Novel Acyclic Receptors for Aromatic Amines using Peptidic Frameworks

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The synthesis, characteristics and recognition ability of a novel class of acyclic peptidic receptors designed to complex aromatic ammonium guests using a combination of hydrogen-bonding, electrostatic and π–π interactions is described.

The development of synthetic molecular systems mimicking certain aspects of enzymes and proteins is a major objective of modern organic chemisty.[1] Almost all systems studied in that area use rigid, mostly macrocyclic, frameworks which are highly preorganized. By contrast, there are few reports on flexible recognition systems[2] even though such receptors could perhaps complex a family of substrates having complementary functions instead of a specific target compound. Such flexible systems would therefore possess the necessary requirements to become functional biomimetic catalysts.

Table 1 Binding of the guests **5–9** to the receptors **1–3** and **4b**[a]

Receptor	10^{-7} K_a/dm^3 mol^{-1} ($-\Delta G$/kcal mol^{-1})				
	$PrNH_3^+$ **5**	$PhCH_2NH_3^+$ **6**	$Ph[CH_2]_2NH_3^+$ **7**	$Ph[CH_2]_3NH_3^+$ **8**	$Ph[CH_2]_4NH_3^+$ **9**
4b	0.0057 (6.5)	0.12 (8.3)	0.53 (9.2)	0.60 (9.3)	18.5 (11.3)
1	0.08 (8.0)	865 (13.5)	2100 (14.1)	225 (12.7)	610 (13.3)
1a	0.05 (7.8)	0.51 (9.1)	0.28 (8.8)	0.49 (9.1)	2.40 (10.1)
2	0.08 (8.0)	1.40 (9.7)	0.66 (9.3)	1.50 (9.8)	14.5 (11.1)
2a	0.26 (8.7)	7.50 (10.7)	0.95 (9.4)	2.31 (9.9)	67.0 (12.0)
3	0.14 (8.4)	2000 (14.0)	192 (12.6)	1100 (13.7)	1000 (13.6)
3a	0.08 (8.0)	2.91 (10.1)	0.88 (9.5)	3.40 (10.2)	6.41 (10.5)

[a] In $CHCl_3$ saturated with H_2O at 25 °C. Values reported are the averages of five independent runs reproducible within ±5%.

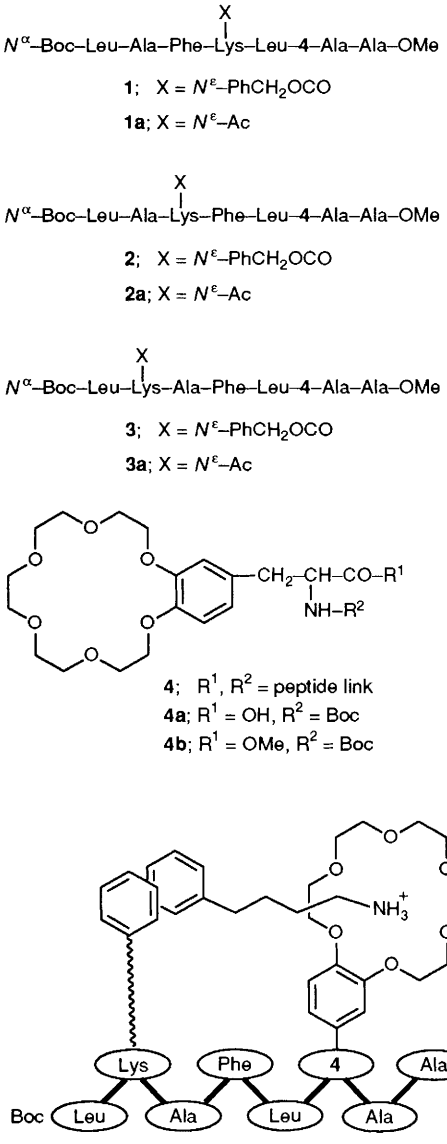

Fig. 1 Proposed binding mode between the peptidic receptor **3** in a β-sheet conformation and the aromatic ammonium guest **9**, on the basis of the results reported

As an approach towards this goal, we now report our results on the synthesis and the substrate binding ability of a novel class of acyclic flexible receptors built on peptidic frameworks. These receptors were designed to complex aromatic amines related to the bioactive family of amphetamines using a combination of hydrogen bonding, electrostatic and π–π aromatic interactions as illustrated schematically in Fig. 1.

Acyclic peptidic receptors such as **1**, **2** and **3** have several noteworthy characteristics. They are chiral and were designed to be soluble and to adopt preferentially a β-sheet conformation in organic media.[3] In addition, the selection of the amino acids and their sequence was made to facilitate the NMR structural analysis. They bear two major binding sites located on different flexible side chains: a crown ether for electrostatic and hydrogen bonding interactions and a benzyloxycarbonyl (Z) group for possible π–π aromatic interactions. Peptidic receptors **1–3** are positional isomers and the relative distance between the amino acids bearing the binding sites was systematically increased by one, two and three residues. This was done in order to study the effect of the relative position of the binding sites on the substrate complexation ability. Finally, their synthesis is rapid, versatile, and allows facile 'engineering' of their properties.

Peptidic receptors **1–3** were prepared by solid phase peptide synthesis using the *p*-nitrophenyl oxime resin.[4]† In addition, in order to verify the contribution of the benzyloxycarbonyl group to the binding capacity, we have also synthesized the crown ether peptides **1a–3a**, three analogues of receptors **1–3**, in which the potential aromatic binding site of the lysine side chain was substituted by an acetyl group.

The recognition ability of all the receptors towards aliphatic and aromatic ammonium guests was investigated by the picrate extraction technique,[7] a good method for determining the relative binding strength between different substrates.[8] The results of the binding studies are reported in Table 1. Several conclusions can be drawn from these results.

(*i*) The peptidic receptors **1–3** bind the monofunctional aliphatic guest **5** better than the monomeric crown ether **4b** ($\Delta\Delta G$ = 1.5–1.9 kcal mol^{-1}; 1 cal = 4.184 J). Similar behaviour was observed with receptors **1a–3a**. The results demonstrate that some hydrophobic interactions are involved in those cases, the apolar side chains of the peptidic receptors offering supplementary hydrophobic contacts with **5**.

(*ii*) Compared with the crown ether **4b** and their acetylated analogues **1a** and **3a**, the peptidic receptors **1** and **3** bearing the additional aromatic binding site complex more tightly the difunctional aromatic ammonium guests **6–9** by 1.5–5.7 kcal mol^{-1}, but as expected, without any great selectivity. These observations illustrate the substrate adaptability of **1** and **3**. They also indicate that the phenyl ring of the lysine side chain protecting group indeed participates in the binding of aro-

† N^{α}-Boc protected amino acids were used and coupled as their hydroxybenzotriazole activated ester.[5] The necessary N^{α}-Boc-18-crown-6 L-phenylalanine **4a** was synthesized from L-dopa following a procedure described previously.[2d,6] Deprotection steps were performed using a 25% solution of CF_3CO_2H in dichloromethane. The desired peptides were cleaved by treatment for 2 h with a 0.5 mol dm^{-3} $CHCl_3$ solution of L-alanine methyl ester and a catalytic amount of acetic acid. After purification by crystallization from $CHCl_3$–MeOH (3 : 1), pure receptors **1–3** were obtained in 20, 35 and 38% overall yields, respectively, and characterized by analytical reverse phase HPLC, FAB mass spectrometry and ^{1}H NMR spectroscopy.

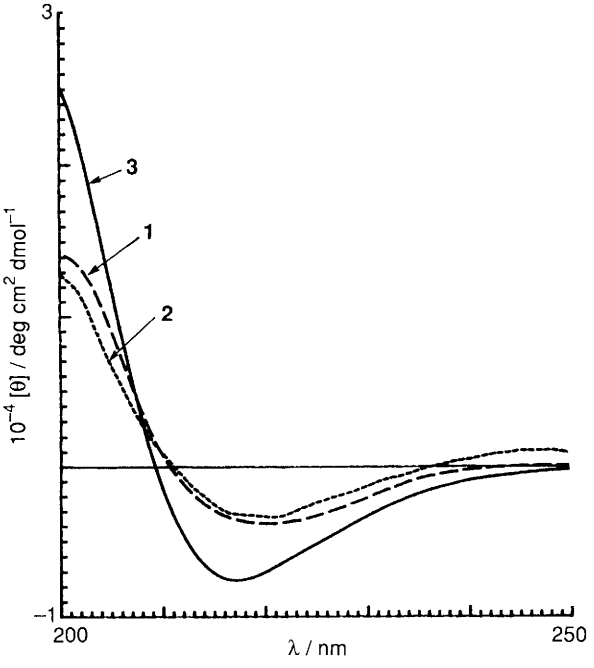

Fig. 2 CD curves of peptidic receptors **1–3** at a concentration of 7.5×10^{-4} mol dm^{-3} in 1,2-dichloroethane at 25 °C. The curves are typical of a β-sheet conformation having minima around 217 nm and maxima lower than 200 nm.

matic guests **6–9** through some π–π interactions. However, the differences observed in the binding energy are higher than the reported theoretical value (*ca.* 1 kcal mol^{-1}) for a pure aromatic–aromatic interaction.[9] Hence, the binding enhancements obtained with the aromatic ammonium guests are not solely due to aromatic interactions but most probably to a combination of this type of interaction with some hydrophobic forces.

On the other hand, these results prove that the aromatic nucleus of phenylalanine is not involved in the binding processes otherwise **1a** and **3a** would have had the same binding ability with the aromatic substrates. Inspection of Corey–Pauling–Koltun (CPK) models of **1–3** indicates that it is difficult to implicate the phenylalanine in the complexation of the aromatic guests owing to the hindered rotation of the aromatic side chain. However, the phenyl ring of the benzyloxy group is quite remote from the backbone and very floppy, therefore allowing better interactions with the aromatic guests. The involvement of π–π interactions is further supported by lower K_a and ΔG values (5.5×10^6 dm^3 mol^{-1}; −8.9 kcal mol^{-1}) obtained in a control experiment with phenethyl ammonium guest **7** and an analogue of receptor **3** where an isoleucine replaces the Z-lysine.

(*iii*) In contrast with **1** and **3**, the positional analogue **2** bearing both important binding sites does not exhibit the same enhanced binding affinity towards aromatic ammonium guests. In fact, the binding ability of receptor **2** is similar to that of its analogue **2a** lacking the aromatic binding site, indicating that the benzyloxy group does not participate to a great extent in the stabilization of the complexes formed between **2** and **6–9**. This phenomenon can be explained by the conformation adopted by **2** that unfavourably orients the two binding side chains in such a way that they cannot act cooperatively to complex difunctional guests. Indeed, circular dichroism studies in 1,2-dichloroethane demonstrated that peptidic receptors **1–3** exist as predicted, mainly in a β-sheet conformation (Fig. 2). In that conformation, **1** and **3** have the two binding side chains nicely organized to participate in the complexation of the difunctional substrates as illustrated in Fig. 1, whereas in receptor **2** they are on the opposite side of the backbone. Therefore, the conformational changes required to reorganize the binding sites correctly in **2** are probably too energetically important and preclude the participation of the Z-group in the binding processes. This hypothesis is supported by the very small conformational changes observed by circular dichroism in dichloroethane when **2** is treated with one equivalent of substrate **7**.

It is also important to note that the crown ring is essential for the complexation. This was demonstrated by a control run with an analogue of receptor **3** lacking the crown portion and **7** where the ΔG of binding was 6 kcal mol^{-1} lower than that obtained with **3**.

The results reported demonstrate the versatility and the utility of peptidic frameworks for the construction of useful acyclic receptors. In the case described, we have shown the ability of such receptors to complex biologically relevant aromatic amines using a combination of weak non-covalent interactions with well oriented side chains, a quintessential feature of natural recognition phenomena. Work is currently underway to establish in detail the solution and the solid-state structure of the complexes reported herein and to investigate the chiral recognition and catalysis abilities of receptors **1–3**.

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References

1 Recent monographs: *Frontiers in Supramolecular Organic Chemistry and Photochemistry*, ed. H.-J. Schneider and H. Dürr, VCH Publishers, Weinheim, Germany, 1991; *Advances in Supramolecular Chemistry*, vol. 1, ed. G. W. Gokel, Jai Press Inc., Greenwich, USA, 1990; *Monographs in Supramolecular Chemistry*, Series ed. J. F. Stoddart: No. 1 *Calixarenes*, C. D. Gutsche; No. 2, *Cyclophanes*, by F. Diederich; No. 3, *Crown Ethers and Cryptands*, G. W. Gokel, The RSC, Cambridge, 1989–1991.

2 Novel flexible receptors displaying important recognition ability have been reported recently: (*a*) J. Rebek, Jr., *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 245; (*b*) T. Tjivikua, G. Deslongchamps and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1990, **112**, 8408; (*c*) J. C. Medina, C. Li, S. G. Bott, J. L. Atwood and G. W. Gokel, *J. Am. Chem. Soc.*, 1991, **113**, 366; (*d*) N. Voyer and J. Roby, *Tetrahedron Lett.*, 1991, **32**, 331; (*e*) A. Galan, D. Andreu, A. M. Echavarren, P. Prados and J. de Mendoza, *J. Am. Chem. Soc.*, 1992, **114**, 1511.

3 M. Mutter, *Angew. Chem., Intl. Ed. Engl.*, 1985, **24**, 639, and references cited therein.

4 W. F. DeGrado and E. T. Kaiser, *J. Org. Chem.*, 1982, **47**, 3258; 1980, **45**, 1295.

5 W. König and R. Geiger, *Chem. Ber.*, 1970, **103**, 788.

6 N. Voyer, *J. Am. Chem. Soc.*, 1991, **113**, 1818.

7 K. E. Koenig, G. M. Lein, P. Stuckler, T. Kaneda and D. J. Cram, *J. Am. Chem. Soc.*, 1979, **101**, 3553. In a typical experiment, 250 mm^3 of a 1 mol dm^{-3} solution of the receptors ($CHCl_3$) and the substrates (H_2O) were shaken vigorously for 10 min. After centrifugation, 50–75 mm^3 of the organic layer was removed by syringe, diluted to 1 dm^3 with MeCN, and the pictrate absorbance measured. According to J. W. H. Smeets, H. C. Vissen, V. E. M. Koats-Richtens and R. J. M. Nolte (*Recl. Trav. Chim. Pays-Bas*, 1990, **109**, 147) a maximum K_d value of 1 dm^3 mol^{-1} was used in the calculations. Values reported are the averages of 5 independent runs reproducible within ±5%. Control experiments with the perchlorate instead of the picrate anion of guest **7** led to the same results within ±10%.

8 G. W. Gokel and J. E. Trafton, in *Cation Binding by Macrocylces*, ed. Y. Inoue and G. W. Gokel, Dekker, New York, 1990, p. 253.

9 W. L. Jorgensen and D. L. Severance, *J. Am. Chem. Soc.*, 1990, **112**, 4768.