3.4 Å) is ideal for such interactions.

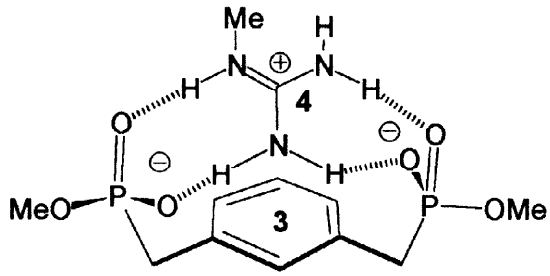
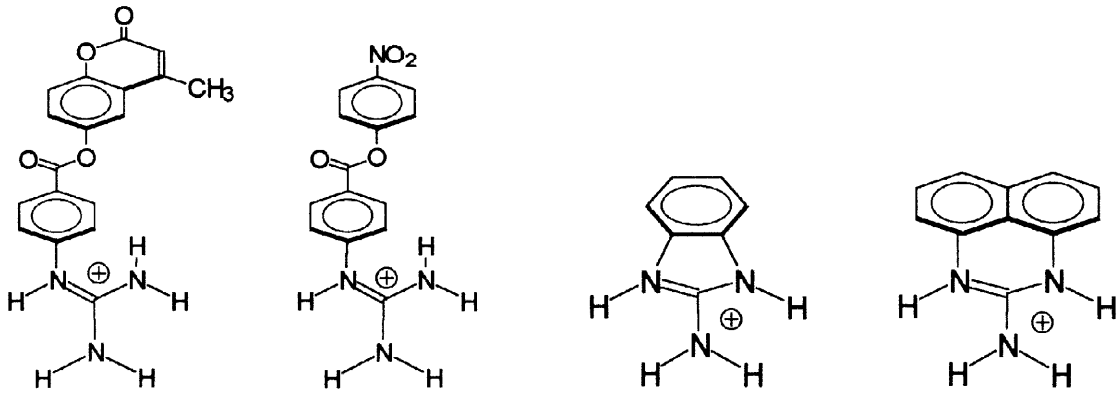


Fig. 2. Molecular recognition pattern found in the guanidinium complexes of **3**

In arylguanidinium ions the NH_2-groups are more acidic than those in the alkyl derivatives as the lower shift of the respective NMR signal demonstrates. This should strenghten the hydrogen bonds formed with the bisphosphonate receptor. In fact both guanidinium benzoates studied produced up to sixfold higher association constants than methylguanidine (Fig. 3, Table 1: **5** and **6**).

Fig. 3. Arylguanidines for the NMR titrations



5 **6** **7** **8**

Another structural feature, however, is much more effective, i.e. incorporation of the guanidine in a benzofused heterocycle, as it is the case in 2-aminobenzimidazole **7** or in 2-aminoperimidine **8**. NMR-titrations in 10^{-3} M solutions resulted in sharp binding curves which were much too inaccurate to give reliable results. Only at concentrations well below 10^{-4} M binding constants could be calculated with an estimated error of 50%. They are both above the 10^5 M^{-1} range and reach 1,600,000 M^{-1} for 2-aminoperimidine. In methanol binding constants of up to 34,000 M^{-1} are produced, even in water these guanidines are complexated strongly with K_a's 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), accompanied with considerable line-broadening of the H^5-signal. 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 Fig. 4.

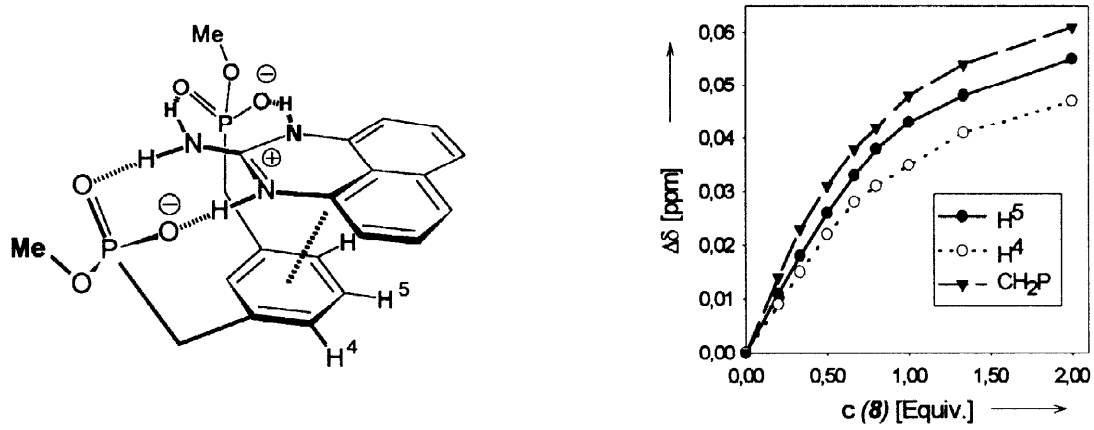
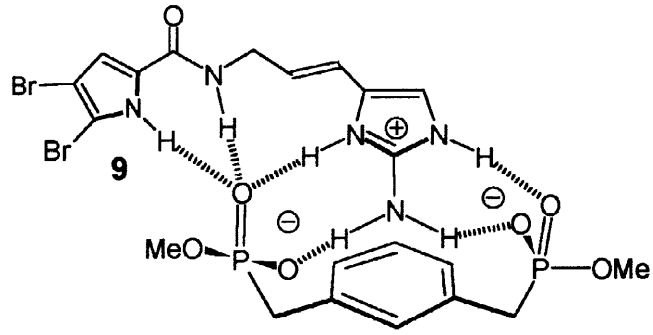


Fig. 4. Left: Complex of **3** with 2-aminoperimidine **8** according to force-field calculations[7]
Right: Dependance of the change in chemical shift of characteristic NMR signals of receptor molecule **3** (c = 5 mM) on the concentration of 2-aminoperimidine **8** in D_2O at 20°C.

These findings thus provide strong experimental evidence for the postulated „endo"-arrangement of the guanidinium-bisphosphonate complex (Fig. 2). The higher binding constant for 2-aminoperimidine correlates with its larger π-system for more efficient overlap with the receptor's π-face. Even in water a distinct highfield shift of H^5 is observed. Due to the low polarizability of water π,π-interactions become more pronounced in this solvent. To the best of our knowledge, the K_a of 2000 M^{-1} in water for the 2-aminoperimidine / **3** complex is the highest value ever observed for a substituted guanidine derivative with a synthetic host.[8]



3

Oroidin **9**, an important natural compound found in marine sponges, is known for its serotonergic and cholinergic antagonist activity.[9] In DMSO, receptor molecule **3** forms a 1:1-complex with oroidin hydrochloride, recognizing simultaneously the aminoimidazole nucleus as well as both the amide- and pyrrole-NH groups by formation of a network of cooperative hydrogen bonds. Consequently, the association constant for oroidin (520.000 M^{-1}) markedly surpasses that for the parent heterocycle 2-aminoimidazole (150.000 M^{-1}).

The high selectivity of the artificial receptor molecule **3** for aromatic guanidines can be used to develop a method for the selective extraction of oroidin. This is especially valuable because the *Agelas* sponges contain many related compounds of the highly diverse family of bromopyrrole alkaloids lacking the 2-aminoimidazole moiety.

Acknowledgments. We thank Dr. Thomas Lindel (University of Heidelberg) for providing a sample of oroidin.

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