Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

Backbone-modified Cyclic Peptides: New Scaffolds for Supramolecular Chemistry

Katrina A. Jolliffe[a]
[a] School of Chemistry, The University of Sydney, NSW, Australia

To cite this Article Jolliffe, Katrina A.(2005) 'Backbone-modified Cyclic Peptides: New Scaffolds for Supramolecular Chemistry', Supramolecular Chemistry, 17: 1, 81 — 86
To link to this Article: DOI: 10.1080/10610270412331328970
URL: http://dx.doi.org/10.1080/10610270412331328970

Supramolecular Chemistry, January–March 2005 Vol. 17 (1–2), pp. 81–86

Taylor & Francis
Taylor & Francis Group

Backbone-modified Cyclic Peptides: New Scaffolds for Supramolecular Chemistry

KATRINA A. JOLLIFFE*

School of Chemistry, The University of Sydney, 2006 NSW, Australia

Received (in Austin, USA) 9 August 2004; Accepted 9 September 2004

The incorporation of aromatic 'spacers' into the backbones of cyclic peptides results in structures that are greatly rigidified. The use of such compounds in supramolecular chemistry applications is reviewed.

Keywords: Cyclic peptide; Macrocycle; Scaffold; Molecular receptor

INTRODUCTION

Macrocyclic molecular scaffolds, for example calixarenes, resorcinarenes, crown and aza-crown ethers, cyclodextrins, porphyrins and calixpyrroles, are frequently used in molecular recognition research. Macrocycles have reduced conformational flexibility and therefore allow a greater preorganization of binding elements when compared to their linear analogues. They also allow functional groups to be arranged in a convergent manner suitable for binding of a guest molecule [1].

For macrocycles to be useful as molecular scaffolds, they must be readily available in gram quantities and easily functionalized. There are two approaches to the synthesis of such scaffolds. The first (and most widely used) strategy is to prepare symmetrical macrocycles by the condensation or 'cyclooligomerization' of repeating monomer units. This is an efficient synthetic approach and a multitude of synthetic procedures have been developed to enable further functionalization of scaffolds prepared in this manner (e.g. calixarenes). However, it is generally difficult to access unsymmetrical or highly functionalized scaffolds using this approach.

An alternative approach to the preparation of macrocyclic scaffolds is to cyclize a linear precursor that has been prepared in a stepwise manner. This approach allows the sequential introduction of individual subunits bearing different functional groups and can be used to prepare both symmetrical and unsymmetrical macrocycles. The stepwise synthesis of the linear precursor allows the sequence of functional groups in the macrocycle to be systematically varied and the incorporation of structural modifications is relatively simple.

Cyclic peptides are ideal candidates for synthesis via the second approach. The large number of amino acid derivatives available for synthesis allows ready incorporation of a wide variety of functionalized pendant arms into these molecules. Additionally, the use of enantiopure amino acid building blocks opens the way to the synthesis of chiral scaffolds. Despite these advantages, cyclic peptides have not been extensively investigated as artificial receptors because they are, in general, relatively flexible. One method for controlling this flexibility is to incorporate rigid aromatic subunits into the backbone of the cyclic peptide. This can be achieved by incorporating unnatural rigid amino acids, such as 3-aminobenzoic acid (Aba), into the peptide or by cyclocondensation of side-chain residues onto the peptide backbone to give azole heterocycles. The introduction of these rigidifying elements into the peptide backbone can result in the adoption of well-defined conformations in solution and allows binding groups to be arranged in a preorganized manner. The use of such 'backbone-modified' cyclic peptides as molecular scaffolds has only recently been explored and forms the subject of this review. The discussion below is not comprehensive but is rather intended to illustrate the potential of these new molecular scaffolds in various

*Corresponding author. E-mail: jolliffe@chem.usyd.edu.au

ISSN 1061-0278 print/ISSN 1029-0478 online © 2005 Taylor & Francis Ltd
DOI: 10.1080/10610270412331328970

areas of supramolecular chemistry. It is specifically limited to cyclic peptides that exhibit a 'head-to-tail' arrangement of amide bonds.

3-AMINOBENZOIC ACID (Aba) DERIVATIVES

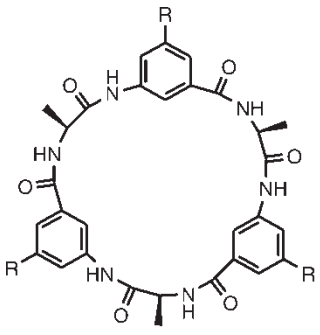
Ishida and co-workers have prepared a number of cyclic peptides containing the unnatural amino acid Aba as a rigidifying element [2–4]. Several cyclic peptides were synthesized by stepwise coupling of Boc-Xaa-Aba-OH (Xaa = any α-amino acid) building blocks onto an oxime resin. Macrocyclization was performed with concomitant release from the resin to produce the free cyclic peptides. UV–vis titration experiments in DMSO indicated that the disodium salt of 4-nitrophenyl phosphate forms 1:1 complexes with the receptors [$K_a = 1.2 \times 10^6\ M^{-1}$ for cyclo-(Ala-Aba)$_3$ (**1**)]. Additional evidence for the binding mode was obtained by ^{1}H NMR spectroscopy, which indicates that **1** has C_3 symmetry that is maintained on binding the phosphoester. On addition of 4-nitrophenyl phosphate, the signals attributable to the amide protons undergo large downfield shifts, consistent with the formation of hydrogen bonds. Changing the side chains of the α-amino acid did not significantly affect the binding affinity. However, increasing the size of the macrocycle to the analogous octapeptide resulted in a decrease in binding affinity of two orders of magnitude [2].

A number of similar molecules have been prepared in which Aba was used to rigidify cyclic peptides bearing the three residues of the serine proteinase catalytic triad. Cyclo(Ser-Aba-His-Aba-Asp-Aba) (**2**) and cyclo(Ser-Aba-His-Aba-Asp-Aba-Ala-Aba) were prepared in an identical manner to **1**, using dipeptide building blocks bearing the appropriate side chains. The ability of these peptides to hydrolyse 4-nitrophenyl acetate was then determined in Tris-buffered DMSO at 35°C by UV–vis spectroscopy. At pH 7.3, modest rate accelerations of 3.3 and 14.3 were observed for the hexa- and octapeptides, respectively [3].

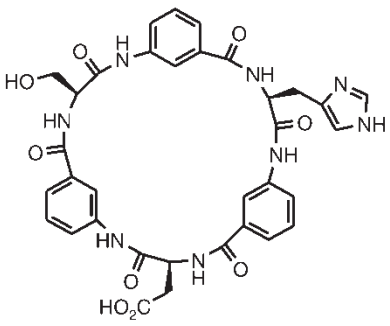
Cyclic peptides containing 5-substituted-Aba derivatives have also been used to prepare artificial ion channels. A series of cyclic peptides of the sequence cyclo[Xaa-(5R-Aba)]$_n$ (e.g. **3**) were prepared and inserted into planar lipid bilayers. The single channel currents were then measured under voltage clamp conditions. All of the cyclic peptides exhibited similar conductance properties (*ca*. 9 pS in a symmetrical 500 mM KCl solution with selectivity for monovalent cations), despite changes in cyclic peptide size and amino acid constitution. Blockage of the channels by Ca^{2+} in a voltage-dependent manner was observed in all cases, suggesting that the ion channels are formed from tail-to-tail dimers of the peptide where the macrocycle forms the channel entrance and the alkyl chains build up the pore [4–6].

Cyclic hexa- and octapeptides containing Aba residues have been used as templates for the formation of three- and four-α-helix bundles, respectively [7–10]. Nishino and co-workers prepared an antiparallel four-helix bundle using cyclo(Lys-Aba-Api-Aba)$_2$ as a template (Api = L-α-aminopimelic acid). The incorporation of both $-NH_2$ (Lys) and $-CO_2H$ (Api) terminated side chains enabled the preparation of a bundle with antiparallel helices. Two of the helices included a 1-pyrenylalanine residue, and the formation of the four-helix bundle was detected using fluorescence spectroscopy. In water/trifluoroethanol mixtures (95:5) a strong pyrene excimer emission indicated that the α-helices were in close proximity. Addition of more than 20% methanol to the mixture resulted in loosening of the bundle to give single α-helices as observed by a sharp decrease in excimer emission [7].

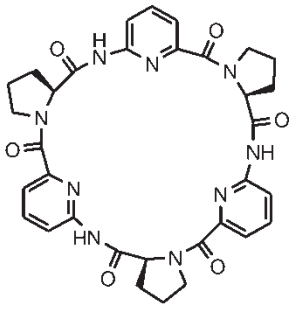
Attachment of amphipathic helices (alamethicin) to cyclo(Lys-Aba)$_n$ scaffolds ($n = 3, 4, 5$) gave helix bundles, which were inserted into lipid bilayer membranes. The cyclic hexa- and octapeptide bundles formed ion channels with single conductance states, while the cyclic decapeptide formed ion channels with more variable conductance states. This difference was attributed to the greater flexibility of the larger cyclic decapeptide scaffold [8].



1: R = H
3: R = NHC(=O)C$_9$H$_{19}$



2



4

The same cyclic hexapeptide, cyclo(Lys-Aba)$_3$, was used as a scaffold for the synthesis of a different three-helix bundle. In this case, the amphiphilic 13-residue helices contained a 5-bipyridylalanine amino acid, and the helix bundle was found to bind tightly to Ni^{2+} ions. A UV–vis titration experiment indicated that the complex had 1:1 binding stoichiometry. While the rate of formation of the complex was relatively slow, the complex was very stable and showed almost no exchange when 100 eq of EDTA were added, suggesting that the 'hydrophobic nest' created for the metal ion is highly shielded from solvent [9].

Rasmussen and Rebek have illustrated the potential application of Aba-derived scaffolds for the synthesis of combinatorial libraries. Cyclo(Asp-Aba)$_3$ was activated *in situ* as its mixed anhydride with isobutylchloroformate and then reacted with a mixture of three amines to give a library containing 11 compounds. Similarly, cyclo(Dpa-Aba)$_3$ (Dpa = L-2,3-diaminopropionic acid) was reacted with mixtures of either three acid chlorides or three sulfonyl chlorides to give 11-component libraries of amides or sulfonamides, respectively. An orthogonally protected scaffold was also synthesized on a gram scale, and sequential deprotection and subsequent reaction with three different reagents was demonstrated [11].

Kubik and co-workers have prepared a number of Aba containing cyclic peptides and their analogues in which the Aba residue is replaced by 3-aminopicolinic acid (Apa). The capabilities of these molecules to bind both anions and cations have been investigated [12–23]. Initial experiments indicated that cyclo[-Glu(*i*Pr)-Aba]$_3$ forms complexes with the cation, via cation–π interactions, when mixed with *n*-butyltrimethylammonium iodide ($BTMA^+I^-$). A binding constant of 300 M^{-1} in $CDCl_3$ was determined by ^1H NMR using the upfield shift of the guest protons, which are shielded by the aromatic Aba residues. The stoichiometry of the complex was confirmed as 1:1 by Job's method. Interestingly, when the iodide was replaced by tosylate, a different complex was observed in which both the anion and cation are bound simultaneously [K_a (TsO^-) = *ca.* $10^9\,M^{-1}$; K_a ($BTMA^+$) = $3.88 \times 10^6\,M^{-1}$]. The increased binding affinity for $BTMA^+$ compared to that observed in the absence of a binding anion is attributed to preorganization of the cyclic peptide upon anion binding [12]. Further rigidification of the peptide by replacing the Glu residues with Pro resulted in increased binding constants for both anions and cations [13]. Substitution of the 4-positions of the Aba residues in the latter compound results in less conformational freedom in the cyclic peptide and also in a loss of anion affinity. However, the increased conformational control results in preorganization for cation binding, which leads to increased cation affinity [14–15]. These chiral hosts have been found to exhibit different affinities towards the two enantiomers of the *N*,*N*,*N*-trimethyl-1-phenylethyl ammonium cation [16].

Cyclo[Pro-(5R-Aba)]$_3$, in which the Aba groups bear substituents at the 5-positions that terminate in carboxylate groups, have been observed to bind both methyl glycosides [$K_a = 160–810\,M^{-1}$ in $CDCl_3$/CD_3OD (4%)] [17] and guanidinium ions, including both L- and D-arginine derivatives [18].

3-AMINOPICOLINIC ACID (Apa) DERIVATIVES

Replacing the Aba residues with Apa residues yields cyclic hexapeptides that do not bind cations, but are capable of binding anions in 80% D_2O/CD_3OD mixtures. ^1H NMR experiments indicated that **4** forms a 1:1 complex with benzenesulfonate (K_a = $44\,M^{-1}$). By contrast, **4** forms 2:1 sandwich-type complexes with Cl^-, Br^-, I^- and SO_4^{2-}, as evidenced by Job plots, mass spectral data and an X-ray crystal structure of the 2:1 iodide complex [19,20]. Subtle changes to the cyclic peptide structure, such as replacement of the Pro residues with 4*R*-hydroxyproline (4*R*-Hyp) results in altered binding behaviour [20].

A compound in which two cyclopeptide units are covalently linked with an adipinic acid spacer (**5**) results in stabilization of the sandwich complexes with halides, sulfate and nitrate, which now exhibit 1:1 binding stoichiometry (Fig. 1). Stability constants of these complexes, determined by ^1H NMR titrations and isothermal titration microcalorimetry, are in the range $10^5–10^2\,M^{-1}$ in 50% water/methanol and decrease in the order $SO_4^{2-} > I^- > Br^- > Cl^- > NO_3^-$. This order was rationalized in terms of size,

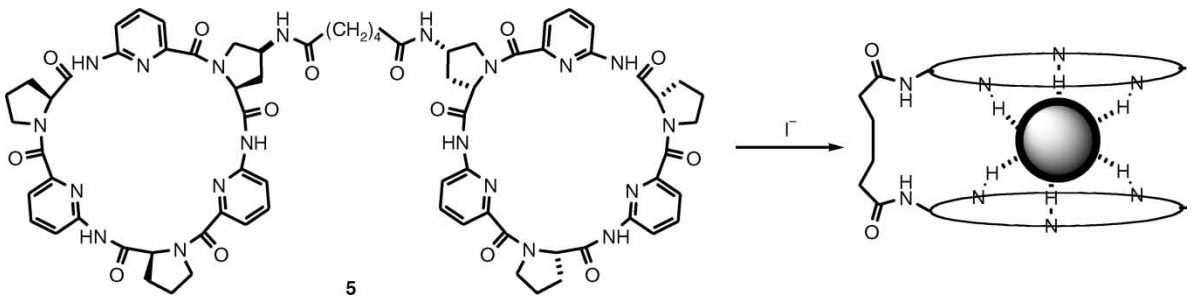


FIGURE 1 Complexation of iodide by a molecular 'oyster'.

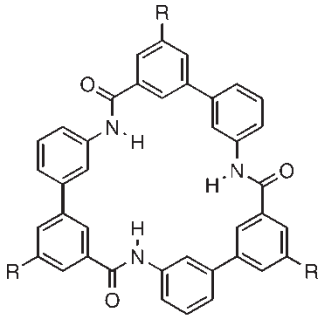
with larger anions having a better fit with the host cavity. The higher stability of the sulfate complex is attributed to the ability of this oxo-anion to form stronger hydrogen bonds with the NH groups of the receptor [21]. Dynamic combinatorial chemistry has now been used to optimize the linking unit to give two new receptors that bind iodide and sulfate anions in 2:1 acetonitrile/water, with association constants of 5.6×10^4 and $6.7 \times 10^6\ M^{-1}$, respectively [22].

3′-AMINOBIPHENYL-3-CARBOXYLIC ACID

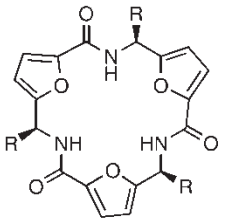
Choi and Hamilton prepared cyclic trimers of 3′-aminobiphenyl-3-carboxylic acids by macrocyclization of the appropriate linear precursor in 40–60% yield under high dilution conditions. The incorporation of the biphenyl spacers into the cyclic peptide backbone reduces the conformational flexibility of the molecule and positions the three amide protons in the correct orientation to bind to tetrahedral anions. ^{1}H NMR titration experiments indicated that **6** binds spherical anions (e.g. I^-, Cl^-) in 2% d_6-DMSO/$CDCl_3$ with some selectivity for larger ions, but that binding affinity for these anions is lost on increasing the polarity of the solvent. However, **6** binds tetrahedral anions (e.g. HSO_4^-, $H_2PO_4^-$) in neat d_6-DMSO with binding constants of 10^5–$10^4\ M^{-1}$ [24,25].

5-(AMINOMETHYL)-2-FURANCARBOXYLIC ACID

Chakraborty and co-workers prepared a cyclic trimer of 5-(aminomethyl)-2-furan carboxylic acid (**7**) as a receptor for carboxylate anions. ^{1}H NMR titrations indicated that **7** binds acetate ions in a 1:1 ratio with an association constant of $8.64 \times 10^3\ M^{-1}$ in CD_3CN [26].



6a: R = CO_2Me
6b: R = NHBoc



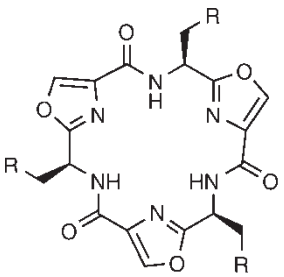
7

AZOLE HETEROCYCLE DERIVATIVES

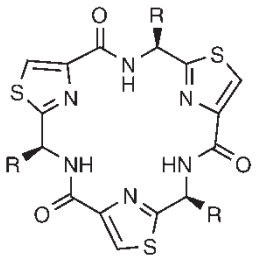
Azole heterocycles can be derived from the condensation of cysteine, serine and threonine side chains with the adjacent amino acids in a peptide sequence. A large number of natural products containing these types of backbone-modified amino acids have been identified in recent years. In particular, the *Lissoclinum* family of cyclic peptides contains cyclic hexa-, hepta- and octapeptides characterized by the presence of oxazoline/oxazole/thiazoline/thiazole heterocycles alternating with proteinogenic amino acid residues [27]. The presence of the modified amino acids influences the three--dimensional structures and bioactivity of these natural products and it has recently been suggested that analogues of the natural products have potential as molecular scaffolds for the development of synthetic receptors and combinatorial libraries.

To date, most of the research on the use of these modified cyclic peptides as molecular scaffolds has centred on cyclic hexapeptides containing three oxazole or thiazole residues (e.g. **8**–**12**). These contain relatively flat heterocycles linked by *trans* amide bonds. The alternating hydrogen-bond donor and acceptor sites that line the interior of the molecules form a network of bifurcated hydrogen bonds that further rigidifies the macrocycle and also inhibits the binding of anions by hydrogen bonding. The orientation of the three amino acid side-chain substituents depends on the absolute configuration at the α-carbon atoms. For all-*syn* substituted compounds the side chains are presented on the same face of the macrocycle, preorganized for recognition of a target molecule.

Rebek and co-workers have investigated the synthesis of a number of these backbone-modified cyclic peptides containing both oxazole and thiazole heterocycles [28–31]. Cyclic hexapeptides cyclo[Asp-Ser(Oxz)]$_3$ **8** and cyclo[Dpa-Ser(Oxz)]$_3$ **9** have been synthesized both by a linear stepwise synthesis followed by macrocyclization and by the cyclooligomerization of a monomer unit. Cyclooligomerization generally gives mixtures of cyclic hexapeptide, cyclic octapeptide and small traces of higher oligomers [28]. By using stepwise linear syntheses, a number of differentially protected platforms have been prepared and sequential deprotection of the side chains has been illustrated [29,30].



8: R = CO_2H
9: R = NH_2



10: R = $CH_2CH_2CO_2H$
11: R = $(CH_2)_4NH_2$
12: R = $(CH_2)_3NH_2$

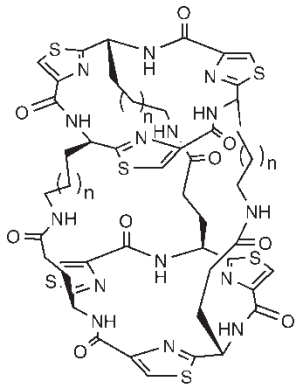
Several cage-type structures have been prepared by either linking two cyclic peptides together via their side chains or alternatively capping the cyclic hexapeptides by reaction with a C_3-symmetric molecule [32,33]. Singh *et al*. prepared the cylinder **14** in 47% yield by coupling the glutamic acid-derived cyclic hexapeptide **10** with the lysine-derived cyclic hexapeptide **11**. Cylinder **14** appeared to trap HMPA and hydroxybenzotriazole (by-products from the BOP coupling reagent) as evidenced by ^{1}H NMR spectroscopy and co-elution from rpHPLC columns. However, these could be removed upon stirring **14** with $NaHCO_3$ in aqueous DMF indicating that the portals in this cavitand are large enough to allow molecules to pass through. Conversion of the triacid **10** to the corresponding tribromide and subsequent reaction with 1,4,7-triazacyclononane gave the cone-shaped molecule **15** (55%). Preliminary studies suggested that **15** interacts with Cu^{2+} in methanol solution indicating the potential host–guest properties of this type of cage structure [32].

In contemporaneous studies, Pattenden and Thompson prepared the cylinder **13** (30%), which contains one less methylene group in the side-chain linkers than does **14**, from the corresponding ornithine-derived cyclic hexapeptide **12**. A cone-shaped structure **16** was prepared upon reaction of the Glu-derived cyclic hexapeptide **10** with tris(aminoethyl)amine [33]. In a different approach to the synthesis of cone-shaped structures, three thiazole subunits or three oxazole subunits were attached to a triscarboxylic acid linker. Deprotection was then followed by a covalently templated macrocyclization step to give the corresponding cages in moderate yield. In each case, two isomers of the cage compounds were obtained, in which the tertiary hydrogen substituent is either 'inside' or 'outside' the cage [34].

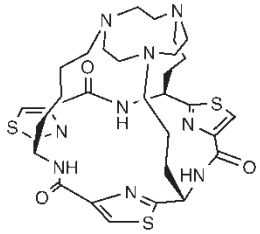
Cyclic hexapeptides containing *N*-methyl imidazole and a bicyclic imidazole species have also been prepared [35–37]. In the case of the bicyclic imidazole-derived platform, **17**, hydroxy groups are directly attached to the outer edges of the bicycles, resulting in a large distance between them (> 11 Å as determined by molecular modelling) and an increase in the preorganization of the system [37].

While a number of azole heterocycle containing cyclic hexapeptide platforms have been prepared and preliminary studies on their potential to form cages and act as molecular receptors have been reported, the analogous cyclic octapeptides have not been widely investigated. This is due to the greater flexibility of the larger macrocycles, which lowers the preorganization of any binding elements they bear. However, the cyclic octapeptide scaffold **18** has recently been used to hold two antiparallel peptide loops in a conformation that mimics that of the interhelical protein loops of helix bundles and the complementarity-determining loops of antibodies [38]. Molecular modelling has been used to illustrate that, while the cyclic octapeptide **20** is more flexible than the corresponding cyclic hexapeptide **19**, it should be possible to use **20** to form larger analogues of the cylinder **13**; molecular troughs, in which one of the arms joining the two macrocycles has been deleted to leave an open-sided cylinder, and as a template to cap both ends of a four-helix bundle. While these structures are yet to be synthesized, the modelling studies suggest that these larger backbone-modified cyclic peptides should be useful as scaffolds in the construction of such supramolecular structures [39].

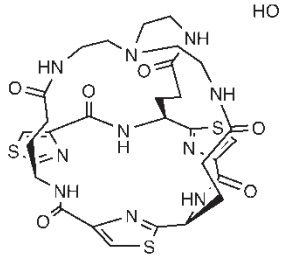
We are currently investigating the use of oxazole-containing cyclic hexa- and octapeptides bearing both proteinogenic and novel amino acid pendant arms as scaffolds for the preparation of enzyme mimics, molecular receptors and self-assembled



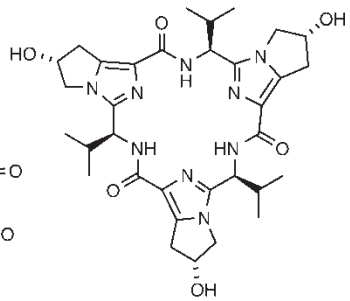
13: n=1
14: n=2



15

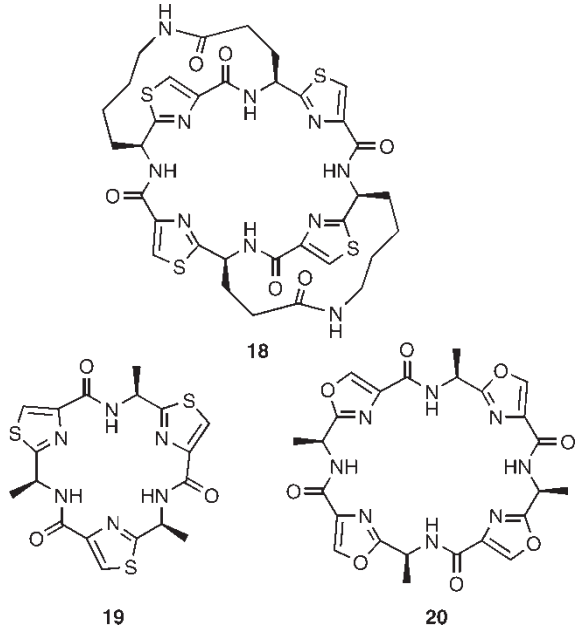


16



17

cages. Preliminary results indicate that such scaffolds are suitable for the construction of anion receptors and binuclear phosphatase mimics [40].



18

19 20

CONCLUSIONS

The incorporation of aromatic residues into the backbone of a cyclic peptide is a useful technique for peptide rigidification. Such compounds can be used as scaffolds in the construction of molecular receptors, enzyme mimics, ion channels and as templates for the assembly of synthetic proteins. Studies directed towards examining the scope of use for such scaffolds in supramolecular chemistry applications are under way in our laboratories.

Acknowledgements

I thank the Australian Research Council for financial support and for the award of a Queen Elizabeth II research fellowship.

References

[1] Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; John Wiley & Sons, Ltd: Chichester, 2000.
[2] Ishida, H.; Suga, M.; Donowaki, K.; Ohkubo, K. *J. Org. Chem.* **1995**, *60*, 5374.
[3] Ishida, H.; Donowaki, K.; Suga, M.; Shimose, K.; Ohkubo, K. *Tetrahedron Lett.* **1995**, *36*, 8987.
[4] Ishida, H.; Donowaki, K.; Inoue, Y.; Qi, Z.; Sokabe, M. *Chem. Lett.* **1997**, 953.
[5] Qi, Z.; Sokabe, M.; Donowaki, K.; Ishida, H. *Biophys. J.* **1999**, *76*, 631.
[6] Ishida, H.; Qi, Z.; Sokabe, M.; Donowaki, K.; Inoue, Y. *J. Org. Chem.* **2001**, *66*, 2978.
[7] Arai, T.; Ide, Y.; Tananka, Y.; Fujimoto, T.; Nishino, N. *Chem. Lett.* **1995**, 381.
[8] Matsubara, A.; Asami, K.; Akagi, A.; Nishino, N. *Chem. Commun.* **1996**, 2069.
[9] Nishino, N.; Kato, T.; Murata, T.; Nakayama, H.; Arai, T.; Fujimoto, T.; Yamamoto, H.; Yoshikawa, S. *Chem. Lett.* **1996**, 49.
[10] Wong, A. K.; Jacobsen, M. P.; Winzor, D. J.; Fairlie, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3836.
[11] Rasmussen, P. H.; Rebek, J., Jr. *Tetrahedron Lett.* **1999**, *40*, 3511.
[12] Kubik, S. *J. Am. Chem. Soc.* **1999**, *121*, 5846.
[13] Kubik, S.; Goddard, R. *J. Org. Chem.* **1999**, *64*, 9475.
[14] Kubik, S.; Goddard, R. *Chem. Commun.* **2000**, 633.
[15] Kubik, S.; Goddard, R. *Eur. J. Org. Chem.* **2001**, 311.
[16] Heinrichs, G.; Vial, L.; Lacour, J.; Kubik, S. *Chem. Commun.* **2003**, 1252.
[17] Bitta, J.; Kubik, S. *Org. Lett.* **2001**, *3*, 2637.
[18] Bitta, J.; Kubik, S. *J. Supramol. Chem.* **2001**, *1*, 293.
[19] Kubik, S.; Goddard, R.; Kirchner, R.; Nolting, D.; Seidel, J. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 2648.
[20] Kubik, S.; Goddard, R. *Proc. Natl Acad. Sci. USA* **2002**, *99*, 5127.
[21] Kubik, S.; Kirchner, R.; Nolting, D.; Seidel, J. *J. Am. Chem. Soc.* **2002**, *124*, 12752.
[22] Otto, S.; Kubik, S. *J. Am. Chem. Soc.* **2003**, *125*, 7804.
[23] Pohl, S.; Goddard, R.; Kubik, S. *Tetrahedron Lett.* **2001**, *42*, 7555.
[24] Choi, K.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 2456.
[25] Choi, K.; Hamilton, A. D. *J. Am. Chem. Soc.* **2003**, *125*, 10241.
[26] Chakraborty, T. K.; Tapadar, S.; Kumar, S. K. *Tetrahedron Lett.* **2002**, *43*, 1317.
[27] Wipf, P. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier: Amsterdam, 1998; pp 187–228.
[28] Mink, D.; Mecozzi, S.; Rebek, J., Jr. *Tetrahedron Lett.* **1998**, *39*, 5709.
[29] Somogyi, L.; Haberhauer, G.; Rebek, J., Jr. *Tetrahedron* **2001**, *57*, 1699.
[30] Boss, C.; Rasmussen, P. H.; Wartini, A. R.; Waldvogel, S. R. *Tetrahedron Lett.* **2000**, *41*, 6327.
[31] Haberhauer, G.; Somogyi, L.; Rebek, J., Jr. *Tetrahedron Lett.* **2000**, *41*, 5013.
[32] Singh, Y.; Sokolenko, N.; Kelso, M. J.; Gahan, L. R.; Abbenante, G.; Fairlie, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 333.
[33] Pattenden, G.; Thompson, T. *Chem. Commun.* **2001**, 717.
[34] Pattenden, G.; Thompson, T. *Tetrahedron Lett.* **2002**, *43*, 2459.
[35] Haberhauer, G.; Rominger, F. *Tetrahedron Lett.* **2002**, *43*, 6335.
[36] Haberhauer, G.; Rominger, F. *Eur. J. Org. Chem.,* **2003**, 3209.
[37] Haberhauer, G. *Synlett* **2004**, 1003.
[38] Singh, Y.; Stoermer, M. J.; Lucke, A. J.; Glenn, M. P.; Fairlie, D. P. *Org. Lett.* **2002**, *4*, 3367.
[39] Lucke, A. J.; Tyndall, J. D. A.; Singh, Y.; Fairlie, D. P. *J. Mol. Graph. Model.* **2003**, *21*, 341.
[40] Jolliffe, K.A., Lee, W.Y.G., unpublished results.