REVIEW

Synthetic receptors for carboxylic acids and carboxylates

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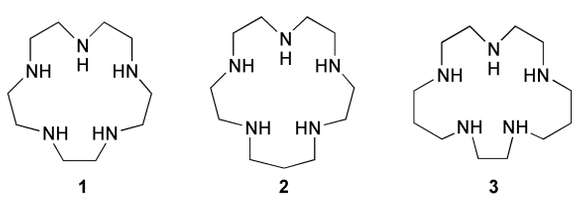
1 Introduction

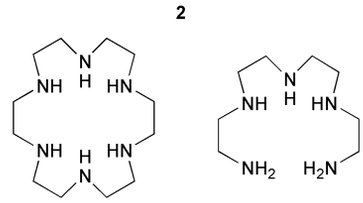
The development of synthetic receptors for a chosen substrate (host–guest chemistry) is a well-established area of research, and selective receptors have now been described for a whole range of substrates, from simple metal cations to polyfunctional molecules such as peptides, proteins and carbohydrates.[1] One approach to the design of a new receptor for a complex substrate is to couple together binding sites for the individual functional groups present in the substrate. A particularly elegant example of this approach was provided some years ago by de Mendoza's receptor for zwitterionic amino acids with aromatic side-chains (described later in this review in section 3.2).[2] By coupling together a guanidinium salt (to bind to the carboxylate of the amino acid), a crown ether (to bind the ammonium) and a naphthalene unit (to interact with the aromatic side-chain), a highly enantioselective receptor for tryptophan and phenylalanine was produced. Carboxylic acids (or carboxylates) are a particularly common functional group in biological and synthetic organic molecules and have inspired the development of a number of different approaches for their recognition. Binding sites have been developed both for simple carboxylic acids and for incorporation into sophisticated receptors for more complex carboxylic acid derivatives, both in polar and non-polar solvents. The purpose of this review is to summarise the different approaches that have been taken to carboxylic acid and carboxylate recognition, reviewing the literature up to and including June 2001.[3]

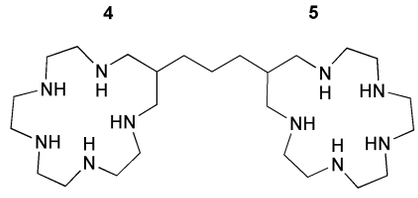
2 Ammonium salts

2.1 Polyaza macrocycles

The interaction between a carboxylate and a protonated amine represents the simplest method, conceptually, for binding a carboxylate anion. The use of ammonium salts to create carboxylate receptors began with studies on polyammonium salts as exemplified by the work of Kimura and Lehn. Kimura produced a series of macrocyclic pentamines **1**–**3** and hexamine **4**.[4] At neutral pH the macrocycles were all triply protonated and formed strong complexes with triscarboxylates (K_a = 55–1000 M^{-1}), such as citrate. The protonated macrocycles **2**–**4** also bound biscarboxylates that had little separation between the two carboxylates (*e.g.* succinate, maleate, and malonate) in a 1 : 1 binding stoichiometry. Biscarboxylates with a larger separation (*e.g.* fumarate, glutarate or aspartate) and monocarboxylates were not bound. In contrast the protonated acyclic pentamine **5** was a poor receptor and only bound citrate ($K_a \approx$ 30 M^{-1}), of the various guests considered.[4,5] Kimura also prepared bis(polyazacrowns) such as **6** which, when quadruply protonated, formed a presumed sandwich complex with citrate ($K_a \approx 480\ M^{-1}$).[6]







Lehn synthesised larger polyaza macrocycles **7**–**9**.[7] All three fully protonated compounds **7**-6H^+, **8**-8H^+ and **9**-6H^+ formed strong complexes with both inorganic and organic polyanions in H_2O but no complexation of monoanions was observed. As with Kimura's receptors, electrostatic interactions were found

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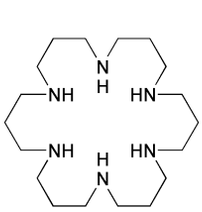
to play a major role in both the strength and selectivity of anion binding. Thus the anions most strongly complexed were usually the smallest, with binding selectivity for biscarboxylates: oxalate > malonate > succinate > maleate > fumarate, although large polyanions such as citrate and benzene-1,3,5-tricarboxylate formed very strong complexes with the large and highly charged **8**-8H$^+$ (K_a = 4 × 10^7 M^{-1} and K_a = 1.3 × 10^6 M^{-1} respectively, pH = 7).



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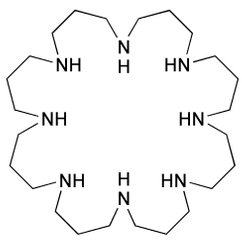

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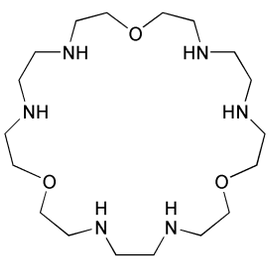

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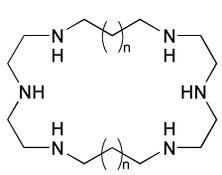
Lehn extended his studies to ditopic receptor molecules for dianionic substrates using the 1,4,7-triazaheptane moiety separated by various alkyl spacers.[8] The fully protonated forms of hexaaza macrocycles **10**–**12** were found to complex biscarboxylate substrates in H_2O with excellent selectivity for substrates whose chain length complemented the size of the cavity *e.g.* **11** bound glutarate dianion most strongly (K_a ≈ 2.5 × 10^4 M^{-1}) and **12** bound pimelate dianion most strongly (K_a ≈ 2.5 × 10^4 M^{-1}) whereas adipate dianion was bound only weakly by either receptor (K_a ≈ 1.5 × 10^3 M^{-1}).



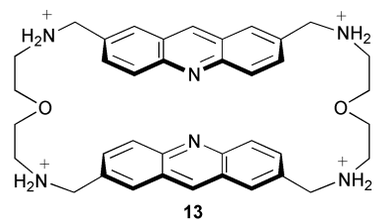
10 n = 3, **11** n = 7, **12** n = 10

More recently, the acridine derived receptor **13** has been described by Lehn and binds *trans* azobenzene dicarboxylates significantly more strongly than the corresponding *cis* azobenzene dicarboxylates in D_2O.[9]

The 1,4,7-triazaheptane motif has also been incorporated into a calix[4]arene by Ungaro[10] to produce carboxylate receptor **14** which formed a 1 : 1 complex with *N*-Ac-D-Ala-D-Ala in H_2O and showed *in vitro* antibacterial activity *cf.* vancomycin.

Studies with aza macrocycles by Bianchi reveal that compounds such as heptaazacrown **15** can exhibit high selectivity for preorganised substrates *e.g.* for triacid **16** over its epimer **17**,[11] while more recently Gotor[12,13] has reported that incorporation of *trans*-cyclohexane-1,2-diamines into tetraaza macrocycles, such as **18**, gives receptors with enantioselective binding properties for tartrate, maleate and aspartate derivatives.[12]

Kodama has demonstrated that protonated polyazacycloalkane-polycarboxylates (known for their metal-complexing properties) form stable 1 : 1 complexes with α-amino acids.[14] Thus receptor H_2**19**$^{3-}$ associates strongly with phenylalanine (K_a = 6.3 × 10^4 M^{-1}), tyrosine (K_a = 5.7 × 10^5 M^{-1}) and tryptophan (K_a = 6.4 × 10^5 M^{-1}) in H_2O. ^{1}H NMR data indicated that hydrophobic interactions—between the methylene pro-



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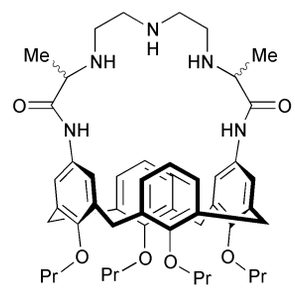

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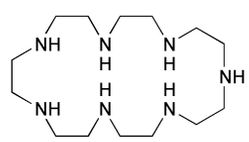

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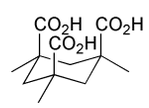

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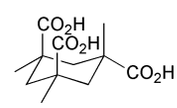

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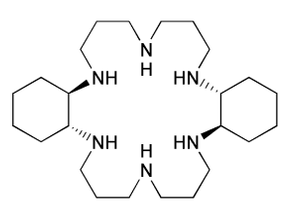

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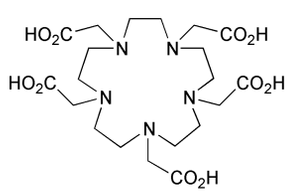
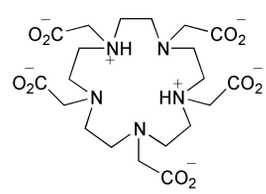
tons of the pendant acetate units of the host and the aromatic rings of the bound guests—are of particular importance in the stabilisation of the host–guest complexes.



H_5**19**

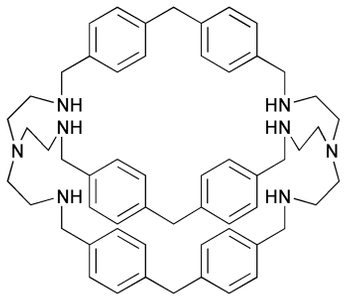


H_2**19**$^{3-}$

Lehn has extended his aza crown series to generate cryptands such as **20** which formed stable complexes with biscarboxylates in weakly acidic aqueous solution.[15] Marked upfield shifts of the ^{1}H NMR signals of the substrate on complexation indicated inclusion of the substrate into the cavity of the receptor molecule. The receptor was elective for adipate (K_a = 2.6 × 10^3 M^{-1}) over biscarboxylates with either shorter or longer alkyl spacers and bound the rigid terephthalate anion particularly strongly (K_a = 2.5 × 10^4 M^{-1}) using both electrostatic and hydrophobic interactions. A crystal structure of 6H$^+$-**20** and three terephthalate dianions revealed that one dianion was located completely within the cavity of the cryptand.

2.2 Other protonated amines

Receptors with a single protonated amine residue as a carboxylate binding site have also been devised. An elegant example comes from Hamilton who synthesised receptor **21** as a synthetic analogue of the carboxylate binding pocket of vancomycin.[16] Binding of the carboxylate is achieved through a combination of hydrogen bonding from the amide and ammonium functionalities and the formation of a zwitterionic



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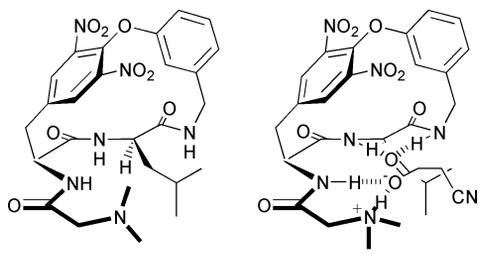
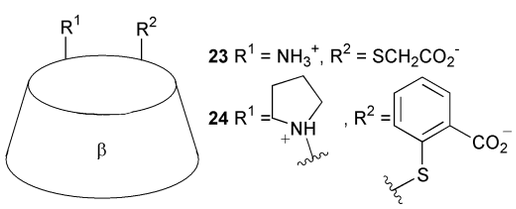
pair. Although no binding constant was reported, large changes in the ^{1}H NMR spectrum of both host and guest upon complexation in $CDCl_3$ and intermolecular NOE experiments suggest that binding of the carboxylate, as in **22**, resembles the mode of binding exhibited by the antibiotic vancomycin. A closely related system has also been described by Pieters (described in more detail in section 6.2).[17]

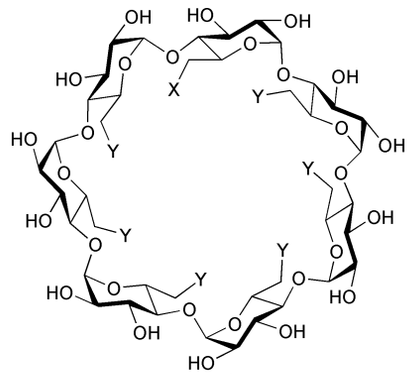


21 **22**

Several groups have studied the complexation properties of aminated cyclodextrins. Important early contributions came from Tabushi who prepared the relatively hydrophilic zwitterionic cyclodextrin derivative **23** and hydrophobic derivative **24**, which bound D-tryptophan ($K_a \approx 15$ M^{-1} and $K_a \approx 50$ M^{-1} respectively) at pH = 8.9. The stronger binding of D-Trp by **24** indicates that the hydrophobic environment created by this receptor enhances the coulombic interaction between ions in aqueous media.[18]

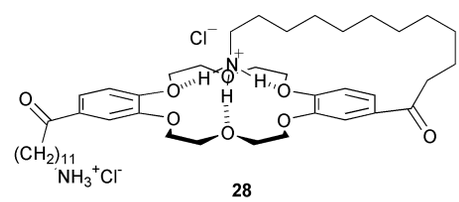


Lincoln[19] has described the modification of β-cyclodextrins by replacement of one of the 6-hydroxy groups with an aminoalkylamine side chain of variable chain length (n = 2–4 and 6).[20] Binding properties with all four receptors and a range of guests were evaluated using potentiometric titrations in H_2O. The strongest binding was found for the complex of **25** (n = 6) with (*S*)-phenylpropanoate ($K_a = 1.8 \times 10^3$ M^{-1}), with slightly lower binding for the enantiomer (*R*)-phenylpropanoate ($K_a = 1.2 \times 10^3$ M^{-1}). Other examples of aminated cyclodextrins include Kano's heptakis(6-amino-6-deoxy) β-cyclodextrin **26** which had high affinity for *p*-methylbenzoic acid ($K_a = 1.5 \times 10^4$ M^{-1}) in H_2O and exhibited some degree of enantioselectivity for L-tryptophan ($K_a = 2.7 \times 10^3$ M^{-1}) over its D-enantiomer ($K_a = 1.9 \times 10^3$ M^{-1}).[21] A large number of cyclodextrin derivatives including polyamine and pyridyl derivatives have been reported by Liu, which in some cases provided high enantioselective recognition of zwitterionic amino acids. For example, cyclodextrin derivative **27** bound L-Leu ($K_a \approx 1.6 \times 10^4$ M^{-1}) approximately 30 times more strongly than D-Leu ($K_a \approx$ 500 M^{-1}) in phosphate buffer (pH = 7.2).[22]



25 X = -(CH$_2$)$_n$NH$_3^+$, Y = OH
26 X = Y = NH$_3^+$
27 X = -NH-*m*-C$_6$H$_4$-CH$_3$, Y = OH

Linking an ammonium salt to a crown ether provides a simple receptor for zwitterionic amino acids. Receptor **28** formed 1 : 1 complexes **29** with a range of zwitterionic amino acids, although complexation requires the receptor to break the intramolecular ammonium–crown ether interaction.[23]



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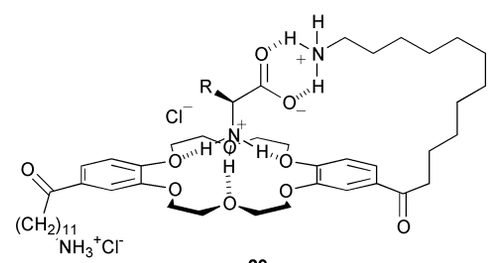

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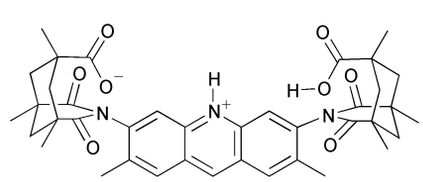
Dendrimers incorporating protonated tertiary amines have been prepared by Meijer and have been reported to bind carboxylates.[24]

2.3 Protonated heterocycles

Rebek has prepared receptor **30** derived from an acridine unit and Kemp's triacid. Receptor **30** is insoluble in H_2O, but exists in MeOH as a zwitterion, with a protonated acridine. Receptor **30** formed complexes in 2 : 1 (host : guest) stoichiometry with amino acids and was able to extract 0.5 equivalents of amino acids phenylalanine, tryptophan and tyrosine methyl ether from H_2O into $CHCl_3$. Selectivity ratios of 2.8 : 1 for Trp over Phe and 1.8 : 1 for Tyr(OMe) over Phe were determined in competition experiments.[25]



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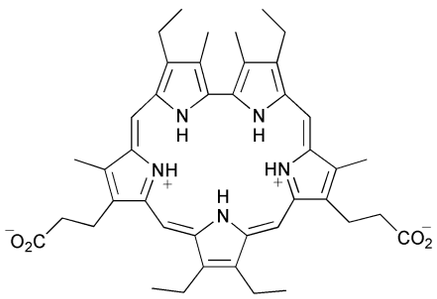
Sessler has shown that protonated sapphyrins are potent receptors for many anions including carboxylates. Sapphyrin **31** with two carboxylate residues, for example, self-assembles into

a dimer. The crystal structure reveals that just one oxygen of the carboxylate anion is hydrogen bonded to the protonated sapphyrin.[26] The carboxylate–sapphyrin interaction has been used to assemble a 1 : 1 porphyrin carboxylate–sapphyrin complex[27] ($K_a = 2.6 \times 10^3$ M^{-1}) in CD_2Cl_2 and sapphyrin–lasalocid conjugates have been used for transport of zwitterionic amino acids across a lipophilic membrane (CH_2Cl_2).[28] Receptor **32**, for example, bound amino acids phenylalanine and tryptophan ($K_a \approx 1 \times 10^5$ M^{-1}) in CH_2Cl_2 with essentially no enantioselectivity but in transport experiments it showed a clear preference for transport of the L-enantiomers.



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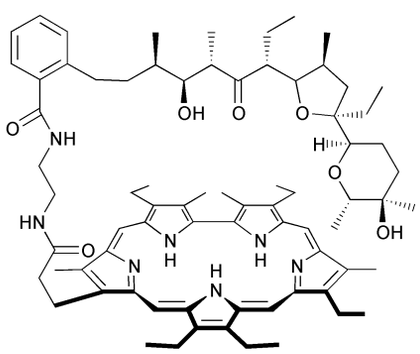

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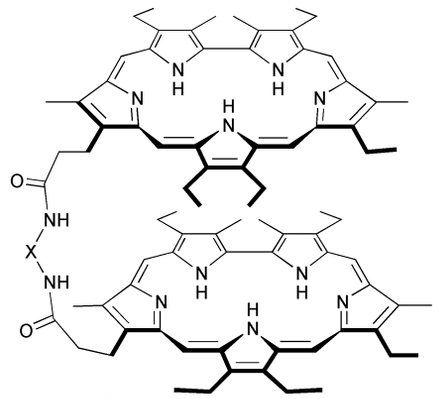
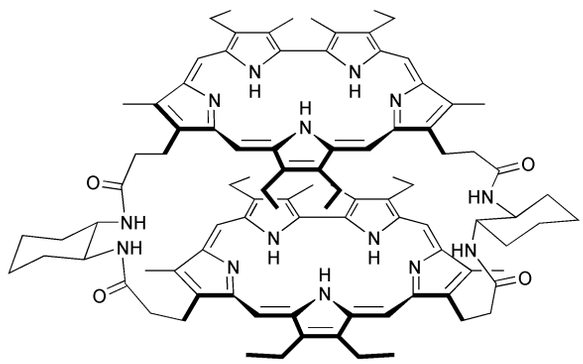
Bissapphyrins such as **33** have also been prepared. Transport and NMR titration experiments showed **33** to be a strong and selective receptor for biscarboxylate anions.[29] There was little affinity for monocarboxylates, such as trifluoroacetate ($K_a < 20$ M^{-1} in MeOH), while biscarboxylates such as *p*-nitroterephthalate ($K_a = 9.1 \times 10^3$ M^{-1}) were tightly bound.

Sessler has extended this work to generate chiral sapphyrin dimers **34**–**36** incorporating rigid chiral spacers.[30] The open chain dimers **34** and **35** bound strongly to a range of biscarboxylates, and showed modest enantioselectivity with *N*-Cbz-glutamate as guest. The cyclic dimer **36**, on the other hand, bound *N*-Cbz-aspartate and *N*-Cbz-glutamate less strongly but showed good enantioselectivity for *N*-Cbz-D-glutamate ($K_a = 1.6 \times 10^4$ M^{-1}) over the L-enantiomer ($K_a = 3.8 \times 10^3$ M^{-1}) in 5% MeOH–CH_2Cl_2.



33 X = -$(CH_2)_3$-
34 X = (1S,2S)-1,2-diaminocyclohexane
35 X = (S)-2,2'-diamino-1,1'-binapthalene



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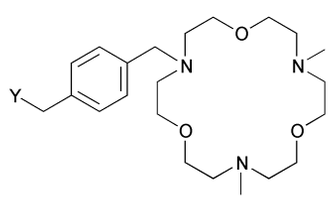
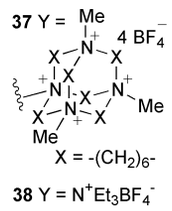
2.4 Quaternary ammonium salts

The use of quaternary ammonium salts, in place of protonated amines, has the obvious advantage that the formation of the ammonium salt is not pH dependent, but has the disadvantage that a hydrogen bond from the ammonium salt to the carboxylate is not available to complement the electrostatic interaction. An early example of the use of quaternary ammonium salts for carboxylate recognition is provided by the macrotricyclic receptor introduced by Schmidtchen as an anion receptor.[31] Receptor **37** was found to bind zwitterionic amino acids, *e.g.* γ-aminobutyric acid ($K_a = 248$ M^{-1}), in 90% H_2O–MeOH containing 0.1 M TBAF. The related peralkylammonium salt **38** was found to bind the same zwitterions with greater affinity, *e.g.* γ-aminobutyric acid ($K_a = 360$ M^{-1}), but showed lower levels of selectivity for the different zwitterionic substrates.





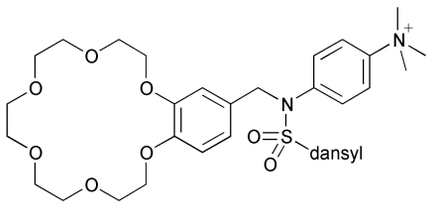
37 Y = Me, 4 BF_4^-
X = -$(CH_2)_6$-

38 Y = $N^+Et_3BF_4^-$

Receptors related to Schmidtchen's **38**, using a peralkyl ammonium salt and a crown ether as recognition sites, have also been described by Schneider.[32] Titration of receptor **39** with tripeptides in H_2O leads to changes in the fluorescence of the dansyl (5-dimethylamino-1-naphthylsulfonyl) group consistent with a 1 : 1 binding stoichiometry as in **40**. As expected receptor **39** shows the strongest association for tripeptides where the second amino acid contains an aromatic side chain to interact with the dansyl group. Titration of receptor **39** with the tripeptides H_2N-Phe-Gly-Gly-OH ($K_a = 220$ M^{-1}), and H_2N-Gly-Gly-Phe-OH ($K_a = 215$ M^{-1}) gives binding constants of similar magnitude to the base tripeptide H_2N-Gly-Gly-Gly-OH ($K_a = 210$ M^{-1}) whereas tripeptides H_2N-Gly-Phe-Gly-OH ($K_a = 1.7 \times 10^3$ M^{-1}) and H_2N-Gly-Trp-Gly-OH ($K_a = 2.2 \times 10^3$ M^{-1}) bind significantly more strongly. Other related receptors for amino acid zwitterions with crown ethers appended to a porphyrin have also been described.[33]

Breslow used the ion pairing of biscarboxylates with benzophenone derived bisammonium salt **41** (Scheme 1) to achieve selective functionalisation of the biscarboxylate on photolysis leading to **42**.[34]

Using a series of similar structures Schneider has carried out a detailed study of the complexation of a series of biscarboxylates with bisquaternary ammonium salts which provides an estimation of the strength of a single carboxylate–ammonium



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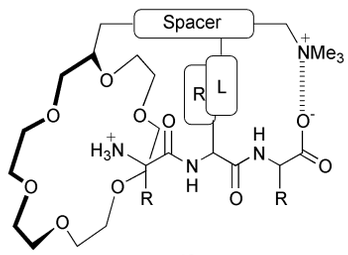

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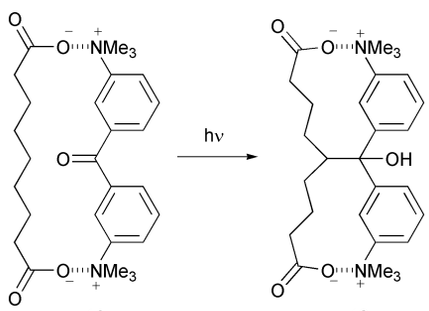
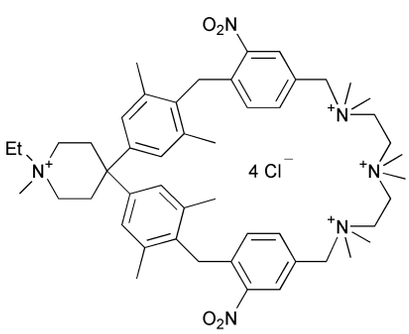


41 42

Scheme 1

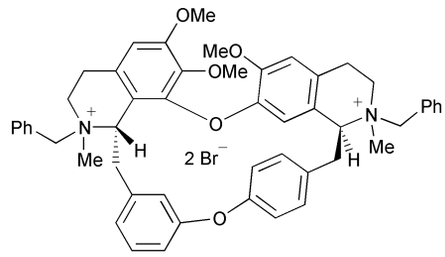
interaction (8 kJ mol^{-1}) in H_2O.[35] In this series the flexibility of the bisammonium salts and biscarboxylate binding partners had a surprisingly small influence on the association constants.

Other examples of polyquaternary ammonium salts as carboxylate receptors include Diederich's water soluble macrocycle **43**, which used the *N*-alkylated 1,4,7-triazaheptane motif to bind a range of carboxylates in D_2O.[36] Monitoring the benzylic CH_2 resonances in ^{1}H NMR titrations gave, for example, binding constants for Ac-D-Ala (K_a = 74 M^{-1}) and Ac-D-Ala-D-Ala (K_a = 51 M^{-1}). Significantly, the control compound **44** with essentially the same cationic recognition site, but lacking the preorganisation of macrocycle **43**, or the hydrophobic aromatics, did not form stable complexes with monocarboxylates under the same conditions.

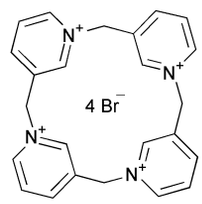


43 44

Eliseev and Yatsimirsky have described the binding of biscarboxylates by a bisquaternary ammonium salt **45** based on (*S*,*S*)-(+)-tetradrine. Receptor **45** bound phthalate (K_a = 135 M^{-1}) and terephthalate (K_a = 110 M^{-1}) more strongly than isophthalate (K_a = 49 M^{-1}) in H_2O.[37] Binding of aromatic carboxylates by ammonium salt derivatives of resorcin[4]arene have also been described.[38] Quaternary tetrapyridiniums have also been used to bind carboxylates.[39] Thus macrocycle **46** bound to conformationally restricted triscarboxylates, in D_2O (pH = 7–8) with some selectivity *e.g.* for acid **47** (K_a = 1.3 × 10^5 M^{-1}) over acid **48** (K_a = 3.2 × 10^4 M^{-1}).



45



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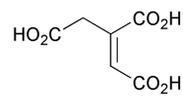

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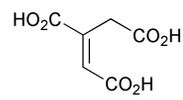
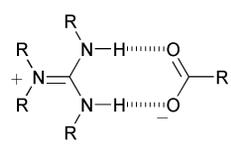


48

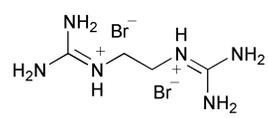
3 Guanidinium salts

Guanidinium salts remain protonated over a much wider pH range than the ammonium salts (pK_a = 13.5, for guanidinium) and the binding of carboxylate salts combines an electrostatic interaction with a bidentate hydrogen bonding pattern as in **49**.



49

Lehn was among the first to investigate the use of guanidinium salts in the complexation of carboxylates by synthesising a series of structurally different guanidinium salts and measuring their association constants with carboxylate salts in a 10% H_2O–MeOH mixture, using pH-metric titration experiments.[40] Bisguanidinium salt **50** bound acetate (K_a = 158 M^{-1}) and the biscarboxylate maleate (K_a = 1.6 × 10^4 M^{-1}). Similarly, trisguanidinium salt **51** bound acetate (K_a = 251 M^{-1}) and maleate (K_a = 2.5 × 10^4 M^{-1}) whereas the simple 1,3-dibenzylguanidinium salt formed weaker complexes *e.g.* with acetate (K_a = 25 M^{-1}) and maleate (K_a = 79 M^{-1}).



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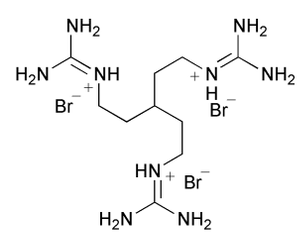
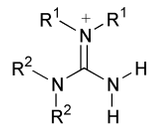


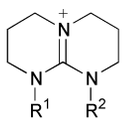
51

A more recent study by Hamilton[41] used isothermal titration calorimetry to measure the association of a range of simple acyclic, monocyclic and bicyclic guanidiniums **52**–**59**, as their tetrafluoroborate salts, with tetrabutylammonium (TBA) acetate in DMSO. Sequential removal of hydrogen bonding sites results in a significant fall in the binding constants in the acyclic systems **52**–**54** (K_a = 7.9 × 10^3 M^{-1}, K_a = 3.4 × 10^3 M^{-1} and K_a = 110 M^{-1} respectively). Similarly bicyclic guanidinium salt **55** bound TBA acetate strongly, (K_a = 5.6 × 10^3 M^{-1}) but no binding was observed for the corresponding methylated compounds

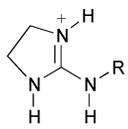
56 and **57**—which was confirmed by ^{1}H NMR titration. Monocyclic guanidinium salts **58** and **59** also display high affinities for acetate, particularly receptor **59**, as the iodide salt (K_a = 7.2 × 10^3 M^{-1} in DMSO, as determined by isothermal titration calorimetry and K_a = 1.2 × 10^4 M^{-1} in DMSO-d$_6$, as determined by ^{1}H NMR titration[42]).



52 $R^1 = R^2$ = H
53 R^1 = Me, R^2 = H
54 $R^1 = R^2$ = Me



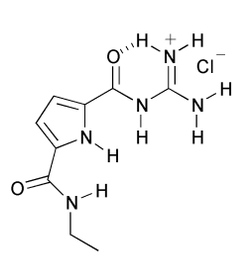
55 $R^1 = R^2$ = H
56 R^1 = Me, R^2 = H
57 $R^1 = R^2$ = Me



58 R = H
59 R = Bn

3.1 Acyclic and monocyclic guanidinium salts

Binding of a simple guanidinium salt to a carboxylate can be enhanced by incorporation of additional hydrogen bonding functionality. Thus Schmuck has recently described guanidinocarbonyl pyrrole receptors such as **60** and **61** which bound carboxylates by ion pairing in combination with multiple hydrogen bonds from the guanidinium salt, pyrrole and amide as in **62**.[43] Receptor **60** bound *N*-Ac-α-amino acid carboxylates in 40% H_2O–DMSO with association constants (K_a = 3.6 × 10^2 to 1.7 × 10^3 M^{-1}) dependent on the structure of the amino acid side chain. Similarly, chiral receptor **61** bound *N*-Ac-α-amino acid carboxylates (K_a = 3.5 × 10^2 to 5.3 × 10^3 M^{-1}) in 40% H_2O–DMSO and showed some enantioselectivity.[44] Schmuck has also used the same interaction to create a series of self-assembling guanidiniocarbonyl-carboxylates.[45]



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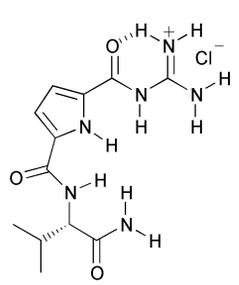

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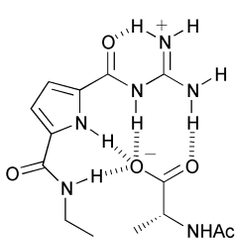
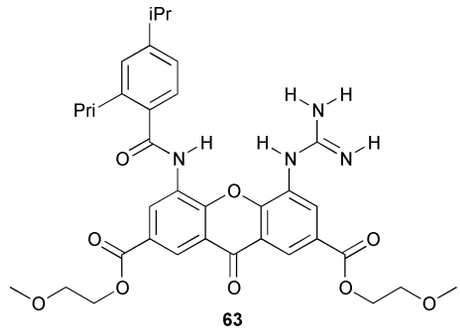


62

Morán has synthesised planar receptor **63** which, in addition to a guanidine moiety, provides a third hydrogen bond from the amide NH to the *syn* lone pair of one carboxylate oxygen, and possible π-stacking interactions with the diisopropylbenzoate residue, as in **64**.[46] The neutral guanidine binds strongly to carboxylic acids in $CHCl_3$ and to monochloroacetic acid in the more competitive solvent DMSO.

Acyclic guanidinium salts have been incorporated into more sophisticated architectures to create a range of receptors for carboxylate derivatives. A simple example is de Silva's receptor for zwitterionic amino acids, combining a guanidinium salt, a crown ether and an anthracene unit, the latter component serving as both a fluorescent sensor and a rigid spacer. Receptor **65** binds a range of amino acids $H_3N^+(CH_2)_nCO_2^-$ with optimal binding when n = 4 (K_a = 84 M^{-1}, 88% H_2O–MeOH, pH = 9.5).[47]



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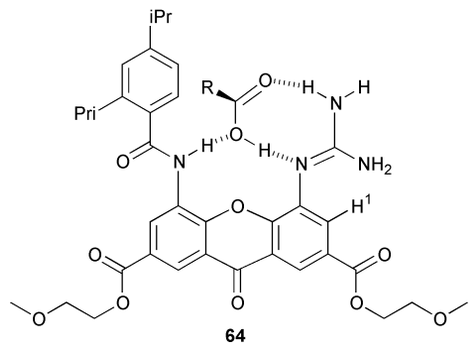

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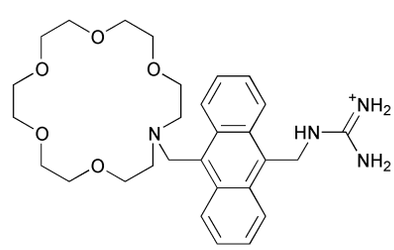
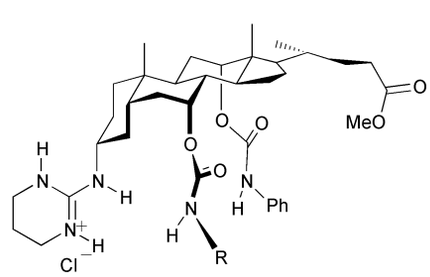


65

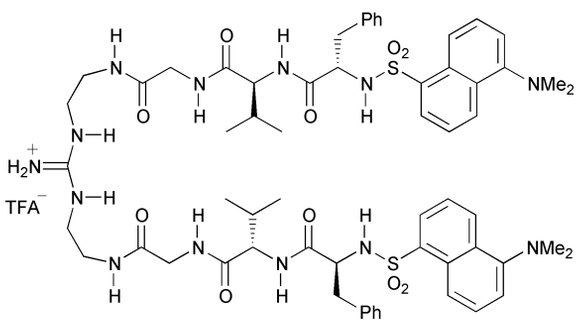


66 R = Ph
67 R = 2,6-dichlorophenyl

Davis has described enantioselective carboxylate receptors created by attachment of a monocyclic guanidinium salt to a cholic acid scaffold.[48] The secondary hydroxy groups of cholic acid could be modified to generate receptors in which three binding moieties were spaced to allow co-operative effects on the substrate with minimum interference from intramolecular interactions. Solutions of **66** and **67** were able to extract *N*-Ac-α-amino acids from neutral or basic aqueous solutions *via* exchange of chloride for carboxylate. The extraction efficiencies were moderate to good (52–87 mol%) for substrates with non-polar side-chains, although neither receptor was effective with the polar asparagine derivative. Receptor **66** proved remarkably consistent in its ability to differentiate between enantiomers of the *N*-Ac-α-amino acids (L : D = 7 : 1) in all cases, irrespective of side-chain bulk. Receptor **67** showed generally higher extraction abilities (74–93 mol%) possibly due to the greater acidity of the dichlorophenylcarbamoyl NH, and was more sensitive to side-chain structure with L : D selectivities between 5 : 2 and 9 : 1, the greatest selectivity being observed with phenylalanine

and methionine side chains. Perhaps surprisingly, the substrate with the most sterically hindered asymmetric centre *N*-Ac-*tert*-leucine gave the lowest selectivity. ^{1}H NMR spectroscopy and molecular modelling both suggested plausible models for the binding geometries.

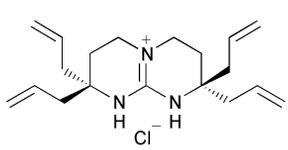
Kilburn has synthesised a 'tweezer' receptor for peptides with a carboxylate terminus using a guanidinium salt to provide the primary binding interaction for the carboxylate, and receptor arms with potential to form both hydrophobic and β-sheet like hydrogen bonding interactions with the backbone of the peptide substrate.[49] Solid phase synthesis of a library of tripeptides, attached to TentaGel resin *via* the amino terminus, was screened with tweezer **68** in an aqueous solvent system. Receptor **68** was found to bind to approximately 3% of the library members and following sequencing of 20 beads, showed 95% selectivity for valine at the carboxy terminus of the tripeptides and 40% selectivity for Glu(O^{t}Bu) at the amino terminus. The binding constant ($K_a = 4 \times 10^5$ M^{-1} in 17% DMSO–H_2O, pH = 9.2) for one of the peptides selected from the screening experiments (Cbz-Glu(O^{t}Bu)-Ser(O^{t}Bu)-Val-OH), with receptor **68** was measured using titration calorimetry.



68

3.2 Bicyclic guanidinium salts

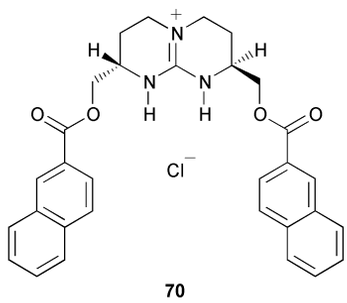
Schmidtchen first reported the use of a bicyclic guanidinium salt for the formation of host–guest complexes with simple carboxylates.[50] In forming part of a bicyclodecane framework as in **69** the guanidinium salt becomes an almost perfect match for carboxylate anions with the two guanidinium salt protons aligned in the same direction. Titration of bicyclic guanidinium salt **69** with TBA *p*-nitrobenzoate in CD_3CN results in a shift of all host resonances in the ^{1}H NMR spectrum, with a pronounced shift in the guanidinium protons of more than 5 ppm. The shape of the titration curve fits the proposed 1 : 1 complex stoichiometry, and gave an estimation of the lower limit of complex stability ($K_a > 1.0 \times 10^4$ M^{-1}) in CD_3CN.



69

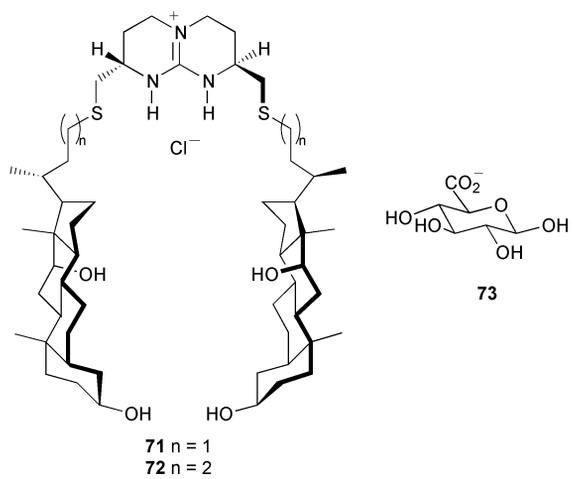
Schmidtchen,[51] de Mendoza[52] and Davis[53] have developed routes to chiral bicyclic guanidinium salts. Coupling of such a bicyclic guanidinium salt with, for example, two naphthoyl units produced receptor **70** which bound *p*-nitrobenzoate, using a combination of carboxylate–guanidinium salt interaction and π–π stacking ($K_a = 1609$ M^{-1} in $CDCl_3$).[54]

The bicyclic guanidinium salt core has also been used to produce a receptor for uronic acid salts.[55] Receptors **71** and **72** rely on the bidentate guanidinium–carboxylate motif, with additional stabilisation of the host–guest complex from the interaction between the hydroxy groups of the glycopyranosyl guest and the convergent hydroxy groups of the deoxycholic acid



70

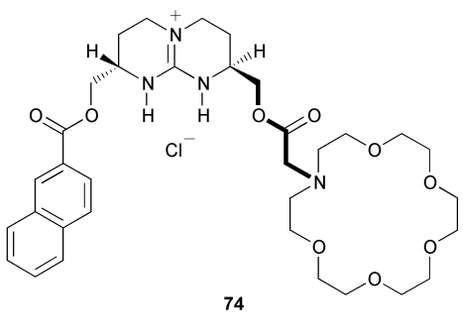
derived arms of the tweezer receptor. The rigid steroid provides an essentially lipophilic outer surface providing good solubility in organic media with convergent hydroxy groups to bind with the guest sugar **73**, although binding studies revealed that in practice the steroids only had a small influence on the binding selectivities.



71 n = 1
72 n = 2

Receptors for amino acids have been developed by coupling the chiral bicyclic guanidinium salt to a crown ether. In de Mendoza's example of this approach an aromatic planar surface provides an additional π-stacking interaction giving receptors with high selectivity for amino acids with aromatic side chains.[2] The affinity of **74** toward amino acids was determined by liquid–liquid extraction experiments, in which an aqueous solution of L-Trp, L-Phe, or L-Val was extracted into a CH_2Cl_2 solution of **74**. The extraction efficiencies, *i.e.* the fraction of receptor molecules occupied by the substrate in the organic phase, as determined by NMR integration, were ~40% for L-Trp and L-Phe, but L-Val, without an aromatic side chain, was not detected. A competition experiment with a mixture of all three amino acids resulted in 100 : 97 : 6 Phe : Trp : Val selectivity. Chiral recognition was confirmed by the observation that the corresponding D-enantiomers were not extracted. A more precise account of the selectivity was achieved by HPLC analysis of diastereomeric dipeptides, prepared from extracts of racemic samples of Phe or Trp and a suitable optically pure L-Leu derivative. The amount of D-isomer in the extracts was lower than 0.5% for D-Trp, determined as L-Leu-D-Trp, and 2% or less for D-Phe, determined as L-Leu-D-Phe. This high degree of chiral recognition can be explained by the three simultaneous non-covalent interactions of the substrate with the flexible and foldable receptor as in **75**.

Schmidtchen synthesised a related receptor **76** that was found to extract amino acids from aqueous buffer (pH > 8.9) into CH_2Cl_2.[56] Clean 1 : 1 host–guest complex formation was observed under conditions of fixed pH and ionic strength. The most hydrophobic guests were extracted best, and even quite hydrophilic amino acids such as glycine and serine had respectable extraction efficiencies, but amino acids with basic



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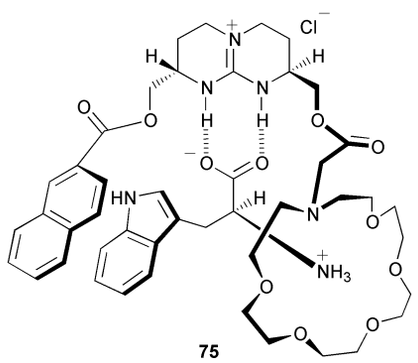
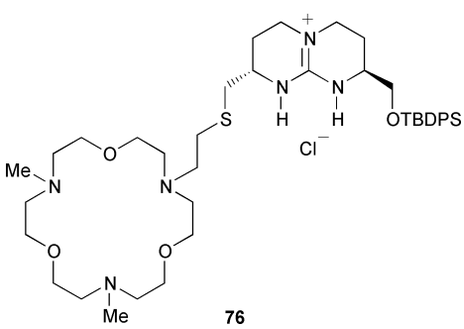


75

and acidic side chains were poorly extracted (< 0.2%). The highest binding affinity (K_a = 1810 M^{-1}) was observed with L-phenylalanine at pH = 8.9. Receptor **76** was also found to favour the extraction of L-Phe (40% ee) into CH_2Cl_2 from a racemic mixture of phenylalanine in an aqueous buffer (pH = 9.1–10.5).

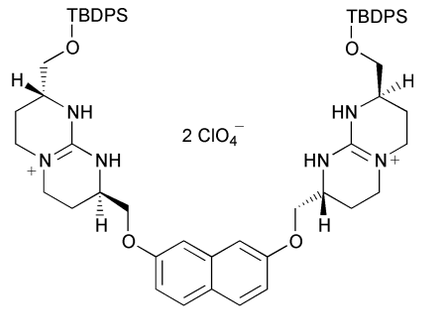


76

3.3 Polyguanidinium salts

Schmidtchen has used the rigid bicyclic guanidinium salt to generate bisguanidinium salt **77**, which was found to bind a range of biscarboxylate anions in MeOH.[57] Host **77** showed a preference for malonate (K_a = 1.6 × 10^4 M^{-1}) over shorter or longer biscarboxylates but even a rigid and extended guest such as **78** is bound with considerable stability (K_a = 633 M^{-1}) indicating the adaptability of the host to the guest structure.

Hamilton also used bisguanidinium salts to bind simple carboxylates[42] and to recognise aspartate pairs in helical peptides. Thus bisguanidinium salt **79** was added to 16mer peptides with two aspartate groups at different positions (i + 3, i + 4, i + 11) in 10% H_2O–MeOH (K_a = 2.2 × 10^3 M^{-1} for i + 3) and resulted in a 6–9% increase in helicity of the peptides i + 3 and i + 4 but only a slight increase for peptide i + 11, for which the helical conformation would place the two aspartates too far apart to form a 1 : 1 complex with the bisguanidinium salt.[58] Hamilton and de Mendoza have extended the bicyclic guanidinium salt motif to create synthetic receptors that similarly stabilise the α-helical conformation of glutamate and aspartate rich peptides.[59] The spacing of the guanidinium salt units in the tetraguanidinium salt **80** complements the carbon–carbon distances between the carboxylates of peptide **81** when in an



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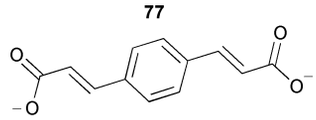
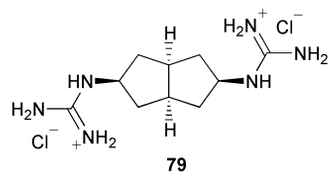


78

α-helix. Addition of receptor **80** to the peptide resulted in strong binding (K_a > 1 × 10^5 M^{-1}) in 10% H_2O–MeOH and a significant increase in helical stability of the peptide. Titration of peptides **82** and **83** with asparagine acting as a neutral isostere for aspartate was carried out under the same conditions and results showed a correspondence between the number of aspartates and the degree of helix stabilisation.



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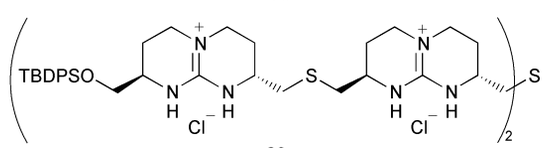
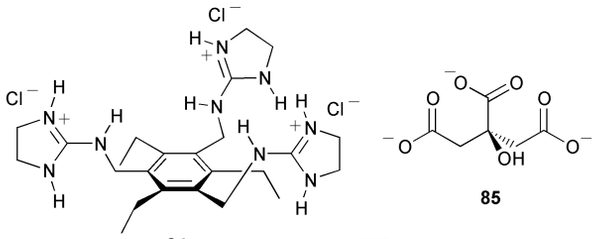


80

81 DDDD Ac-A-A-A-A-**D**-Q-L-**D**-A-L-**D**-A-Q-**D**-Q-Q-Y-NH_2
82 DDDN Ac-A-A-A-A-**D**-Q-L-**D**-A-L-**D**-A-Q-N-Q-Q-Y-NH_2
83 DDNN Ac-A-A-A-A-**D**-Q-L-**D**-A-L-N-A-Q-N-Q-Q-Y-NH_2

Anslyn has synthesised trisguanidinium salt **84**, as a chemosensor for citrate **85**.[60] The steric gearing imparted by the ethyl groups on the 2-, 4-, and 6-positions ensures that the guanidinium salts are preorganised on the same face of the benzene ring. This conformation yields several hydrogen bonds and three sets of ionic interactions in the host–guest complex with citrate, leading to good binding in H_2O. Receptor **84** was selective for citrate in H_2O over bis- and mono-carboxylates, phosphates, sugars, and simple salts. The binding constant for the trisguanidinium–citrate complex (K_a = 2.9 × 10^5 M^{-1}) was determined by UV competition assay in which a solution of citrate **85** was added to a mixture of receptor **84** and a fluorescent probe **86**. Recently Anslyn described a modified citrate sensor based upon the scaffold **84** in which one guanidinium salt is replaced by a tethered copper(II) species to create an internal fluorescence probe. Receptor **87** again formed highly stable complexes with citrate **85** (K_a > 8.3 × 10^6 M^{-1}) in H_2O.[61]

Kelly has described the first example of a molecular Vernier **88**, where three molecules of a biscarboxylate were found to combine with two molecules of a trisguanidinium salt to give a pentamer of predetermined dimension.[62] In the Vernier mechanism, two complementary components having different unit lengths undergo side-by-side linear aggregation. Growth continues until the tips of the adjacent aggregates come into register, whereupon growth ceases. Generation of **88** was achieved simply by mixing solutions of the biscarboxylate and the trisguanidinium salt. Vernier **88** spontaneously precipitated from the solution in >95% yield and in analytically pure form.



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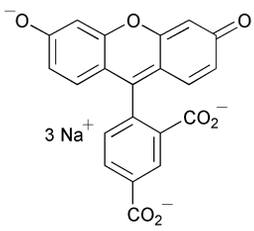

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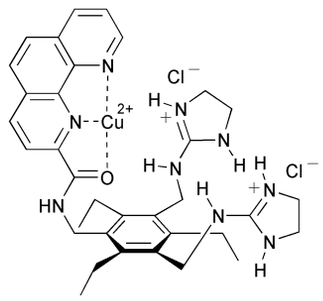
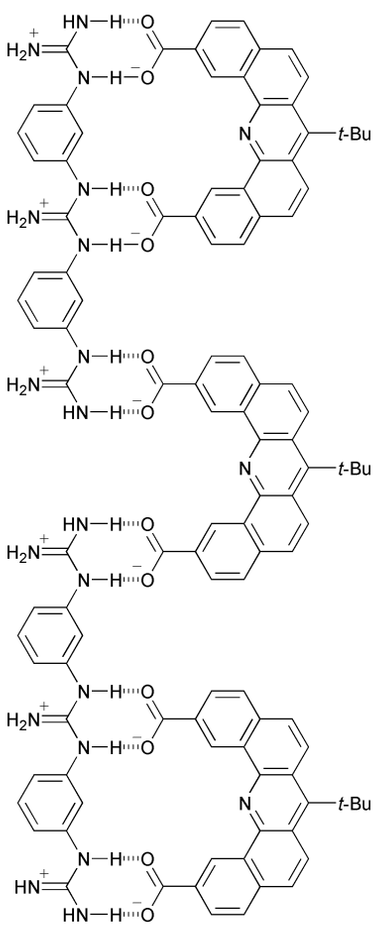


87

Vernier formation was found to proceed until all of the limiting component was consumed and gave a near quantitative yield regardless of the stoichiometry of the two components.

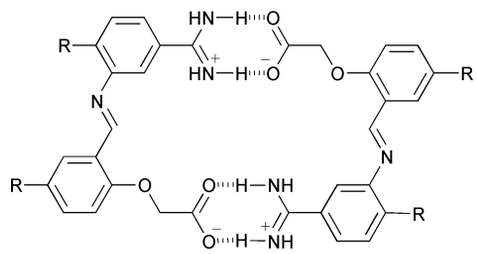


88

3.4 Amidinium salts

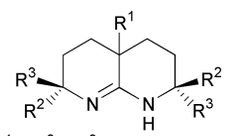
The amidinium salts provide a similar binding motif for carboxylates to that of the guanidinium salts with a pair of hydrogen bonds and a complementary electrostatic interaction although the former are less basic and may therefore provide a stronger H bond donor on protonation.

The first example of supramolecular architectures using the amidinium–carboxylate interaction were described by von Kiedrowski.[63] Benzylamidinium tetrafluoroborate formed sufficiently strong complexes (K_a = 350 M^{-1}) at 35 °C with caesium acetate in DMSO-d_6 to allow this motif to be used as a template for a self-replicating imino condensation reaction to generate complex **89** in DMSO-d_6.



89

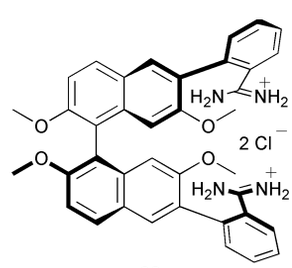
Davis has produced bicyclic amidines **90** and **91** analogous to the bicyclic guanidines described earlier (section 3.2). An X-ray crystal structure of the naproxenate salt of chiral amidinium **90** confirms the expected carboxylate–amidinium interaction with two hydrogen bonds. The nitrate salt of chiral bicyclic amidinium salt **91** was also prepared but did not show significant enantioselectivity in extraction experiments with *N*-Boc-phenylalaninate.[64]



90 $R^1 = R^2 = R^3 = Me$

91 $R^1 = -SO_2Ph$, $R^2 = CHPh_2$, $R^3 = H$

Diederich has attached two phenylamidinium salts to 1,1′-binaphthalene scaffolds to produce the 1,1′-binaphthalene derivative (±)-**92** which was found to be an efficient receptor for biscarboxylates, such as bis(TBA) glutarate (K_a = 8.2 × 10^3 M^{-1}) and isophthalate **93** (K_a = 1.0 × 10^4 M^{-1}), in competitive protic solvents such as MeOH.[65] A van't Hoff analysis of variable-temperature ^{1}H-NMR titrations and isothermal microcalorimetry revealed that complexation in MeOH is strongly entropically driven, with an unfavourable enthalpic change. These thermodynamic quantities were best explained by a particularly favourable solvation of the binding partners in the unbound state and the release of the MeOH molecules into the bulk solution upon complexation. Receptor (±)-**92** binds flexible glutarate and rigid isophthalate **93** with similar association constants and the lack of response to guest preorganisation and poor guest selectivity is explained by the non-directionality of the coulombic charge–charge interactions in the complexes. Attempts to investigate the complexation of biscarboxylates by receptor (±)-**92** in H_2O led to the precipitation of a solid which was re-dissolved in DMSO-d_6, and integration of the ^{1}H NMR resonances confirmed that it consisted of the host–guest complex, with a 1 : 1 stoichiometry.



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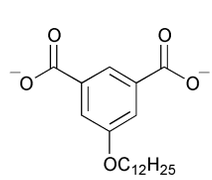
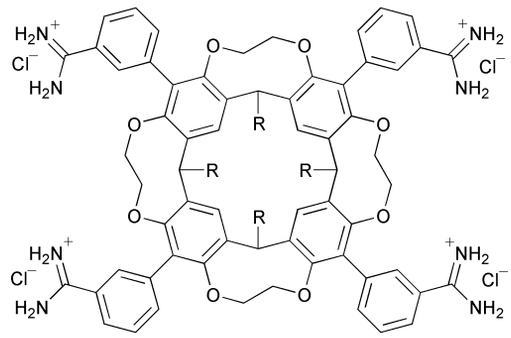


93

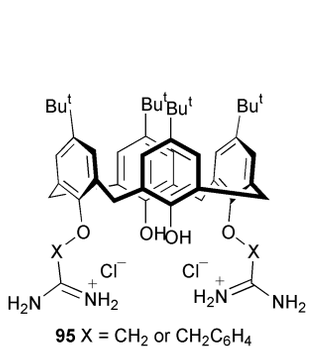
Diederich has also reported the complexation of biscarboxylates by tetrakis(phenylamidinium) salt **94** derived from a resorcin[4]arene.[66] ^{1}H NMR titration of cavitand **94** with TBA 5-nitroisophthalate in MeOH and in H_2O gave data consistent

with a 1 : 2 (host : guest) binding stoichiometry. Binding studies indicated that complexation in MeOH occurs in the rim of the cavitand whereas in H_2O one of the two isophthalates is bound such that the hydrophobic aromatic ring is included in the receptor cavity.

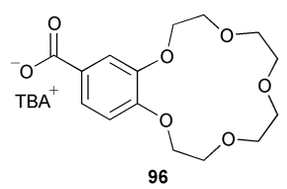


94 R = $(CH_2)_3(OCH_2CH_2)_3OMe$

Gale has described the use of calixarene derived bisamidinium salt as a template for the self-assembly of ditopic receptors.[67] Thus bisamidinium salt **95** bound carboxylates, including crown ether and calixpyrrole derived carboxylates **96** and **97**, with a 1 : 2 stoichiometry in DMSO.



95 X = CH_2 or $CH_2C_6H_4$



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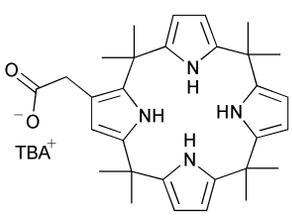
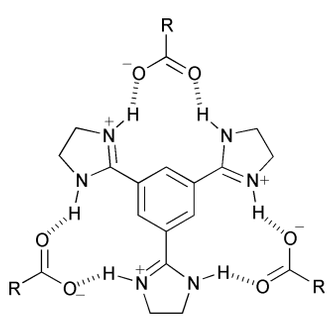


97

Kraft has described a tris(imidazoline) which forms a 1 : 3 complex with carboxylates **98**. The combination of hydrogen bonds and charge complementarity results in a stable complex (K_a = 990 M^{-1}, R = Ph) in 3% CD_3OD–$CDCl_3$.[68]

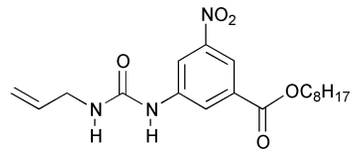


98

The amidinium–carboxylate interaction has also been used for the assembly of ordered molecular layers[69] and self-assembled solid-state architectures.[70]

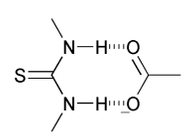
4 Ureas and thioureas

Despite lacking the electrostatic complementarity offered by the guanidinium salt, ureas and thioureas have been shown to provide a strong binding site for carboxylates, using a bidentate hydrogen bonding motif. Wilcox was the first to utilise ureas and thioureas for carboxylate binding and reported that urea **99** bound, for example, TBA benzoate in $CDCl_3$ (K_a = 2.7 × 10^4 M^{-1}).[71] Large downfield shifts of the signals for the NH protons were observed in ^1H NMR titration experiments, indicating strong hydrogen bonding between the urea hydrogens and carboxylate oxygens.



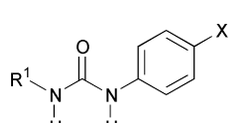
99

Hamilton examined the binding of carboxylates by ureas and thioureas in polar solvents such as DMSO.[42] Addition of tetramethylammonium (TMA) acetate to a DMSO-d_6 solution of 1,3-dimethylurea gave large downfield shifts (> 1 ppm) of the urea NH resonance, which was again consistent with the formation of a bidentate hydrogen bonded complex as in **100** (K_a = 45 M^{-1}). Stronger binding was achieved when the acidity of the hydrogen bonding donor sites was increased by replacing the urea (pK_a = 26.9) with a thiourea (pK_a = 21.0). Thus 1,3-dimethylthiourea bound TMA acetate with ~8 fold increase in binding constant (K_a = 340 M^{-1}) compared to 1,3-dimethylurea.



100

Kelly has conducted an extensive study with urea **101** as a receptor for benzoate and a range of isosteric anions including nitro, mono- di- and trianionic phosphate, phosphonate and sulfonate.[72] Anions were titrated as their TBA salts in $CDCl_3$, when solubility allowed, and in DMSO-d_6 or CCl_4, and binding constants were determined. The binding affinity correlates well with the basicity of the binding group. Thus, nitrobenzene is the most weakly bound substrate (binding only observed in CCl_4) and phosphonate the most strongly bound. Benzoate lies in the middle of the series (K_a = 1.3 × 10^3 M^{-1} in $CDCl_3$ and K_a = 150 M^{-1} in DMSO-d_6).



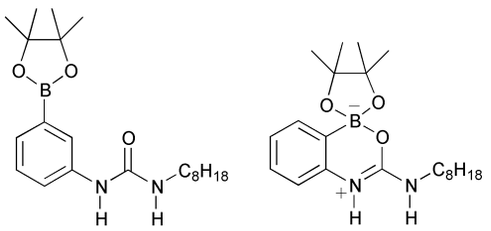
101 R^1 = Bu, X = Me

102 R^1 = *p*-$C_6H_4NO_2$, X = NO_2

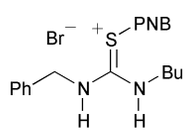
Recently Teramae has described the related receptor **102** which bound TBA acetate (K_a = 3 × 10^5 M^{-1}) in 1% H_2O–MeCN and was found to be a selective chromoionophoric sensor for acetate with selectivity over a range of monovalent inorganic anions.[73]

A number of strategies have been employed to enhance the binding affinities of carboxylates with simple ureas and thioureas. Smith incorporated Lewis acid coordination to polarise the urea moiety.[74] Binding studies were carried out with a range of receptors **103**–**106** in DMSO-d_6 using TBA acetate as guest. Receptors **103** and **104** gave similar binding constants (K_a = 390 M^{-1} and K_a = 370 M^{-1} respectively) due to the similarity in electronegativities of hydrogen and boron, and in each case 1 : 1 binding was verified by Job plot analysis. Boronate ureas **105** and **106** gave significantly higher association constants (K_a = 7 × 10^3 M^{-1} and K_a = 6 × 10^4 M^{-1} respectively) due to the generation of a strong molecular dipole in the host and

improved host hydrogen bond donation. The greater binding ability of **106** compared to **105** reflected the use of a more electron withdrawing boron difluoride. The effectiveness of such Lewis acid coordination is further underlined by the fact that **106** was a better acetate binder than guanidinium tetrafluoroborate[41] ($K_a = 7.9 \times 10^3$ M^{-1}) in DMSO-d_6.

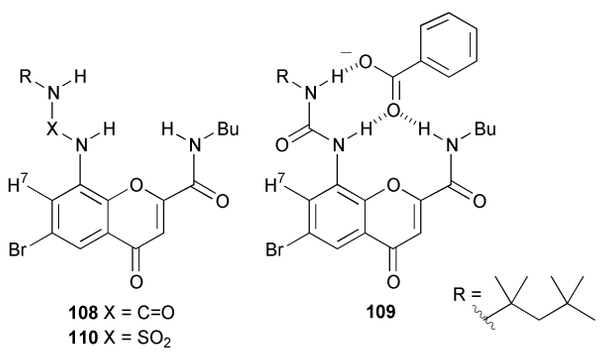


Hong has used a related, but synthetically simpler approach to Smith by preparing thiouronium based receptor **107** (PNB = *p*-nitrobenzyl).[75] Receptor **107** bound acetate in DMSO-d_6 ($K_a \approx 800$ M^{-1}) which is stronger than the reported binding of acetate by 1,3-dimethylthiourea ($K_a \approx 300$ M^{-1}).[42,76] The thiouroniums, however, showed poorer binding affinity than guanidinium salt receptors, despite their apparent structural similarities, presumably because sulfur disperses the positive charge more than nitrogen.



Morán has described urea **108**, which provides an additional amide interaction with one of the carboxylate oxygen atoms on binding as in **109**.[77] The association constant of **108** with tetraethylammonium (TEA) benzoate in DMSO-d_6 was surprisingly small ($K_a = 20$ M^{-1}) compared with other known urea receptors but CPK models revealed some steric interference between the aromatic ring of the guest and the butyl substituent of the receptor. Moreover, the urea function had to be twisted with respect to the chromenone ring due to the hindrance between the urea carbonyl and chromenone H-7, making the cleft wider, and preventing the formation of linear hydrogen bonds. To overcome this drawback the sulfuryl amide **110** was prepared. The tetrahedral geometry of the sulfur atoms allows H-7 to be placed between the two sulfuryl oxygens, leaving the NH bond in the chromenone plane. The improved geometry combined with the higher acidity of the sulfuryl amide hydrogens led to a higher binding constant with TEA benzoate ($K_a = 330$ M^{-1}) in DMSO-d_6.

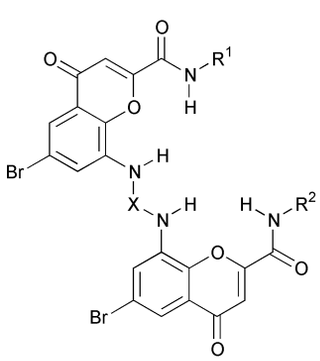
The chromenone scaffold has been expanded to generate receptor **111** with two chromenone fragments and a urea function that was able to form four linear hydrogen bonds with a carboxylate guest as in **112**. The association constant with benzoate in DMSO-d_6 ($K_a = 1.5 \times 10^4$ M^{-1}) was significantly higher than with receptors **108** and **110**. As before, to prevent the twisted geometry of the urea receptors, the symmetric sulfuryl amide **113** was prepared. A competitive titration in DMSO-d_6 using both **111** and **113** showed that the latter bound

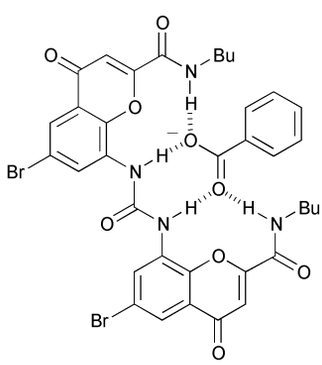


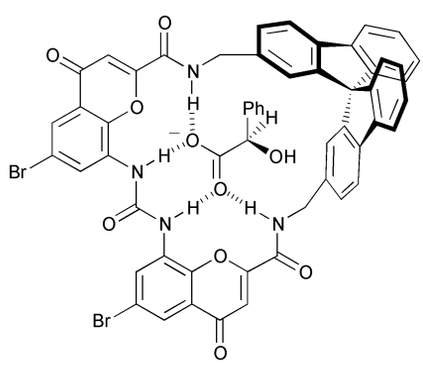
benzoate at least ten times higher ($K_a > 1 \times 10^5$ M^{-1}). Moran has also described the closely related spirobifluorene capped macrocyclic receptor **114** which forms complexes with (*R*)-mandelic acid with a 16 : 1 selectivity for the (*R*,*R*)-complex over the (*R*,*S*)-complex in DMSO-d_6.[78] The chromenone scaffold has been further extended to incorporate a fifth hydrogen bond from a hydroxamic acid moiety. Receptor **115** bound TEA heteroaromatic carboxylates (*e.g.* 2-furoic acid and fusaric acid) and TEA α-keto carboxylates (*e.g.* pyruvic acid). The highest binding was observed for fusaric acid carboxylate ($K_a = 4.3 \times 10^5$ M^{-1}) in 1% CD_3OD–$CDCl_3$ compared to TBA benzoate ($K_a = 1.1 \times 10^3$ M^{-1}), indicating the importance of the fifth hydrogen bond.[79]

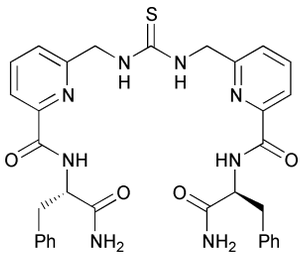
Kilburn has recently described the enantioselective binding of *N*-protected amino acids by a pyridyl thiourea receptor.[80] Receptor **116** was titrated with a range of amino acid carboxylates (TBA salts) and exhibited some selectivity particularly for amino acids with electron rich aromatic side chains *e.g.*, *N*-Ac-D-Trp ($K_a = 1.5 \times 10^4$ M^{-1}) in $CDCl_3$. Receptor **116** was modestly enantioselective with a general preference for L-amino acids *e.g.* for *N*-Ac-Gln-CO_2^- ($K_a^L : K_a^D \sim 2 : 1$).

Kilburn has also synthesised a bowl shaped receptor **117** for amino acid derivatives, which incorporated a thiourea as the carboxylate binding site, and amide functionality to provide further hydrogen bonding interactions with suitable guests.[81] Binding studies showed little apparent selectivity for the various









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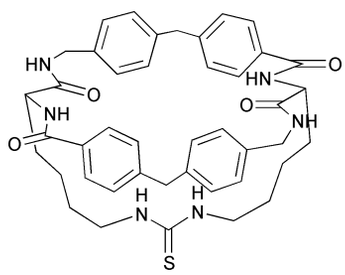
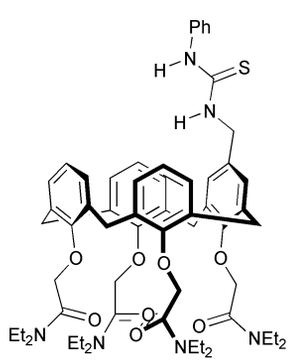


117

substrates investigated in $CDCl_3$. However, detailed NMR studies revealed that D-amino acid substrates bound predominantly on the outside of the macrobicycle cavity by a strong carboxylate–thiourea interaction. L-Amino acid substrates bound predominantly on the inside of the cavity, also establishing a strong carboxylate–thiourea interaction, but with the acetyl amide in a *cis* amide configuration . Molecular modelling studies suggested that the energetic penalty associated with the guest adopting a *cis* amide configuration was compensated by intermolecular hydrogen bonds between the *cis* amide and macrocycle amide functionality. More recently, the modification of receptor **117** by introduction of pyridines in the place of one or two benzene rings in the upper rim has been reported.[82]

Ungaro has used a calixarene supported thiourea to create ditopic receptors capable of recognition of a carboxylate at the upper rim of the calixarene and binding a counterion in the cation binding pocket appended to the lower rim.[83] Solid–liquid extraction of stoichiometric amounts of sodium acetate with receptor **118** in $CDCl_3$ revealed that the ^1H NMR signals for both the thiourea protons and protons α to the amide groups were substantially shifted, indicative of the ditopic nature of the complexation. The binding of carboxylates by related tetrathiourea calix[4]arenes has also been reported.[84]



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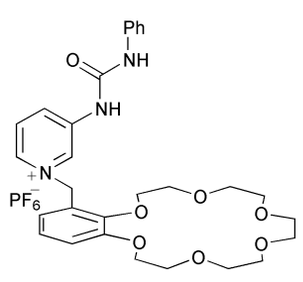
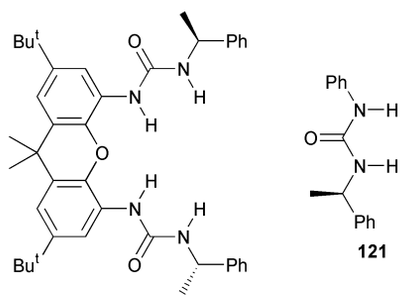


119

Jeong has described the extraction of zwitterionic amino acids by a urea-crown ether receptor. Solid–liquid and liquid–liquid extraction experiments with receptor **119** showed a preference for the extraction of amino acids with hydrophobic side chains into CH_2Cl_2. Shifts in the ^1H NMR of receptor **119** in the presence of phenylalanine indicated the formation of a strong complex in $CDCl_3$.[85]

4.1 Binding monocarboxylates with bisthioureas

Although mono-ureas and -thioureas provide potent carboxylate binding sites using a bidentate array of hydrogen bonds, bis-ureas and -thioureas can be used to provide even stronger binding using four hydrogen bonds. For example, Rebek found that bisurea receptor **120** bound monocarboxylates in $CDCl_3$ (*e.g.* $K_a = 2 \times 10^5$ M^{-1} with TMA benzoate) significantly more strongly than the corresponding monourea **121** ($K_a = 400$ M^{-1} with TMA benzoate),[86] indicating that in the former system both ureas co-operate in the binding of the carboxylate. The enantioselective binding properties of receptor **120** were also investigated using the enantiomers of TMA naproxenate as guests in MeOH, but negligible selectivity was observed.



120 121

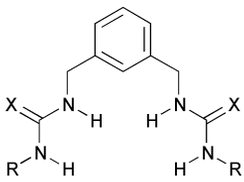
Umezawa used even simpler structures to show that bisthioureas, such as **122**, are stronger receptors than the corresponding mono-ureas/thioureas.[76] Thus bisurea **123** bound TBA acetate ($K_a = 43$ M^{-1}) whereas bisthiourea **122** bound the same guest more strongly ($K_a = 470$ M^{-1}) in DMSO-d_6. Job plot analysis clearly indicated a 1 : 1 stoichiometry consistent with complex **124**, and large changes in chemical shifts were observed for the NH protons. Whereas bisurea **123** was insoluble in solvents of low polarity such as $CDCl_3$, bisthiourea **122** was well solvated in $CDCl_3$ and no evidence of self-association was reported although closely related bisthiourea **125** has been reported to self associate in $CHCl_3$ ($K_{dimer} = 130$ M^{-1}). Hong has used such a bisthiourea binding site to create colorimetric sensors **126** for anions including acetate.[87] Receptor **126** bound TBA acetate ($K_a = 1.9 \times 10^4$ M^{-1}) and binding led to a pronounced red shift in the UV spectrum of **126**.

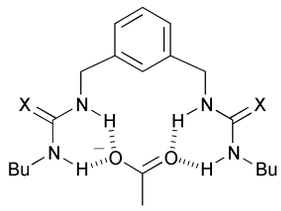
Again, as with monothioureas, binding potency can in principle be increased by using thiouroniums. Thus bisthiouronium **127** bound TBA benzoate in DMSO-d_6 ($K_a = 590$ M^{-1}).[75] Rigidification of bisthioureas in cyclophanes, such as **128**, can also increase the binding strength. Thus *ortho-meta* cyclophane **128** bound TBA acetate in DMSO-d_6 ($K_a = 2.2 \times 10^3$ M^{-1}) significantly more strongly than the analogous *meta-meta* cyclophane **129** ($K_a = 390$ M^{-1}) in DMSO-d_6.[88]

As with monothiourea receptors, calixarenes have been popular scaffolds on which to mount bisthioureas to generate carboxylate receptors. Nam and Jeon have described calix[4]arene and calix[4]quinone receptors with two ureas appended on the lower rim which bind acetate in $CDCl_3$ and CD_3CN.[89] Recently Stibor has described calix[4]arene tetrakis(urea) **130** in the 1,3-alternate conformation, as an anion receptor, which bound benzoate and acetate ($K_a \approx 2 \times 10^3$ M^{-1}) in 20% CD_3CN–$CDCl_3$. The receptor exhibited an unusual negative allosteric effect since binding of an anion by one pair of ureas locks the calixarene in a conformation which suppresses binding of a second anion by the other pair of ureas.[90]

4.2 Binding bis- and tris-carboxylates

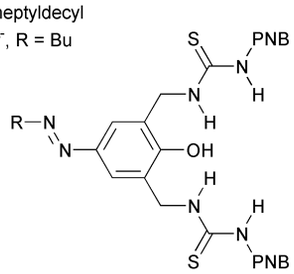
Hamilton used simple bis-ureas/thioureas, with an aromatic spacer to keep the two binding sites from converging, to produce receptors for biscarboxylates. Receptors **131** and **132** bind the bis-TBA salt of glutaric acid in DMSO-d_6 ($K_a = 6.4 \times 10^2$ M^{-1} and $K_a = 1.0 \times 10^4$ M^{-1} respectively).[42]





122 X = S, R = Bu
123 X = O, R = Bu
125 X = S, R = heptyldecyl
127 X = S^+MeBr^-, R = Bu

124



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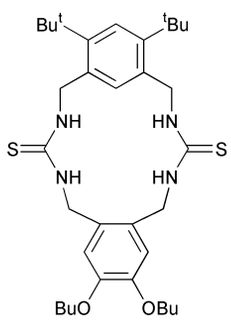

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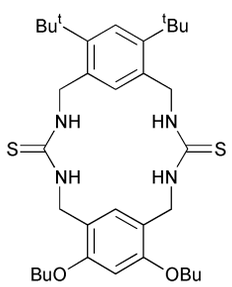

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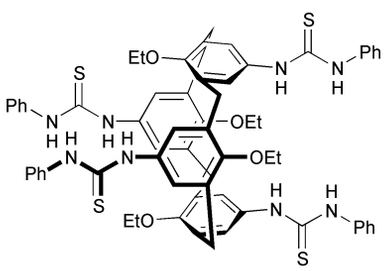

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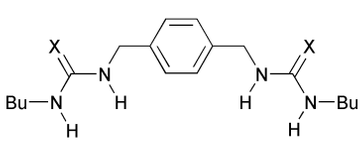
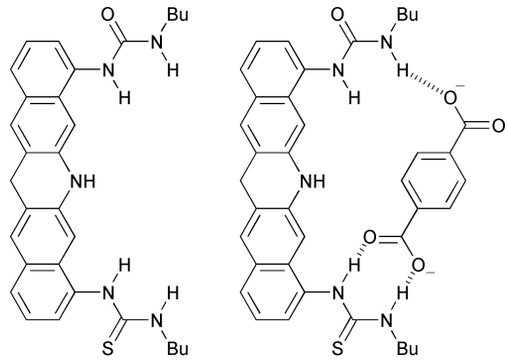


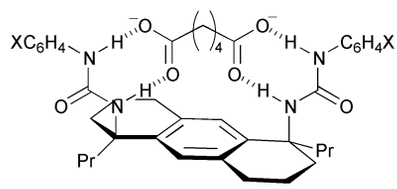
131 X = O, **132** X = S

Kelly found that rigid bisurea **133** complexed both isophthalate (K_a = 6.3 × 10^4 M^{-1}) and terephthalate (K_a = 745 M^{-1}) in $CDCl_3$ with considerable selectivity towards the former.[72] However, receptor **133** binds terephthalate considerably more strongly than simple benzoate (K_a = 104 M^{-1}) and although this may reflect a slightly greater basicity of terephthalate, or the fact that either carboxylate can bind in the normal bidentate array, it may be due to a third hydrogen bond between the 'free' carboxylate and one proton of the 'free' urea as in **134**.

By modifying the size of the aromatic spacer, Jeong has synthesised bidentate bisurea receptor **135** that exhibited a strong affinity for adipate biscarboxylates (such as bis(TBA) adipate in DMSO-d_6) over other structurally similar biscarboxylates.[91] In this series of receptors, the *para*-substituent X had a significant influence on the binding constants, so that for example bis(TBA) adipate was only weakly bound in DMSO-d_6 when X = NMe_2 (K_a = 510 M^{-1}), but strongly bound when X = NO_2 (K_a = 2.2 × 10^4 M^{-1}).[91,92]

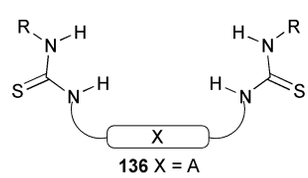


133 **134**

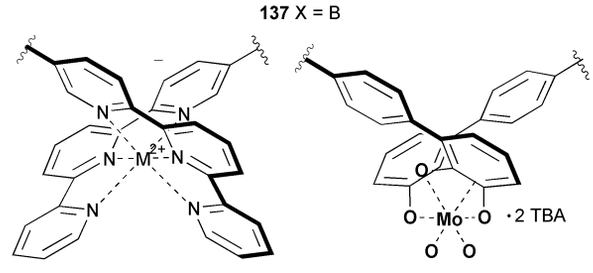


135

Using a combinatorial approach Hamilton has identified a self-assembling bisthiourea receptor **136** (X = A) for the recognition of biscarboxylates.[93] Receptor **136** is derived from the association of two terpyridyl derived thioureas with appropriate metal(II) salts. Titration of receptor **136** with small aliquots of TBA biscarboxylates in DMSO-d_6 led to significant shifts in the signals in the ^1H NMR of the host–guest complex, with particularly large shifts observed for the thiourea protons. Chemical shift changes were indicative of a 1 : 1 binding stoichiometry in which a single guest molecule bridges the Ru^{2+} complex and binds to both thiourea moieties through four hydrogen bonds. Binding constants in neat DMSO-d_6 were too high to be accurately measured (K_a > 1 × 10^4 M^{-1}) presumably due to additional electrostatic interactions between the doubly charged ruthenium complex and the dianionic guest. Binding studies with receptor **136** in 5% D_2O–DMSO-d_6 were also carried out with a range of structurally related TBA biscarboxylates (K_a = 2.9–8.3 × 10^3 M^{-1}) with the strongest binding being observed for glutarate. A similar metal assembled receptor has been synthesised by Weiss.[94] Assembly of two functionalised catechol ligands around a molybdenum(IV) core provides receptor **137** (X = B) that was found, by UV titration, to bind biscarboxylates in a 1 : 1 stoichiometry. Association constants were determined for simple alkyl biscarboxylates, from succinate to pimelate (K_a = 5.0 × 10^5 − 7.9 × 10^6 M^{-1}) in CH_3CN.

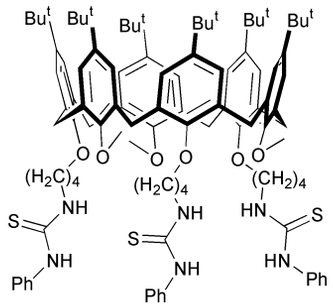


136 X = A
137 X = B



A B

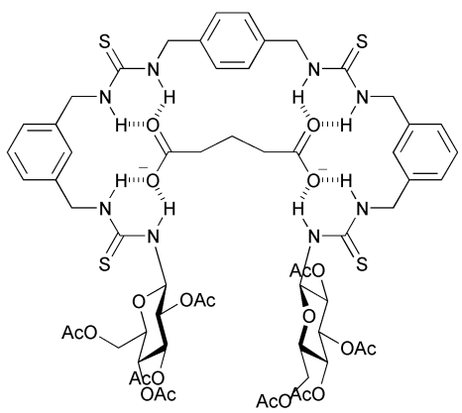
Reinhoudt used a calix[6]arene scaffold to carry three thioureas on the lower rim.[95] Receptor **138** bound TBA cyclohexane-1,3,5-tricarboxylate in $CDCl_3$ (K_a ≈ 1 × 10^5 M^{-1})



138

more strongly than a range of aromatic mono-, bis- and tris-carboxylates.

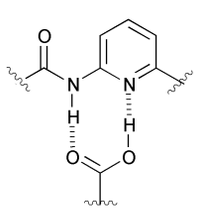
Finally, a series of carbohydrate derived multiple thiourea receptors have been described incorporating elements of both receptor **122** and **132**. These receptors were effective in binding glutarate in DMSO-d_6, with a variety of different binding stoichiometries including 1 : 1 stoichiometry as with complex **139**.[96]



139

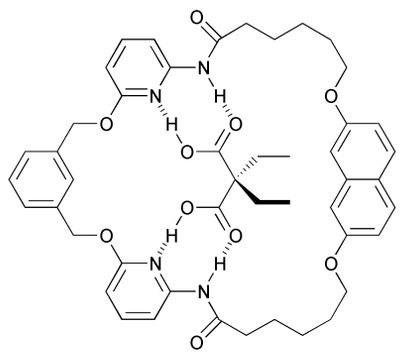
5 Amidopyridines

Amidopyridines provide an excellent structural motif for binding carboxylic acids with the ability to form two complementary hydrogen bonds from the carboxylic acid hydrogen to the pyridine nitrogen and the carboxylic acid carbonyl to the amide hydrogen as shown by complex **140**. In such a binding motif, unfavourable secondary interactions, particularly between the relatively electropositive carboxylic acid and amide protons, make amidopyridines a less potent binding site for carboxylic acids than ureas and thioureas are for carboxylates, and thus amidopyridines are generally only effective in relatively non-polar solvents.

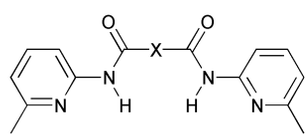


140

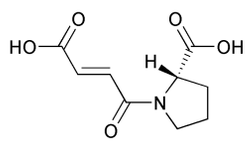
Hamilton was the first to use amidopyridines when he incorporated two such units in macrocycle **141** and the structurally simpler **142** to produce receptors for biscarboxylic acids. Macrocycle **141** bound ethylmalonic acid ($K_a = 7.3 \times 10^3$ M^{-1}) and diethylmalonic acid ($K_a = 1.1 \times 10^3$ M^{-1}) in $CDCl_3$.[97] The relatively low binding constants presumably reflect the unfavourable planar conformation of the diacid required for binding in the cavity of **141**. However, the acyclic receptor **142** forms strong complexes with a range of diacids and particularly with adipic acid ($K_a > 10^5$ M^{-1}) in $CDCl_3$. An important aspect of this early work was the observation, by X-ray crystallography, that complexation does not involve proton transfer from the carboxylic acid to the pyridyl nitrogen.



141



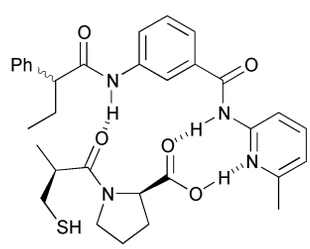
142 X = -*p*C_6H_4-
143 X = -*m*C_6H_4-
145 X = 2,6-napthylene



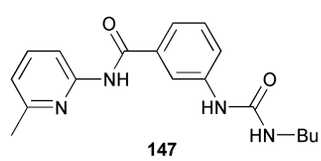
144

Bisamidopyridine **143** has been shown to stabilise the s-*cis* rotamer of proline diacid **144** in preference to the s-*trans* rotamer, whereas the naphthalene derived bisamidopyridine **145** stabilises the s-*trans* rotamer.[98] Bisamidopyridines have also been co-crystallised with biscarboxylic acids to create self-assembled helical and ribbon solid state architectures.[99]

Monoamidopyridine derivatives with additional amide or urea functionality that can bind both the carboxylic acid and amide functionality are effective receptors for acylated amino acids such as *N*-Ac-Pro-OH. Thus the chiral receptor **146** bound ACE inhibitor captopril in $CDCl_3$ with a 2 : 1 enantioselectivity in favour of (*R*)-captopril (K_a = 500 M^{-1}).[100] The related receptor **147** binds the maleimide acid **148** ($K_a = 4.8 \times 10^3$ M^{-1}) in $CDCl_3$ and accelerates the 1,4 addition of a thiol to the maleimide.[101]



146



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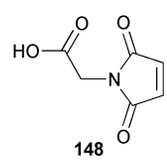
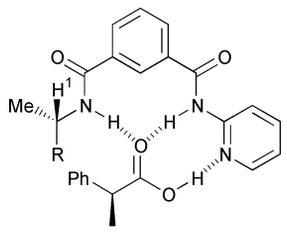


148

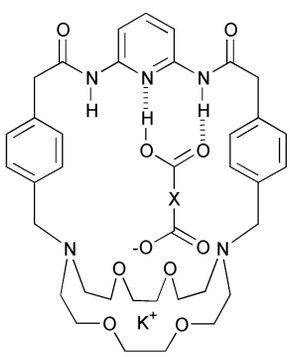
Both Helmchen[102] and Goswami[103] have extended the amidopyridine–carboxylic acid binding motif by incorporating an additional hydrogen bond for the carbonyl oxygen *syn* lone pair, in molecular clefts such as **149**. In Helmchen's studies a series of sterically similar, but electronically different, hosts were prepared in order to develop chiral solvating agents for carboxylic acids. When R = Ph or 1-napthyl, complexation of aromatic carboxylic acid guests (*e.g.* naproxen, phenylacetic acid and hydratropic acid) led to upfield shifts of the signals for the α-H's of the guests in the ^{1}H NMR in $CDCl_3$ ($\Delta\delta \approx$ 0.28 ppm) suggestive of π–π stacking interactions. Receptor **149**

(R = Ph) was also moderately enantioselective binding the (*S*)-enantiomer of hydratropic acid ($K_a = 1.1 \times 10^3$ M^{-1}) with a stronger association constant than for the (*R*)-enantiomer ($K_a = 700$ M^{-1}) in $CDCl_3$.



149

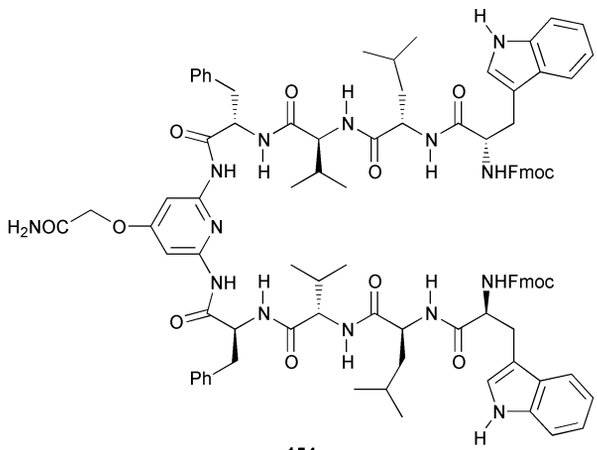
Amidopyridines have been incorporated into a number of more complex macrocyclic architectures for binding various carboxylic acid derivatives. For example, Kilburn synthesised receptor **150** that was found to bind the monopotassium salts of various biscarboxylic acids in $CHCl_3$,[104] using a combination of hydrogen bonding interactions and an electrostatic association between the carboxylate anion and a crown ether bound potassium cation. The binding mode proposed was supported by considering the various extraction experiments, intermolecular NOE experiments and FAB mass spectrometry data, although absolute binding constants were not reported. Significantly **150** bound the monocarboxylate salt of maleic acid but not of fumaric acid which was judged to be too large for the macrocyclic cavity.



150

A series of macrocyclic receptors **151**–**153** incorporating a diamidopyridine moiety have also been synthesised by Kilburn.[105] These were found to be sequence selective receptors for *N*-protected dipeptides with a free carboxylic acid terminus in non-competitive media ($CDCl_3$). The amidopyridine–carboxylic acid interaction contributed 11–19 kJ mol^{-1} of the binding energy to the overall binding of dipeptides in these systems. The most significant selectivity with these receptors was found for receptor **153** which bound Cbz-L-Ala-L-Ala-OH ($K_a = 3.3 \times 10^4$ M^{-1}) with ~ 8 : 1 selectivity over Cbz-D-Ala-D-Ala-OH ($K_a = 4.5 \times 10^3$ M^{-1}).

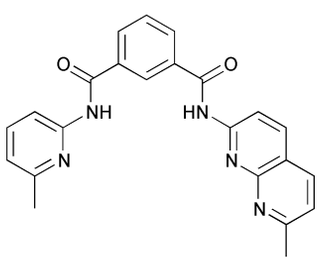
Kilburn has also incorporated diamidopyridines in tweezer receptors and used a solid phase approach to synthesise libraries of receptors that could be screened for selective binding of peptides with a carboxylic acid terminus.[106] Using this approach, tweezer **154** was identified as a receptor for the protected tripeptide DNS-L-Glu(O^{t}Bu)-L-Ser(O^{t}Bu)-L-Val-OH ($K_a = 2.6 \times 10^5$ M^{-1}) in 2% DMSO–$CHCl_3$ by UV titration.



154

5.1 Bisamidopyridines

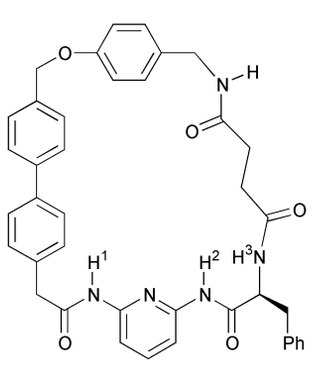
As described above, Hamilton has used a range of bisamidopyridines, such as **142**, to bind biscarboxylic acid derivatives. Extending this idea to incorporate naphthyridine units Goswami produced a receptor **155** which bound otherwise insoluble tartaric acid in $CHCl_3$.[107]



155

Diederich has produced a series of chiral bisamidopyridines and examined their binding properties. Thus helicopodand **156**, in the productive 'in–in' conformation, forms stable 1 : 1 complexes with α,ω-biscarboxylic acids and, for example, bound the fumaric acid derivative **157** ($K_a = 2.6 \times 10^3$ M^{-1}) approximately eleven times more strongly than the maleic acid derivative **158** ($K_a = 230$ M^{-1}).[108]

The chiral molecular cleft **159** incorporated a spirobifluorene spacer and two amidonaphthyridine moieties as hydrogen bonding sites.[109] Solution binding studies in $CDCl_3$ showed that



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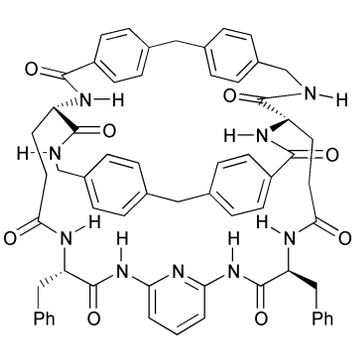

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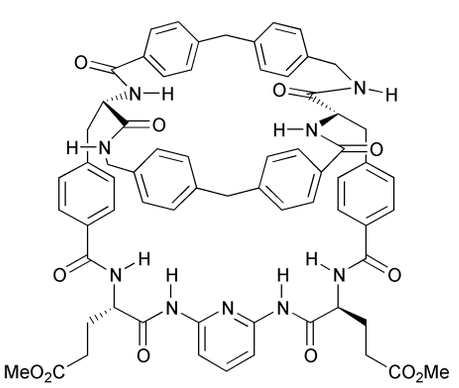

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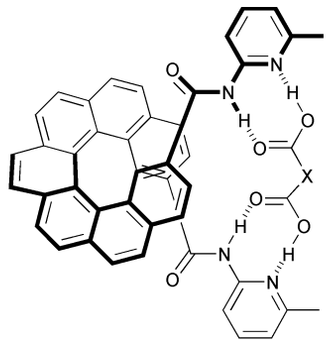

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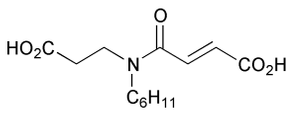

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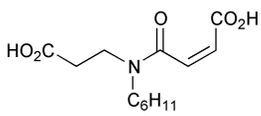
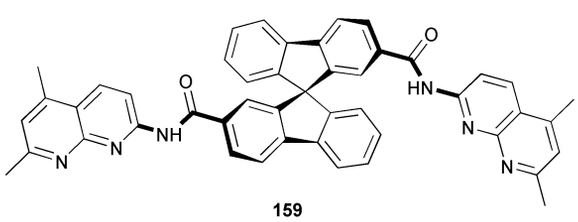


158

159 was able to complex chiral biscarboxylic acids with some enantioselectivity. By covalently linking a closely related structure to silica gel, a chiral stationary phase was generated. HPLC separations of racemic diacids in different solvents using this material suggested that the attractive interactions between solute and immobilised chiral selector were a combination of hydrogen bonding, which prevails in non-polar eluents, and aromatic π–π stacking, which dominates in polar eluents. Changing the hydrogen bonding sites from amidonaphthyridine in **159** to amidopyridine in **160** did not significantly alter the binding properties. This initially surprising observation was rationalised by considering two compensating effects. Naphthyridine *N*-atoms are weaker hydrogen bond acceptors than pyridine *N*-atoms. On the other hand, the naphthyridine provides two lone pairs that can potentially form a bifurcated hydrogen bond with the carboxylic acid proton.



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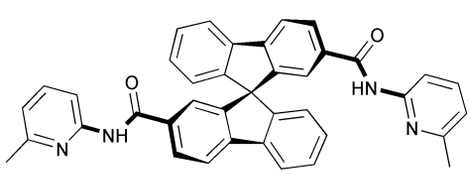
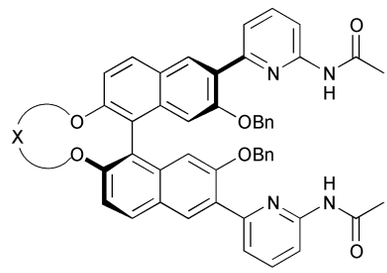


160

Diederich has also synthesised a highly enantioselective amidopyridine receptor for Cbz-aspartate based around a 1,1-binaphthalene scaffold.[110] Receptor **161** was found to bind aspartate with good enantioselectivity when the binaphthalene groups were locked in an appropriate conformation by a spacer X. The highest enantioselectivity was observed when X = $-(CH_2)_2-N(Me)-(CH_2)_2-$ with a 15-fold higher binding constant observed for Cbz-L-aspartate ($K_a = 8.7 \times 10^4$ M^{-1}) over Cbz-D-aspartate ($K_a = 5.6 \times 10^3$ M^{-1}) in $CDCl_3$. A proposed binding mode **162** for the **161**–aspartate complex was derived from computational studies of the host–guest complex in conjunction with NOE studies. Goswami has reported similar chiral bisamidopyridine receptors using Troger's base as the molecular scaffold.[111]

The synthesis and binding properties of metal templated bisamidopyridine receptors **163** and **164** for biscarboxylic acids in $CDCl_3$ has been reported by Hamilton.[112] Binding constants



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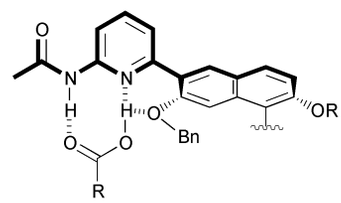
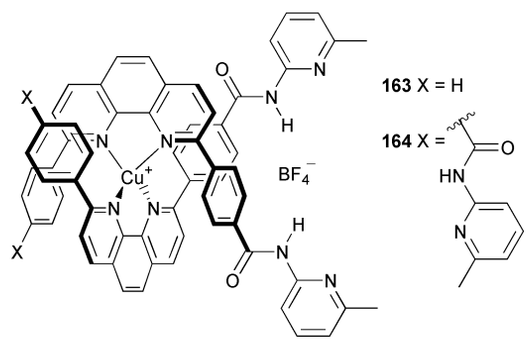


162

were determined by both ^1H NMR and UV titration studies. Receptor **163** binds glutaric acid ($K_a = 4.3 \times 10^4$ M^{-1}) and related diacids in a 1 : 1 stoichiometry, whereas receptor **164** binds glutaric acid with a 1 : 2 (host : guest) stoichiometry ($K_a = 7.8 \times 10^4$ M^{-1}).



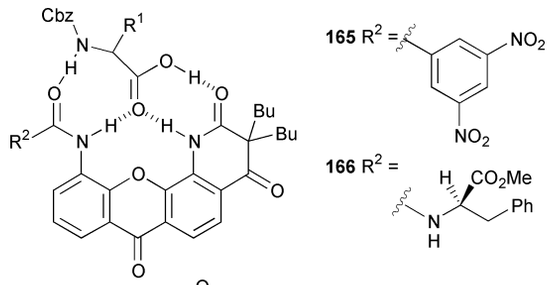
163 X = H

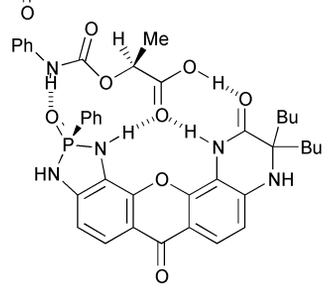
164 X =

6 Amides and other neutral receptors

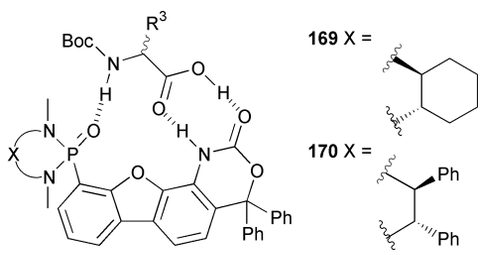
6.1 Binding carboxylic acids

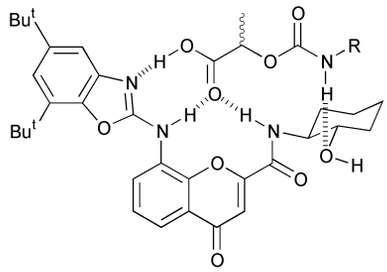
Conformationally restricted (cyclic) *cis* amides and carbamates provide a complementary pair of hydrogen bond interactions for carboxylic acid recognition. Thus, Moran has described the chromenone derived receptor **165** which binds benzoic acid derivatives in $CDCl_3$ with large binding constants when the aromatic guest had a *para* electron donating substituent (*e.g.* $K_a = 1.6 \times 10^6$ M^{-1} with 4-methylaminobenzoic acid).[113] The chiral receptor **166** also bound *N*-Cbz-amino acids in $CDCl_3$,[114] and the highest binding constant was observed for *N*-Cbz-glycine ($K_a = 1.3 \times 10^4$ M^{-1}). Using larger guest molecules (*e.g.* alanine and phenylalanine), steric repulsion leads to reduced binding strength. Modest enantioselectivity (~2 : 1) was observed for both Cbz-alanine and Cbz-phenylalanine in favour of the L-enantiomer in each case. Receptor **167** uses both a cyclic amide and a chiral phosphonamide to produce a highly enantioselective receptor for lactic acid derivatives using four hydrogen bond interactions. Thus (*R*)-**167** binds (*S*)-lactic acid derivative **168** ($K_a = 5.0 \times 10^5$ M^{-1}) ninety times more strongly than (*S*)-**167** ($K_a = 6.3 \times 10^3$ M^{-1}) in $CDCl_3$, as determined by competition experiments. Wills has synthesised structurally similar receptors **169** and **170** which utilise cyclic carbamates as the recognition site for Boc-amino acids with additional stabilising interactions between the amino acid carbamate NH and a chiral phosphonamide in the receptor.[115] ^1H and ^{31}P NMR titration studies in $CDCl_3$ generated data consistent with the proposed binding mode and a 1 : 1 binding stoichiometry. Modest selectivity was again observed with these receptors in favour of the L-enantiomers of amino acid guests.





(R)-**167**:(S)-**168** complex





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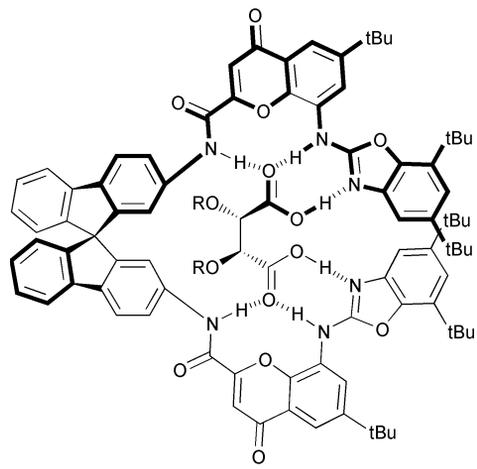
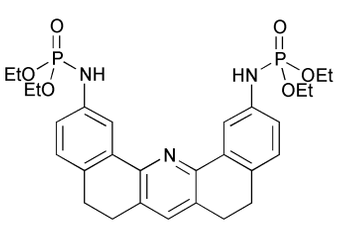


172

Related chromenone derived benzoxazoles also serve as receptors for carboxylic acids and receptor **171**, incorporating an aminocyclohexanol unit to provide chirality, bound the (*S*)-enantiomer of a lactic acid derivative ($K_a = 3 \times 10^5$ M^{-1} when R = *p*-C_6H_4Cl) with 9 : 1 enantioselectivity in $CDCl_3$. The proposed structure of the complex includes a hydrogen bond from the carbamate NH of the guest and the cyclohexanol oxygen.[116] The same chromenone–benzoxazole unit has been attached to a spirobifluorene unit to create chiral receptor **172** for biscarboxylic acids, which was particularly effective at discriminating between tartaric acid derivatives ($K_a = 9.7 \times 10^8$ M^{-1} for L-dibenzoyltartaric acid and $K_a = 3.0 \times 10^7$ M^{-1} for D-dibenzoyltartaric acid) in $CDCl_3$ as determined by competitive NMR binding studies.

Moran has also used a tetrahydrodibenzacridine scaffold to produce a series of receptors for malonic acid derivatives. Both phosphoric amide **173** and the more preorganised cyclic amide **174** bound dibutylmalonic acid ($K_a = 1.5 \times 10^5$ M^{-1} and 2.8×10^5 M^{-1} respectively) in $CDCl_3$ using the expected pair of carboxylic acid–*cis*-amide hydrogen bond interactions. Somewhat surprisingly bisurea **175** and bisthiourea **176**, normally used for carboxylate recognition, also bind to substituted malonic acids.[117] Molecular modelling suggested that there is little energetic preference for the ureas to adopt an *anti*,*anti* conformation **177** or an *anti*,*syn* conformation **178**. The latter conformation allows the receptor to bind dibutylmalonic acid with one carboxylic acid adopting the preferred s-*cis* conformation and the other the s-*trans* conformation stabilised by an intramolecular hydrogen bond. The stronger binding of dibutylmalonic acid by bisurea **175** ($K_a = 2.6 \times 10^4$ M^{-1}) in $CDCl_3$ compared with the bisthiourea **176** ($K_a = 7.8 \times 10^3$ M^{-1}) was attributed to the greater H-bond acceptor properties of the urea oxygen over the thiourea sulfur. Studies with this series of receptors also revealed that they can stabilise the transition state of isoquinoline mediated decarboxylation of dibutylmalonic acid, leading to modest rate enhancements for this reaction.[117] Other related cyclic amide receptors have also been described by Caballero.[118]

Diederich has described cage like receptors containing amide bonds, which bound to a range of *N*-protected amino acid derivatives, including L-glutamic acid.[119] Thus (*S*,*S*,*S*)-(+)-**179**



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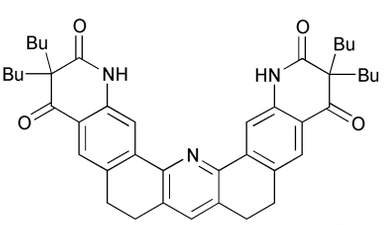

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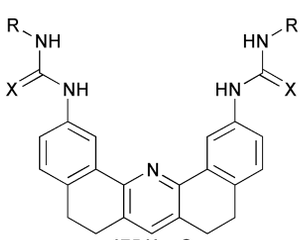
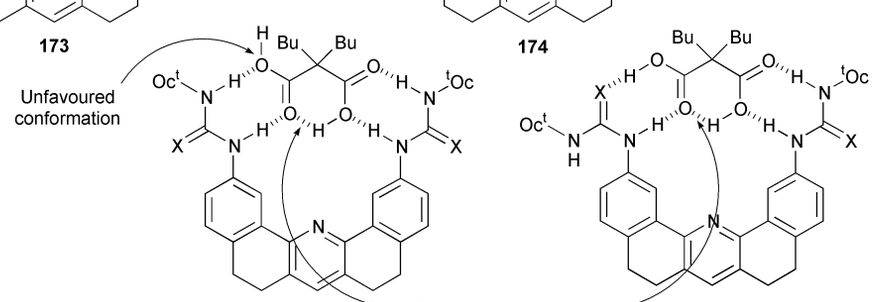
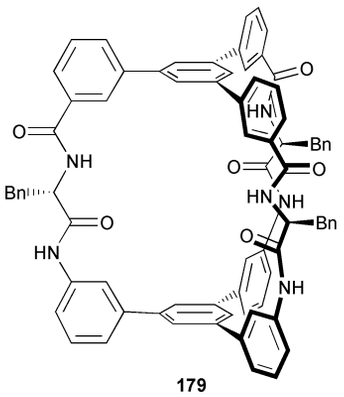


175 X = O
176 X = S



177 **178**

exhibited good enantioselectivity for *N*-Cbz-L-Glu-OH (K_a = 186 M^{-1}) over *N*-Cbz-D-Glu-OH (K_a = 43 M^{-1}) in $CDCl_2CDCl_2$. Molecular modelling and NMR studies support the proposed binding model **180** in which the carboxylic acid forms a pair of hydrogen bonds with the amide NH and amide carbonyl of a phenylalanine unit.



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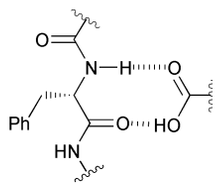
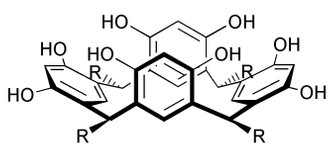


180

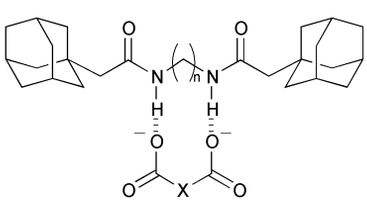
Binding of carboxylic acids using hydrogen bonding interaction with alcohols has also been described. For example resorcinol–aldehyde tetramer **181** binds biscarboxylic acids with considerable selectivity for glutaric acid in non-polar solvents,[120] and an alcohol–carboxylic acid interaction has been reported in the binding of amino acids by metalloporphyrin receptors.[121]



181 R = $(CH_2)_{10}CH_3$

6.2 Binding carboxylates

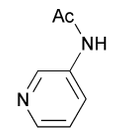
Amide NH's can also be used as hydrogen bond donors to bind carboxylate anions. The stability of bisamide–biscarboxylate complexes **182** has been studied in detail by Schneider.[122] Modification of the biscarboxylate spacer and the length of the alkyl spacer in the bisamide allowed a study of the effect of the number of single bonds on complex stability (n = 2–8, K_a = 0.3–120 M^{-1} in $CDCl_3$).



182

Very simple amide based receptors have been described by Jeong.[123] 3-Acetylaminopyridine **183** was found to bind weakly to TBA benzoate (K_a = 16 M^{-1}) in DMSO-d_6. Alkylation of **183** gave the pyridinium salt **184** which bound TBA benzoate significantly more strongly (K_a = 300 M^{-1}) and downfield shifts of the pyridinium protons H^o and H^p ($\Delta\delta_{max}$ = 0.3–0.6 ppm) suggest that binding of the carboxylate involves hydrogen bonding to both the NH and one of the pyridinium CH's as in **185** and **186**. Alkylation of the pyridine increases the hydrogen bond donor ability of these protons as well as providing electrostatic complementarity. Bispyridinium salts were also prepared and bound biscarboxylates (K_a = 1.8 × 10^3 to 3.1 × 10^3 M^{-1}) in DMSO-d_6.

Hamilton used receptor **21**, described earlier, to bind a carboxylate anion using a combination of amide and ammonium



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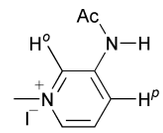

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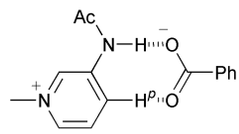

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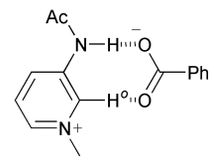
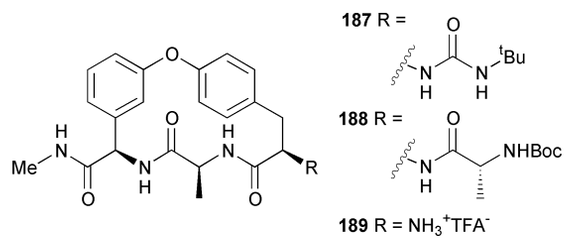


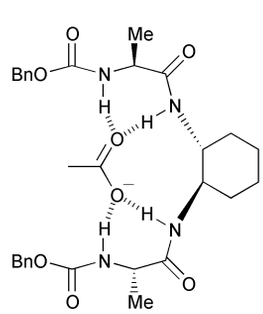
186

binding functionality to create a mimic for the vancomycin carboxylate binding pocket.[16] Similarly, Pieters has reported that the series of receptors **187**–**189** bind Ac-D-Ala in $CDCl_3$. Indeed the neutral Boc-Ala derivative **187** and urea **188** are reported to bind Ac-D-Ala essentially as strongly as the ammonium salt **189** ($K_a \approx 3 \times 10^4$ M^{-1}).[17]



189 R = $NH_3^+TFA^-$

Hamilton also produced a family of structurally simpler amide derivatives derived from cyclohexanediamine.[124] Tetraamide **190** bound TBA acetate (K_a = 340 M^{-1}) in CD_3CN using a combination of four amide donor hydrogen bonds. The serine derivative **191** however bound TBA acetate significantly more strongly (K_a = 2.8 × 10^5 M^{-1}) in CD_3CN and it was concluded that in this case two of the amide NH's and the two serine OH's provide a tighter binding pocket for the carboxylate.



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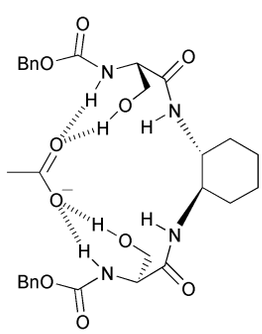
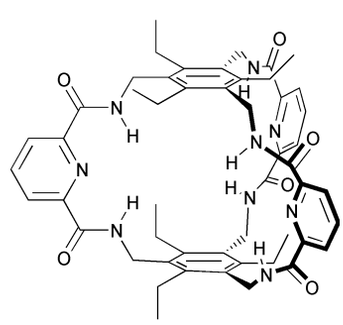


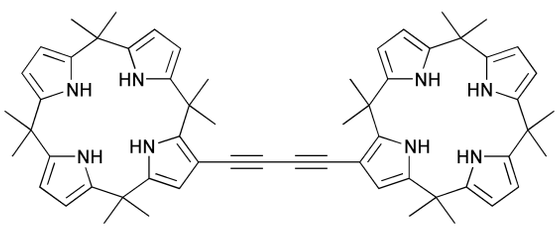
191

Amides incorporated into rigid macrocyclic structures have also been used to bind carboxylates. Thus, Anslyn has described a bicyclic cyclophane receptor **192** incorporating pyridine diamide building blocks which bound TBA acetate selectively over other inorganic anions in 75% CD_3CN–CD_2Cl_2.[125]



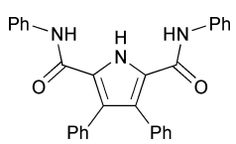
192

Calixpyrroles also provide a convergent array of acidic NH's, and have been used to bind carboxylates, albeit weakly. When attached to silica calixpyrroles have been used as solid supports[126] for the separation of carboxylate derivatives. As with carboxylate binding by protonated sapphyrins, the crystal structure of a calixpyrrole–carboxylate dimer indicates that just one of the carboxylate oxygens is hydrogen bonded by the calixpyrrole NH's.[26] Calixpyrrole dimers with rigid spacers have also been produced and found to bind biscarboxylates in non-polar solvents. Thus receptor **193** binds isophthalate (K_a = 4.2 × 10^3 M^{-1}) in CH_2Cl_2.[127] Eichen has recently described studies with an extended calix[6]pyrrole, which bound trifluoroacetate (K_a = 1.2 × 10^3 M^{-1}) and other inorganic anions *e.g.* fluoride (K_a = 1.1 × 10^3 M^{-1}) in 10% CD_3CN–$CDCl_3$.[128] In contrast, octamethylcalix[4]pyrrole binds trifluoroacetate only weakly (K_a = 70 M^{-1}) with a strong preference for fluoride (K_a = 2.4 × 10^4 M^{-1}).



193

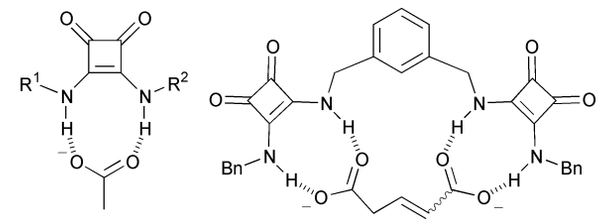
Recent studies by Gale have revealed that simple acyclic pyrrolic diamides can also bind carboxylates, and in relatively polar media. Thus, receptor **194** binds TBA benzoate (K_a = 560 M^{-1}) in 0.5% D_2O–DMSO-d_6.[129]



194

'Squaramides' (3,4-diaminocyclobutene-1,2-diones) provide two acidic NH's suitable for binding a carboxylate anion in a similar fashion to ureas and thioureas.[130] A series of squaramide derivatives have been shown to be effective receptors for carboxylates in polar solvents. The simple dibenzyl derivative **195** binds TMA acetate in DMSO-d_6 and 10% D_2O–DMSO-d_6 (K_a = 2.0 × 10^3 M^{-1} and 48 M^{-1} respectively) with large shifts in the ^{1}H NMR for the NH signals on complexation. Incorporation of a quaternary ammonium salt to provide electrostatic complementarity as in **196** leads to stronger binding of TMA acetate (K_a = 1.4 × 10^4 M^{-1} in DMSO-d_6, K_a = 311 M^{-1} in 10% D_2O–DMSO-d_6). Bis- and tris-squaramides have also been produced and for example bissquaramide **197** binds glutarate (K_a = 1.4 × 10^3 M^{-1}) in 10% D_2O–DMSO-d_6, while trissquaramide **198** binds TBA *cis*-cyclohexanetricarboxylate (K_a = 7.7 × 10^3 M^{-1}) in 10% D_2O–DMSO-d_6. Detailed thermodynamic data for these squaramide–carboxylate complexes obtained using isothermal titration calorimetry have recently been reported.[131]

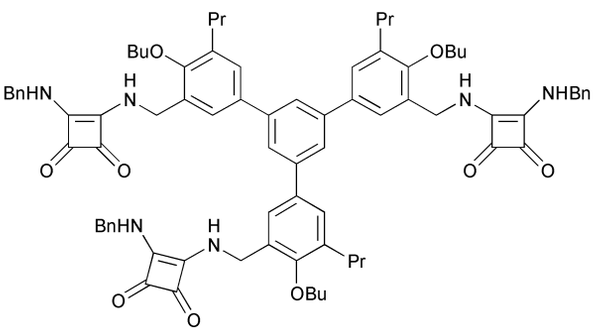
Calixarenes have again proved a popular scaffold on which to mount binding functionality to create receptors. Thus Ungaro has described upper rim peptidocalix[4]arenes[132] which form weak complexes (K_a = 12–49 M^{-1}) with simple carboxylates and carboxylic acids in $CDCl_3$ and DMSO-d_6. Binding of acetate by two perfluoroalcohols appended to the upper rim of a calix[4]arene in $CDCl_3$ has also been reported.[133] Loeb has used a calixarene scaffold to hold two amides in close proximity and in an appropriate orientation for carboxylate recognition.[134] Receptor **199** was found to bind TBA benzoate (K_a = 107 M^{-1}) selectively over a range of other simple anions in $CDCl_3$. A downfield shift of the amide protons ($\Delta\delta$ = 1.33 ppm) indicates



195 R^1 = R^2 = Bn

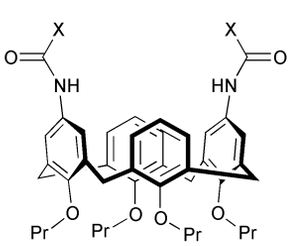
196 R^1 = Bn, R^2 = $-CH_2CH_2NMe_3^+$

197



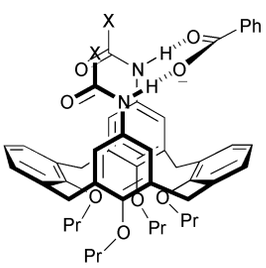
198

that a carboxylate amide interaction is key in the binding of these substrates as in **200**. Increasing the acidity of the amide proton as in **201** increased the affinity of the receptor for benzoate as expected (K_a = 5.2 × 10^3 M^{-1}), and titration of **201** with a range of biscarboxylates in $CDCl_3$, gave ^{1}H NMR data consistent with the formation of a 2 : 1 (host :guest) complex.



199 X = CH_2Cl

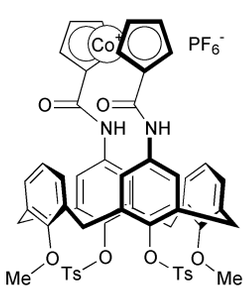
201 X = $CHCl_2$



200

A similar motif has been used by Beer with an upper rim cobaltocenium bridged calixarene **202** which selectively binds carboxylates, particularly benzoate (K_a = 3.8 × 10^4 M^{-1}) and acetate (K_a = 4.2 × 10^4 M^{-1}) in DMSO-d_6, over other simple anions *e.g.* Cl^-, NO_3^-, $H_2PO_4^-$.[135] The selectivity of receptor **202** is attributed to the rigidly held cobaltocenium unit which orientates the two acidic amide NH's for the complexation of bidentate anions such as carboxylates in conjunction with the electrostatic complementarity provided by the metal cation. Biscobaltocenium receptor **203** on the other hand, bound biscarboxylates, in particular adipate.[136] Titration of receptor **203** with TBA salts of oxalate, malonate and adipate in acetone-d_6 gave ^{1}H NMR data consistent with the formation of a 1 : 1 complex with the largest shifts in the ^{1}H NMR observed for the complexation of adipate. Other related tetracobaltocenium receptors for biscarboxylates have also been described[137] and resorcinarene derivatives bearing ruthenium(II) bipyridyl units or ferrocenyl moieties have been reported to bind anions including carboxylates.[138]

A combination of electrostatic and hydrogen bonding interactions have also been used for carboxylate recognition in a series of ruthenium(II) and rhenium(II) bipyridyl receptors produced by Beer.[139] For example, bipyridyl calixquinone derivative **204** binds acetate (K_a = 9.99 × 10^3 M^{-1} in DMSO-d_6) with pronounced selectivity over $H_2PO_4^-$ and complexation of



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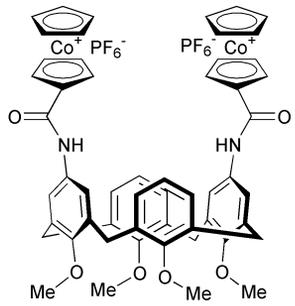

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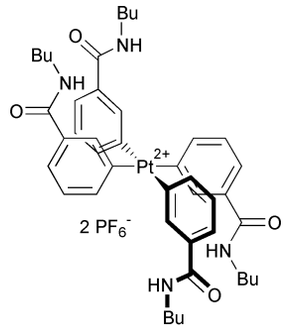
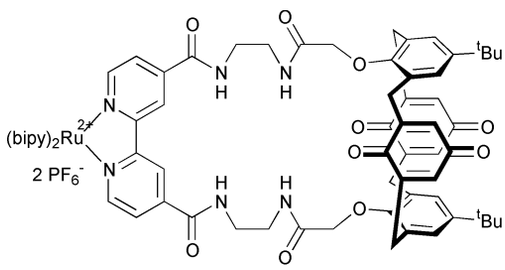


207

acetate has a dramatic effect on the luminescence properties of the receptor. A series of chiral bipyridyl receptors **205** have also been produced which also bind carboxylates effectively in DMSO-d_6 although there was little enantioselectivity when chiral guests were used.[140] A related receptor has been described by Watanabe to which complexes a range of dicarboxylates ($K_a > 1 \times 10^4$ M^{-1} in DMSO-d_6), for example *cis*-cyclohexane-1,4-dicarboxylate ($K_a = 5.6 \times 10^4$ M^{-1}) using up to four hydrogen bond interactions as in **206**.[141]



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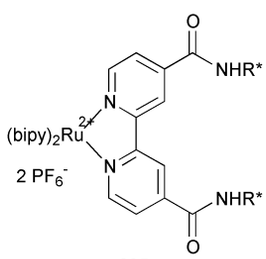

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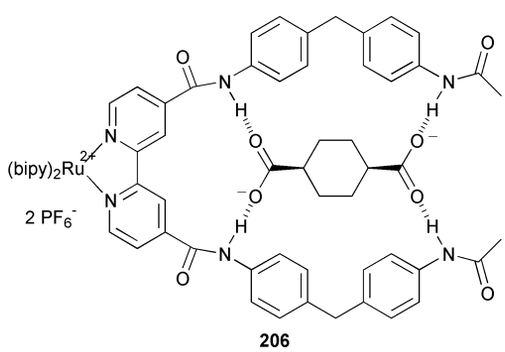
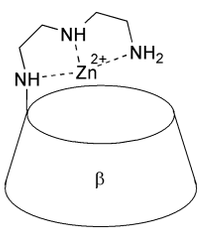


206

Gale and Leob have recently described a platinum(II) templated amide receptor **207** which binds acetate in competitive media.[142] The receptor exhibits a positive allosteric effect in that after complexation of one acetate ($K_a^1 = 230$ M^{-1} in 90% DMSO-d_6–CD_3CN), using one pair of amide NH hydrogen bonds, a second acetate is bound even more strongly ($K_a^2 = 491$ M^{-1}) using a second pair of amide NH's.

7 Metals

A number of examples of receptors incorporating metal centres to provide electrostatic complementarity with anionic (carboxylate) guests have already been described above. Direct coordination of the carboxylate to a bound metal centre can also be used very effectively for carboxylate recognition.[143] Early results in this area come from Tabushi who used metallocyclodextrins to bind cycloalkyl and aromatic carboxylates in H_2O (borate buffer, pH = 10.0).[144] Receptor **208**, for example, with a triazaalkane attached to bind zinc(II), formed stable complexes with adamantane-1-carboxylate ($K_a = 5.3 \times 10^3$ M^{-1}) in H_2O at pH = 10. 2-Oxoadamatane-1-carboxylate ($K_a = 2.8 \times 10^5$ M^{-1}) was bound more strongly due to a secondary coordination between the ketone and the zinc. Receptor **209** with two imidazolyl units is also an effective carboxylate receptor at neutral pH, binding cyclohexanecarboxylate ($K_a = 720$ M^{-1}) in H_2O (HEPES buffer, pH = 7.0).[145] A related histamine derived cyclodextrin–Cu(II) complex has been used to prepare diastereomeric complexes with D- and L- Trp which could be separated using an achiral reverse phase (RP-18) column chromatography.[146] As a further extension a fluorescent cyclodextrin derivative has been used to again produce a copper(II) complex **210** which could be used as an enantioselective fluorescent sensor for amino acids.[147] Binary and ternary metallocyclodextrins have also been described recently, and their complexation properties with tryptophan have been studied in detail.[148]



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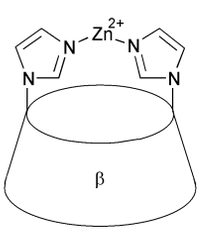

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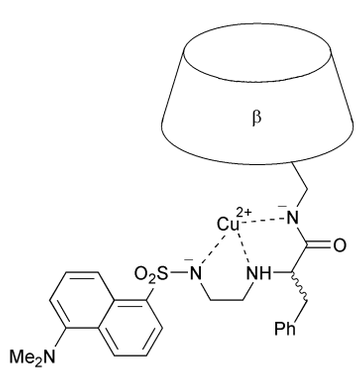
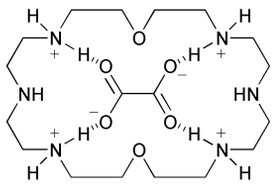


210

Polyaza macrocycles are particularly interesting as carboxylate receptors since, when protonated, they are effective carboxylate receptors in their own right (see section 2.1), but in the neutral form can bind transition metals to again produce carboxylate receptors. An early example was described by Martell.[149] Hexaaza-24-crown-8 binds oxalate dianion when the former is tetra-, penta- or hexa-protonated as in **211**. In its neutral form the hexaazacrown binds to copper(II) and cobalt(II) ions and an oxalate dianion can bridge between the two metal centres as in **212**. In the di- or tri-protonated forms it can bind a single metal allowing carboxylate coordination to the metal centre at one end of the macrocycle and to the protonated amines at the other end as in **213**. Similar results have been obtained with the larger polyazamacrocycle **214** which

forms complexes with pimelate dianion when protonated or the corresponding mono- and di-nuclear copper complexes, which again bind pimelate in an analogous fashion to **211**, **212** and **213**.[150]



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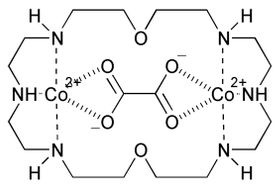

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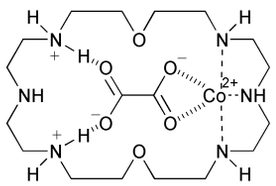

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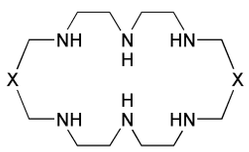
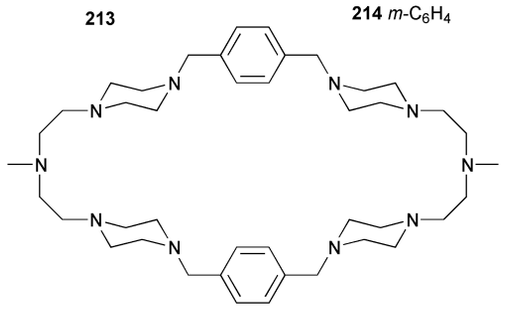


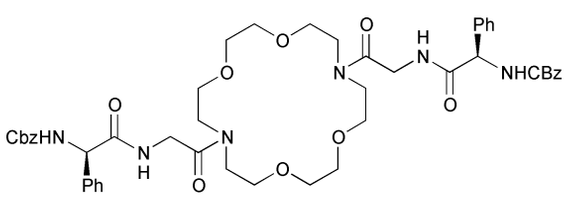
214 *m*-C_6H_4



215

Herman has also used hexaaza macrocycle **215** to form a dinuclear complex with copper(II) but the resulting complex was used to bind amino acid carboxylates using one metal centre to bind the carboxylate and the other to bind the free amine of the guest.[151] Zinc(II) complexes with a smaller tetraaza macrocycle have also been shown to bind carboxylates.[152]

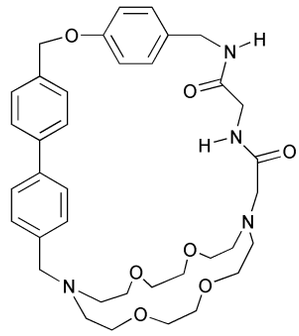
Crown ether bound alkali metals also bind carboxylates. Zinic used dipeptide derived lariat crown ethers, such as **216**, to effect enantioselective transport of the potassium salts of various amino acids and dipeptide carboxylates across a lipophilic membrane ($CHCl_3$).[153] More recently Voyer has used octapeptides incorporating a benzo crown ether unit also for the enantioselective transport of potassium salts of amino acid carboxylates.[154]



216

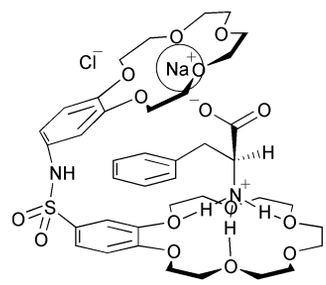
Crown ethers have been incorporated into macrocycles *e.g.* **150** (see section 5) with an amidopyridine moiety which bound to monocarboxylate salts of various biscarboxylic acids. Macrocycle **217** similarly used diaza 18-crown-6 and additional amide functionality. The binding properties of **217** were probed using mass spectrometry techniques and indicated that the receptor could bind *N*-Ac amino acid carboxylates (K^+ salts) but not the sterically more demanding *N*-Boc amino acid carboxylates.[155]

A biscrown ether has been used for the membrane transport of zwitterionic phenylalanine in the presence of Na^+, using simultaneous binding of the sodium carboxylate by the 15-crown-5 moiety and of the ammonium salt by the 18-crown-6 as in **218**, with additional π–π interactions between the aromatic rings of host and guest. Transport of phenylalanine



217

was also possible in the presence of K^+, but here complexation probably involved formation of a biscrown ether sandwich complex with K^+, which can then associate with the amino acid carboxylate.[156]



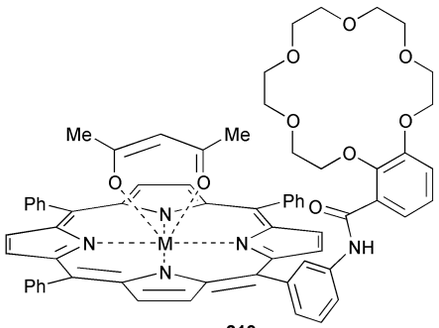
218

A metalloporphyrin–crown ether adduct **219** has been used for the extraction of zwitterionic amino acids from H_2O, now using the metalloporphyrin to bind the carboxylate and the crown ether to bind the ammonium ion of the amino acid guest.[157] Using a similar approach a crown ether functionalised manganese(III) salicylaldimine has been used for the transport of amino acids such as tryptophan.[158]

Other 'strapped' chiral zinc porphyrins have been used for enantioselective recognition of *N*-protected amino acid carboxylates.[159] For example, macrocycle **220** can be used to extract the sodium salt of racemic *N*-Cbz-amino acid carboxylates from water with a strong preference for the L-configured guest. Investigation using IR and ^1H NMR suggested that binding involved an electrostatic zinc–carboxylate interaction and additional hydrogen bonds and van der Waals interaction as in **221**.

A number of other metal complexes have been used to bind unprotected amino acids. Lanthanide tris(β-diketonate) complexes have been shown to be effective receptors for anionic substrates, such as carboxylates. The resulting anionic complex **222** can be further used to bind an ammonium salt *via* an electrostatic interaction, providing a binding site for zwitterionic amino acids as in **223**.[160] For example the chiral tris(β-diketonate) lanthanide complex **224** was used to transport amino acids with hydrophobic side chains from acidic aqueous solution (pH ≈ 6.2) into CH_2Cl_2. For the extraction of racemic mixtures of amino acids the highest enantioselectivity (49% ee) was observed for phenylglycine as guest, using receptor **224** (M = Yb).

The chiral cobalt(III) complex produced using tetradentate ligand **225** provides a particularly effective enantioselective receptor for amino acid carboxylates.[161,162] The carboxylate of the amino acid guest prefers to bind *trans* to the carboxylate of the ligand. Binding of L-amino acids is then disfavoured as it would lead to a steric clash between the α-proton of the bound amino acids and the methyl groups of the ligand as in **226** and hence preferential binding of D-amino acids is observed, as in **227**. The structures of the diastereomeric complexes were confirmed by X-ray crystallography. Interestingly complex **226** can be epimerised to **227** in basic D_2O, providing a means of converting L-amino acids to D-amino acids in basic media.



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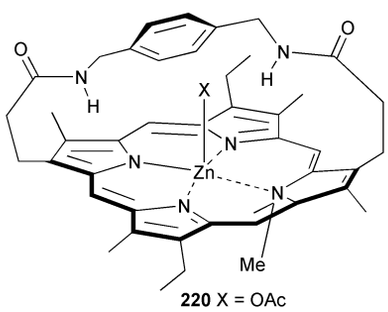
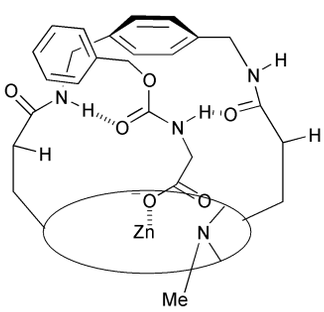


220 X = OAc



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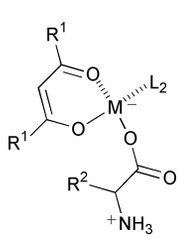

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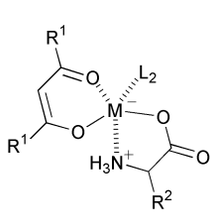

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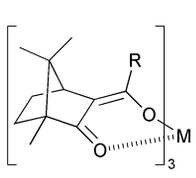
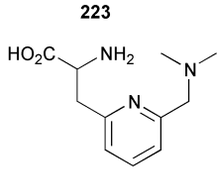


224 R = -$CF_2CF_2CF_3$



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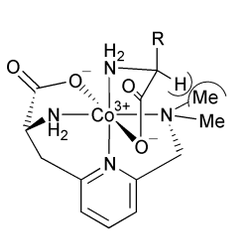

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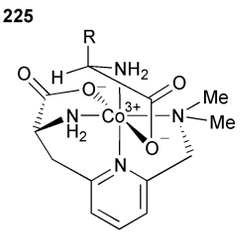

227

8 References

1 For an overview of developments in host–guest chemistry see J. H. Hartley, T. D. James and C. J. Ward, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3155 and references therein. For a recent review on anion recognition (including aspects of carboxylate recognition) see P. D. Beer and P. A. Gale, *Angew. Chem., Int. Ed.*, 2001, **40**, 487 . For a recent review on carbohydrate recognition see A. P. Davis and R. S. Wareham, *Angew. Chem., Int. Ed.*, 1999, **38**, 2979.

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