Role of amide and urea moieties in molecular recognition[†]

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The amide and urea moieties due to their unique stereoelectronic character interact with electron deficient centres through carbonyl group and with electron rich centers through N–H units. This dual character has been successfully used for the design of urea/amide based receptors for recognizing variety of guests. This review discusses the salient examples of such receptors to bring out the unique scope of urea and amide units in designing receptors for recognition of cations, anions and neutral molecules.

Molecular recognition is quite essential to most of the biological and chemical processes. Enzymes, antibodies, membranes, and other receptors; carriers, and channels all involve molecular recognition as a key step in their biochemical functioning¹. Molecular recognition in general involves multimolecular assemblies, called supramolecular complexes, formed between two or more topologically complementary chemical entities which are held together by non-covalent forces^{1,2}. For a deep insight into the basis of noncovalent interactions and biological functions of receptors and to emulate the basic principles of nature, the investigations on complementarity of various host guest interactions in structurally simpler model receptors have been carried out. In fact the concept of molecular recognition grew out of such studies in the mid-sixties from the observations of selective recognition of alkali metal cations by ionophoric antibiotics^{3–5} and synthetic macro(poly)cyclic polyethers⁶.

Molecular recognition character of a receptor is governed by its overall structural topology where primarily the constituent functionalities trigger and influence the nature of its bindings. Amongst various functional groups such as ethers, thioethers, sulphides, disulphides, imines, amines, ureas and amides etc. used in the design of model receptors, amide and urea moieties enjoy a pre-eminent position because of their unique stereoelectronic character⁷. As depicted below amides elaborate electron rich O, N centres and electron deficient N–H units, and thus can bind with both electron deficient guests (at O, N) and electron rich guests through hydrogen bonding (at N–H unit). Resonance assists amides to attain more negative charge than any other neutral oxygen functionality and also provides desirable rigid spatial geometry. The spatial orientation of the amide could

be effectively controlled by the bulk and nature of substituents on the amide nitrogen.

Urea moiety also owes its importance to somewhat similar electronic character as the amide. Additional electron donation by the second nitrogen atom in the case of urea further increases the negative charge on the oxygen atom and provides rigidity to the geometry.

Nature has quite generously used amides in evolving receptors such as valinomycin³, baeuvericin⁴, westiellamide⁵ etc. and many other molecules of biological importance.

Importance of urea moiety in biological systems is quite evident from the fact that out of the five nucleobases, all three pyrimidine bases i.e. cytosine, thymine and uracil have urea moiety in their structure, which efficiently participates in double helix formation (H-bonds) and co-ordinates with metal ions⁸.

In this article, the unique role of amide and urea moieties in molecular recognition of both electron rich and electron deficient guests in synthetic receptors has been highlighted. The presentation is categorized into cationic, anionic and neutral recognition and in each category the receptors in order of podands, coronands, cryptands, cyclophanes and calixarenes etc. are arranged.

[†]Dedicated to Professor S. M. Mukherji.

Valinomycin K^+ selective Westiellamide Ag^+ selective R = N-methyl-L-phenylalanine
Baculovirin Ba^{2+} selective

I: Cationic recognition

A pioneering effort to develop open chain amide based podands of utility in the development of ion selective electrodes was initiated by Simon and co-workers in Zürich and as early as 1972, Ca^{2+} selective carrier **1**⁹ was reported.

Numerous other ligands such as **2-5** were developed. From amongst a series of N,N,N',N' -tetrasubstituted diamides, the ionophores **3c** and **5a-c** showed a high Li^+ selectivity with **5b** showing highest Li^+ selectivity over alkali (>1000 times) and alkaline earth (>100 times) cations. The ionophores **5b** and **5c** have been used for Li^+ assay determination¹⁰⁻¹².

Amongst podands **6-8**, **6b** co-ordinates with Li^+ through four amide oxygens in a 2 : 1 (Ligand : Li^+) complex. Li^+ selective electrodes based on ionophores **6h**, **8a**, **8b**, **8d** have also been reported¹³.

Amongst 3-oxapentanediamides **9-11**, the compound **9d** forms an ideal co-ordination sphere of nine atoms in 3 : 1 ligand- Ca^{2+} complex for the uptake of Ca^{2+} and induces a selectivity in membranes for Ca^{2+} over Mg^{2+} ,

Na^+ , and K^+ by a factor of 10^4 , $10^{7.4}$ and 10^8 respectively¹⁷. The IR monitored solubilization studies on complexes of a series of *N*-bridged benzimidazolones **12** with alkali and alkaline earth metal cations exhibit significant selectivity in complexation and transportation of Ca^{2+} in preference to the other cations¹⁸.

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11

12

N,N-Di(8-quinolyl)malonamide derivative **13** selectively extracts Cu^{2+} amongst the transition metal ions from the aqueous phase. However, **14** hardly extracts any metal ion but effectively transports Cu^{2+} with high selectivity through liquid membranes¹⁹, whereas **13** exhibits poor transport character probably due to high binding ability. The *N*-benzyloxyamide derivatives **15** and **16** selectively formed complexes with Hg^{2+} . Podand **15** can be used as ionophore for ion selective electrodes to detect Hg^{2+} with good reproducibility^{20,21}. Podand **16** formed stable complexes accompanied by deprotonation of the amide groups only when Hg^{2+} was added.

Amongst the amide functionalised macrocyclic tweezer shaped coronands, the receptor **17a** displays significant

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14

15

a $\text{R}^1 = \text{R}^2 = \text{CH}_3$
 b $\text{R}^1 = \text{H}, \text{R}^2 = n\text{-C}_{14}\text{H}_{27}$

16

selectivity for Li^+ over Na^+ in polymeric membranes²². The optically active macrocycles **18** incorporating both ester and amide functionalities have been synthesized to mimic the highly selective binding character of natural ionophores²³. Thus the 24-membered **18** ($n = 1, m = 3$) mimics valinomycin in its ability to transport K^+ and Na^+ ions. Meso **18** ($n = 1, m = 3$) is more efficient than ($\pm$) **18** ($n = 1, m = 3$) for the transport of alkali metal cations ($\text{Na}^+, \text{K}^+, \text{Rb}^+, \text{Cs}^+$) but both exhibit negligible transport of alkaline earth ($\text{Ba}^{2+}, \text{Sr}^{2+}, \text{Mg}^{2+}$ and Ca^{2+}) picrates.

17

$n = 0, m = 1, 3$
 $n = 1, m = 0-3$
 $n = 2, m = 3$

18

19

a $\text{R}, \text{R}' = \text{Bn}$
 b $\text{R} = \text{H}, \text{R}' = \text{Bn}$

20

- a R, R' = Bn, X = N-C₆H₅
 b R, R' = Bn, X = N-C₆H₄F-p
 c R = H, R' = Bn, X = N-C₆H₅
 d R, R' = Bn, X = O

21

- a X = CH₂(CH₂OCH₂)_nCH₂
 n = 1, 2
 b X = CH₂(C₆H₅N)(CH₂

22

For similar lipophilicity but lower number of binding sites and smaller ring size, **20a** extracts alkaline earth metal picrates better than the more flexible **19** in the order Ba²⁺ ~ Sr²⁺ > Ca²⁺ but **20b** shows higher selectivity in extraction for Ba²⁺ ions²³. Both **20a** and **20b** furnish 1 : 1 complexes with Ba²⁺ picrate²⁴. However, the increase in the ring size in **21a**, **21b** over that of **20a** reveals order Ca²⁺ ~ Sr²⁺ > Ba²⁺ but **21c** is selective for Ba²⁺ over Ca²⁺ and Sr²⁺ ions²⁵.

Ferrocene containing unsymmetrical cryptand **22a** (*n* = 1) employs carbonyl oxygens in binding to di and trivalent metal ions^{26a}. The **22a** (*n* = 2) gives 2 : 1 (host-guest) complex with an yttrium cation^{26b}. The ferrocenophane **22b** containing a pyridine unit, forms complexes with a series of guest cations (Na⁺, Ca²⁺, Ba²⁺ or Y³⁺).

Macrocycles **23** and **24** with amine-amide combination undergo deprotonation at amide NH with divalent transition metal ions to form neutral complexes.

23

X = NH, O

24

- 25 (E)** X = CH
26 (E) X = N

- 25 (Z)** X = CH
26 (Z) X = N

The ionophore **23** acts as a carrier for proton coupled transport of Cu²⁺ against concentration gradient²⁷. Ligand

24 (X = NH, O) transports Pb²⁺ and Ag⁺ picrates rejecting alkali metal picrates²⁸.

Lignad **25(E)** having photosensitive azobenzene cap shows selective binding to Na⁺ while **25(Z)** formed by photomerization, encapsulates K⁺ more strongly suggesting the expansion of N₂O₄ ring photoinduced by (*E*) to (*Z*) isomerization²⁹. The ligand **26** in which azobenzene cap is replaced by pyridine unit, strongly binds to heavy metal cations particularly Cu²⁺ and no such binding is encountered in **26(Z)**³⁰.

Amide functionalized appendages to the macrocyclic backbone also influence the binding character. Among the series of chiral mono- and di-substituted 14-crown-4 derivatives, the macrocycles **27a** and **27b** with amides as appendages induce the best Li⁺ to Na⁺ selectivity (630 : 1) in liquid membrane electrodes³¹.

- a R = H, R' = CH₂CONMe₂
 b R, R' = CH₂CONBu₂

27

In ligand **28** though amide groups do not participate in complexation but position the two 15-crown-5 units to form 1 : 2 host-guest complex with Na⁺ and 1 : 1 complexes with K⁺, Rb⁺, Cs⁺ and NH₄⁺ ions. The ligand reveals high selectivity for K⁺ over other cations³².

28

A series of ether-ester macrocycles and podands containing one or two cyclic urea oxygens show selective extraction of Sr²⁺ picrate³³ over Li⁺, Na⁺, K⁺, Tl⁺, Mg²⁺ and Ca²⁺ picrates with macrocycle **29** showing maximum selectivity. Macrocycles **30a** and **30b** selectively extract lead picrate over silver, alkali and alkaline earth metal picrates³⁴. Pyridine based diamide-diester 18-membered macrocycle **31**

extracts Ag^+ picrate with remarkable selectivity over alkali, alkaline earth, Tl^+ and Pb^{2+} picrates³⁵.

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Octamides **32** of *p*-alkoxycalix[8]arenes extract alkaline earth metal picrates from water to dichloromethane, and the corresponding nitrates from acidic water solution simulating radioactive waste to 2-nitrophenyl hexyl ether (NPHE)³⁶. In case of simulated waste solutions, the distribution coefficients for strontium removal by octamides are much higher than the corresponding value found for dicyclohexyl-18-crown-6 (DC18C6). Amongst various heterocalix[6]arenes with different number of uracil and benzimidazolone units and three aryl units, the heterocalix[6]arene **33** exhibits *t*- $\text{BuNH}_3^+/\text{K}^+$ selectivity³⁷.

- a R = Bn
b R = CH_3
c R = $(\text{CH}_2)_4\text{CH}_3$
d R = $(\text{CH}_2)_7\text{CH}_3$

32

33

Tetraamide **34** in its partial cone conformation forms a 1 : 1 complex with lanthanum picrate³⁸ through three amide and two etheral oxygens co-ordination. The cyclophane **35** with amine, carboxylate and amide as three electron donor

groups complexes with Ni^{2+} , Cu^{2+} and Zn^{2+} ³⁹.

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35

A cyclic pseudo-peptide receptor **36** has been isolated from a combinatorial library which shows a binding towards *N*-methylammonium salts⁴⁰.

36

Carboxamido nitrogens may be used in the synthesis of different receptors for binding Fe^{3+} ion. Thus the compounds **37-42** are used for the synthesis of the Fe^{III} complexes⁴¹.

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38

More recently, receptors have been appended with appropriate fluorescent moieties and the change in fluorescence during complexation provides direct means of both qualitative and quantitative estimation of guest species. The solution of **43**⁴² in acetonitrile-water at pH 7.1 adjusted with 2,6-lutidine shows fluorescence quenching on addition of Cu^{2+} whereas no decrease in fluorescence is observed with Ni^{2+} , Mn^{2+} and Co^{2+} cations.

The chiral diaza-9-crown-3 derivative **44** displays "off-on" switching⁴³ of fluorescence when treated with various lithium salts in organic solvents such as CH_3CN and discriminates against a variety of group I and group II metal ions.

The optically⁴⁴ active cyclic hexapeptides **45a** and **45b** exhibit intense pyrene monomer emission at 375–418 nm and an additional pyrene excimer band at 487 nm (intramolecular) in **45a** and 481 nm (intermolecular) in **45b**. The addition of $\text{Ca}^{2+}/\text{Ba}^{2+}$ perchlorate to a solution of cyclic peptide **45a** causes a considerable increase of the excimer to monomer emission ratio (I_e/I_m) which is more pronounced in case of Ca^{2+} . Mg^{2+} does not affect the emission of **45a**. Peptide **45b** shows analogous fluorescence characteristics but I_e/I_m ratio is much lower in comparison to that observed in **45a**.

Ureylene crown ether **46**⁴⁵ binds with 2 equivalent of Li^+ co-operatively and selectively [$K = 3 \times 10^7 \text{ dm}^3 \text{ mol}^{-1}$] over other alkali metal ions such as Na^+ , K^+ and Cs^+ .

The calix[4]arene **47**⁴⁶ shows fluorescence enhancement with Zn^{2+} but fluorescence quenching with Ni^{2+} .

II. Anionic recognition

Anions are larger in size than isoelectronic cations (Table 1) and therefore have a lower charge to radius ratio. This causes lower electrostatic binding interactions and lower

47

binding in case of anion receptors than observed for the cation receptors.

Table 1. A comparison of the radii (r) of isoelectronic cations and anions in octahedral environment

Cation	r [Å]	Anion	r [Å]
Na ⁺	1.16	F ⁻	1.19
K ⁺	1.52	Cl ⁻	1.67
Rb ⁺	1.66	Br ⁻	1.82
Cs ⁺	1.81	I ⁻	2.06

Additionally, anions are more sensitive to the pH (becoming protonated at lower pH), and therefore receptors must function within the pH range of the target anion. Anionic species have wide range of geometries and therefore a higher degree of design may be required to make receptors complementary to their anionic guest. Anionic receptors involving varied non-covalent interactions viz. electrostatic interactions, hydrogen bonding, hydrophilicity, co-ordination to a metal ion, and combination of these interactions have been developed. Receptors which use the amide moiety for binding anions, make use of the hydrogen bonds. Being directional in nature, hydrogen bonds allow the designing of receptors with specific shapes capable of differentiating anionic guests with different geometries.

48

In 1986, Pascal prepared the first purely amide based anion receptor **48**⁴⁷ which binds fluoride ion in [D₆]DMSO. In 1993 Reinhoudt and co-workers produced a series of acy-

clic tripodal receptors containing amide groups **49-54**⁴⁸ whereas Raposo *et al.* synthesized a preorganized and extended amide embroidered cyclohexane ring derived receptor **55**⁴⁹.

- 49** R = CH₂Cl
50 R = (CH₂)₄CH₃
51 R = C₆H₅
52 R = 4-MeOC₆H₄

- 53** R = 4-MeC₆H₄
54 R = 2-Naphthyl

55

Receptors **49-55** are all C₃-symmetric and are consequently organized to bind tetrahedral anions. Anslyn and co-workers have reported the synthesis of a cage like molecule **56**⁵⁰. Since the amide NH groups in **56** are arranged in a trigonal prismatic array, they are able to co-ordinate to the π -electron system of planar anions such as carboxylates and nitrate.

56 NO₃⁻

Ureas and thioureas are particularly good hydrogen bond donors and are excellent receptors for Y-shaped anions such as carboxylates through the formation of two hydrogen bonds. The urea based receptor **57** forms highly stable complexes with bidentate ligands⁵¹.

The acyclic cleft molecules⁵² **58** and **59** bind anions very strongly with stability constants upto 19500 M⁻¹ for receptor **59** and H₂PO₄⁻ ions in [D₆]DMSO. The selectivity for H₂PO₄⁻ ions can be attributed to the complementary hydro-

57

58 R = Bu

59 R = Ph

gen bonding array present in these clefts that can form four hydrogen bonds to each H_2PO_4^- ion.

Ferrocene units appended with secondary amides have also been used for anion recognition^{53,54}. For example, **60-63** were capable of detecting H_2PO_4^- ions in the presence of a ten-fold excess of HSO_4^- and Cl^- ions in acetonitrile as shown by large cathodic shifts of upto 240 mV.

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In evolving amide based anion receptors tris(2,2'-bipyridyl)ruthenium(II) ($[\text{Ru}(\text{bpy})_3]^{2+}$), because of its chemical stability, redox properties, excited-state reactivity, and luminescent emission⁵⁵ had been one of the most extensively investigated platforms. Beer and co-workers have incorporated this moiety into acyclic, macrocyclic, and calix[4]arene structural frameworks to produce new class of anion receptors **64-68** capable of optical and electrochemical sensing⁵⁶⁻⁵⁸.

Watanabe *et al.* has produced imidazole-functionalized ruthenium-bipyridyl complexes such as **69** which recognizes anionic and neutral phosphodiester with luminescent signal enhancement observed for anionic phosphodiester in acetone⁵⁹. Similar complexes have been proposed to be

64 Z

65 Z

67 Z

66 Z

68 Z

formed between **69** and tetraethylammonium diphenyl phosphate (TDPP) or dibenzylphosphate (DBHP).

69 DBHP

Ruthenium(II)- and rhenium(I)-bipyridylcalix[4]diquinone receptors **70** and **71** selectively bind and sense acetate ion through remarkable retrieval effects of luminescent emission intensity⁶⁰.

70 Z = $\text{Ru}(\text{bpy})_2^{2+}$ 71 Z = $\text{Re}(\text{CO})_3\text{Cl}$

Diamides **72** are readily synthesized and are found to bind strongly to the acetate and halides in organic solvents⁶¹.

72

A structurally designed strategy for improving the binding ability of neutral urea and amide based receptors had been described⁶². A series of boronate ureas **73** and a related bis(boronate-amide), **74** were prepared. Their enhanced binding towards carboxylate anions is explained due to the co-operative polarization effect which is induced by intramolecular co-ordination of urea or amide carbonyl to a Lewis acidic boronate group.

Beer and co-workers have synthesized some tripodal tris-amidic receptors **75-77**⁶³. Tripodal ligand **76** binds chloride, iodide, and perchlorate anions via co-bound crown ether and efficiently extracts and transports the perchlorate (ReO₄⁻) anion from simulated aqueous nuclear waste solution via co-operative ion-pair binding effect.

The co-ordination of four *n*-butylnicotinamide ligands to a platinum(II) centre provides a facile method of organizing amide H-bond donors for anion binding; the PF₆⁻ complex **78** is an effective receptor for a variety of oxo-anions⁶⁴.

Different 2,2'-biimidazoles **79a-f** with various amide groups at the position 4- and 4'- exhibit quenching in emission intensity in the presence of H₂PO₄⁻ and Cl⁻. The binding constants for 1 : 1 biimidazole-anion complexation are 10 M⁻¹ for H₂PO₄⁻ and Cl⁻⁶⁵.

Simple 2,5-diamidopyrroles such as **80** and **81** function as oxo-anion selective receptors in acetonitrile-*d*₃ and DMSO-*d*₆ 0.5% H₂O solutions⁶⁶.

Amongst different amine, ammonium, and amide pendant arm diamidopyrroles **82-84**, the receptor **82** binds

strongly with HSO_4^- . This strong binding is attributed to the protonation of the receptor by the anion. Evidence to this fact is given by the fact that **84** has a lower affinity constant for HSO_4^- , as protonation is not possible in this case. Receptor **83** shows enhanced binding with halide ions in comparison to **82** reflecting the extra electrostatic component to the binding interactions⁶⁷.

The colorimetric anion sensor **85** allows for the naked eye differentiation⁶⁸ of F^- , AcO^- , and H_2PO_4^- . The association of **85** with various polar solvents such as $\text{DMSO}-d_6$ and CD_3CN was studied by NMR. The selectivities trends of **85** with $\text{DMSO}-d_6$ were: $\text{F}^- \gg \text{AcO}^- > \text{H}_2\text{PO}_4^- > \text{HSO}_4^- \sim \text{Cl}^- \sim \text{Br}^-$.

C_3 symmetric macrocyclic anion receptor **86** binds tetrahedral anions such as sulphate and phosphate with high affinity. Titration of **86** with tosylate anion as its tetrabutylammonium salt gave 1 : 1 binding isotherms for amide and aryl protons of **86**⁶⁹.

86 a R = CO_2Et
b R = NHBoc

III. Neutral molecular recognition

The interactions between a neutral (usually organic) molecular guest and the host framework may vary from very limited (e.g. van der Waals interactions) to significant stability (e.g. hydrogen bonds). Unlike charged species, neutral molecules are neither bound by strong permanent electrostatic forces, nor do they undergo well-defined co-ordination interactions, and hence their bindings are weaker. Also the sizes of the neutral guests are larger than metal cations or simple anions. Despite these features, the importance of this phenomenon in biological systems has lead to an enormous diversity of hosts or lattice compounds, which can bind neutral molecules through H-bonding⁷⁰⁻⁷⁶.

Hydrogen bonds are simulated in molecular mechanics as attraction between the bridge-forming proton and the donor and acceptor hetero element bearing negative partial charges. Many supramolecular systems have been devised which are based essentially on the simultaneous action of properly arranged hydrogen bond donors and acceptors. Amides because of facility of their modification and lipophilicity have been widely used as H-bond donors.

In combination with pyridine group, receptor **87** prepared by Hamilton and co-workers⁷⁷ complexes glutaric acid with $K = 6.4 \times 10^2 \text{ M}^{-1}$ in $\text{THF}-\text{CDCl}_3$ in an enthalpy driven process.

Cyclic hexaamides **88** where the skeleton is stiffened by three *p*-phenylene spacer units and cavity diameter approaches that of small cyclodextrins, showed affinity to haloforms and some other molecules in organic solvents⁷⁸.

Systems **89** possessing six-basic heteroarenes are tailor-made for encapsulating sterically and functionally complementary trihydroxybenzene⁷⁹. Such hosts are sensitive to the introduction of methyl or ammonium groups into the guest molecules as 2,4,6-trihydroxytoluene or 2,4,6-trihydroxytoluene hydrochloride are not complexed. The more strongly acidic nitrophloroglucinol simply forms, like picric acid, 1 : 3 complexe.

In contrast to the tris(bipyridine)hosts, the macrobicyclic ligand **90** has pronounced proton donor character, due to six hydroxyl groups of the catechol units. As a consequence, it complexes organic molecules with basic functional groups as long as the pK_S and pK_B values are mutually compatible⁸⁰. Strongly basic triamines, form salt like aggregates by an acid-base reaction. Purine, pyrimidine and other less basic compounds are solubilised by **90** in dichloromethane in which they are otherwise sparingly soluble.

The macromonocyclic bis(catechol) host **91**⁸⁰ constitutes a hydrogen bond receptor for piperazine-type guest molecules in organic solution and association for guests **92** (piperazine) and **93** (1,4-diazacycloheptane) are around 10^2 M^{-1} . Extraction and transport studies show that host **91** is quite efficient in binding nucleic bases too.

91 piperazine-complex

The basket shaped molecule **94** in $CDCl_3$ solubilizes ammonium *p*-nitrophenolate by the formation of the complex⁸¹.

The macrobicyclic hosts **95** and **96**⁸² employ multiple hydrogen bonds to bind organic guests with donor and acceptor functionalities arranged in a manner complementary to the cyclourea units and amide groups of the molecular cavities^{83,84}. Binding energy for the complex of 4-pyridone and **95** is approximately -21 $kJ\ mol^{-1}$. Potential guests such as pyridine or *N*-substituted imidazoles are discriminated,

since they do not possess proton donor properties.

- 95** $Z = \text{CH}_2$, $R = \text{H}$
96 $Z = m\text{-phenylene}$, $R = \text{Bn}$

The water soluble macrobicyclic compound **97** ($R = \text{Me}$) constitutes a ditopic host for zwitterionic amino acid⁸⁵ and binds γ -aminobutyric acid (GABA) with an association constant of $3.2 \times 10^3 \text{ M}^{-1}$ (D_2O). Glycine, which is too small, and 6-aminocaproic acid, which is too large, are only weakly bound.

97.

98

- 99** $W = X = Y = Z = \text{CH}$
100 $W = X = Z = \text{CH}$, $Y = \text{N}$
101 $W = Z = \text{CH}$, $X = Y = \text{N}$
102 $W = Z = \text{N}$, $X = Y = \text{CH}$
103 $W = Y = \text{N}$, $X = Z = \text{CH}$

Fig. 3

Macrocyclic host **98**⁸⁶ complexes flat, disk shaped aromatic guest pyrene in aqueous phase⁸⁷. Several macrocyclic hosts such as **99-103** have been prepared⁸⁸ as domains for binding quinone, which play a key role in the photosynthetic energy conversion. Complexation of *p*-benzoquinone by the macrocycles was investigated using ^1H NMR titrations. The limiting change in chemical shift observed for the 1 : 1 complexes support the structure shown in the Fig. 3. The signals due to amide protons show ~ 1 ppm downfield shifts characteristic of hydrogen bonding and the signals due to the quinone protons show ~ 2.5 ppm upfield shifts, which indicate that they lie over the host side walls.

A lipophilic glucose derivative is known to form a mul-

tiple hydrogen bonded 1 : 1 inclusion complex with a cholaphane host **104** having a significantly large internal cavity⁸⁹.

104

Aliphatic mono(poly)ols and even hydrocarbon adamantane can be bound as guests to well designed cyclophane hosts in water as trans-1,4-cyclohexanediol, trans-1,4-cyclohexanedicarboxylic acid, and adamantanecarboxylic acid bind to host **105**⁹⁰.

105 **(+) - 106**

Cage like host **106** is an example of chiral hosts having L- or D-valine moieties as chiral building blocks. This host binds steroid hormones such as α -estradiol, β -estradiol and estradiol enantioselectively in water-methanol (75 : 25)⁹¹. Testosterone having no aromatic moiety can not be bound to host **106**.

107 **108** **109** **109 Adenine**

Rebek has prepared a versatile series of rigid C-shaped tweezer hosts such as **107-109**⁹². The imide tweezer host **109** forms 1 : 1 complex with adenine and is able to extract adenine, and even nucleosides such as adenosine and deoxyadenosine, from aqueous solution and transport them across liquid organic membranes.

One of the most effective early designs for guest inclusion via hydrogen bonding was reported by Chang and Hamilton⁹³. Recognising the possibility of multiple interactions offered by the barbiturate family **110** they designed the complementary macrocyclic host **111** and its acyclic analogue **112**. NMR solution complexation studies in chloroform indicated the selective binding of the barbital **110b** over bulky **110d**.

The complexation via complementary hydrogen bonds of three novel ferrocene receptors **113-115** with barbital **110b**, ethylene urea **116** and trimethylene urea **117** is described⁹⁴ and the binding mode shown in the Fig. 4 is derived from NMR and X-ray studies.

6-Aryl-2,4-(acyldiamino)-s-triazines **118** constitute hosts

- (a) $R^1 = R^2 = R^3 = H$
 (b) $R^1 = R^2 = Et, R^3 = H$
 (c) $R^1 = Et, R^2 = Ph, R^3 = H$
 (d) $R^1 = Et, R^2 = Ph, R^3 = Me$

110

for flavins **119** as depicted in Fig. 5⁹⁵. In these synthetic hosts, systematic variation of the spatially remote substituents on the 6-aryl ring alters the hydrogen bond-donating abilities of the amide functionality and the hydrogen bonding accepting properties of the triazine-N.

Fig. 4

The binding mode of the host *N,N'*-bis(6-pivalamidopyrid-2-yl)-3,5-pyridine dicarboxamide **120** to

Fig. 5

three different ruthenium complexes with an attached barbituric acid and barbital moieties **121-123** has been studied in chlorinated solvents by NMR and fluorescence titrations⁹⁶. Significant binding was only observed between **120** and **122** series while steric hinderance significantly diminished binding between **120** and **121** or **123**.

Synthetic receptor **124** has been found via fluorescence titration to compete effectively with cytochrome c peroxidase for binding cytochrome c forming 1 : 1 complex⁹⁷. Chiral imidazole cyclophane receptors **125** exhibit good chiral recognition toward the enantiomers of L- and D-amino acid derivatives in chloroform⁹⁸.

Encapsulation of guests in self-assembled tetraurea calix[4]arene **126** and **127** dimers in organic solvents has been probed by PGSE NMR technique⁹⁹.

New polypyridine-macrocyclic receptors **128-130** for glucopyranoside recognition were designed and synthesized¹⁰⁰. The receptors possess a terpyridine skeleton as a hydrogen-bonding site and a flexible polyoxyethylene chain as a bridge for the macrocyclic structure, in which the cavity of the receptor is large enough to incorporate pyranosides. The receptors showed high affinities for *n*-octyl- β -(D)-glucopyranoside, and selective binding of the receptors was observed between epimeric pyranosides.

A new rationally designed receptor molecule **131** binds adrenaline derivatives in water. Its binding pattern imitates the interplay of non-covalent interactions operating in the nature. High shape selectivity is achieved for the slim dopamine skeleton, and leads to the rejection of substrates with an α -substituent, such as amino acid derivatives¹⁰¹.

Conclusion

Thus, the pre-eminent role of amide and urea moieties in recognition of both electron-rich (anions and neutral molecules) and electron deficient (cations and neutral molecules) guest species exemplified here points to the scope of exploration of abiotic receptors of these categories for evolving sensors and new models for recognition.

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