Abiotic Receptors

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'*Life is beginning to cease to be a mystery and becoming practically a cryptogram, a puzzle, a code that can be broken, a working model that sooner or later can be made*'.

J. D. Bernal[1]

1 Requirements for Recognition

—the question of how a chemical entity might go about recognizing other molecules or ions

The fundamental element of specific catalysis is substrate recognition. The interaction between two species can be either repulsive or attractive. With the latter interaction, complexation will occur to give a new entity in a process uniquely definable by the overall energy change (information) involved in the association. Thus, the design of discriminating molecular ligand systems (recognition) becomes a problem of information storage and retrieval at the molecular level.[2] Emil Fischer's 'lock-and-key' theory of enzyme–substrate interaction and Paul Ehrlich's search for bactericidal 'magic bullets' were early demonstrations of an awareness that in biological systems at least, there was specificity in the interaction (assembly) of the components of functional complexes.[3]

The requirements placed upon a recognition process may be stated as follows. Ligand L should be able to complex with only a particular complementary species (S_i) out of the N substrates presented; $S_0, S_1, S_2, \ldots S_N$ as perhaps 1 : 1 complexes in simple chemical equilibria:

$$L + S_i \rightleftharpoons LS_i$$

$$\frac{[LS_i]}{[L][S_i]} = K_i = e^{-\Delta G_i/RT}; \; i = 0, 1, 2, \ldots, N$$

Such might be the case in the binding of metal cations or in the formation of an enzyme–substrate complex. Suppose that recognition is when a 1 : 1 complex forms

[1] J. D. Bernal, 'The Origin of Life', Weidenfeld and Nicolson, London, 1967.
[2] K. R. H. Repke and F. Dittrich, *Trends Pharmacol. Sci.*, 1980, **1**, 398.
[3] J. Parascandola, *Pharm. Hist.*, 1974, **16**, 54.

between L and S_0, the probability (P_f) of false recognition will depend on the number of possibilities of combination:

$$P_f = \frac{\sum_{i=1}^{N-1} [LS_i]}{[LS_0] + \sum_{i=1}^{N-1} [LS_i]} = \frac{\sum_{i=1}^{N-1} [S_i]K_i}{[S_0]K_0 + \sum_{i=1}^{N-1} [S_i]K_i}$$

Thus, the selectivity of the recognition process will improve as the value of the ratio of binding constants for the correct and false partners, *viz.*, $K_0 : K_i$, increases. Specific recognition, or fidelity of information 'read-out' thus requires the maximal difference between the free-energy changes associated with complexation of the substrate and false substrates. The high selectivity associated with natural receptors implies therefore, an evolutionary optimum of complementarity between substrate and receptors involving a minimum of recognizing interactions.[4]

The 'asymmetry' of the free-energy change in the interaction (selectivity) might be simplistically, but usefully, controlled by modifying the palette of topological, molecular, and environmental contributions used as information storage. The critically hidden variables and interdependencies could be expected to be revealed by model compounds accessible from chemical synthesis. Conversely, if control could be attained over these variables, it would be possible to design systems for predictable specific recognition.

Recognition by a receptor need not be the beginning and end of the recognition process. Complexation will result in a new entity with new properties and so a higher order of molecular behaviour might be expected than specific complexation alone. It is possible that thermodynamics could be cheated by some dynamic (kinetic) process.[5] Hence, such functional behaviour of the complex as transport or reaction might become involved. Two substrates might show similar kinetic and thermodynamic complexation behaviour, but if perhaps only one of them underwent some reaction when complexed, then recognition (editing) would occur.

To draw analogy with a plastic gramophone record, the chemical structure of the receptor (record) is important to hold the pattern of information, but the music (function) which emerges from this pattern is more important.

2 To Design A Receptor

—the incorporation of what amounts to information into a synthetically feasible target molecule

From the previous discussion, it should be clear that a pre-requisite for high selectivity would be the largest number of substrate–ligand interactions possible in a generalized 'lock-and-key' relationship not limited to steric fit alone. Further, if this information is to have a fidelity unchanged by interaction with different substrates, a supplementary part of the molecule will be required to impart rigidity and

[4] E. J. Ariëns, *Trends Pharmacol. Sci.*, 1979, **1**, 11.

[5] I. Ninio and F. Chapeville, in 'Chemical Recognition in Biology', ed. F. Chapeville and A.-L. Haenni, Springer-Verlag, 1980, vol. 32, p. 78.

convergence of the functional entities. A lower limit is therefore imposed to the structural simplicity of abiotic receptors.

To form stable complexes in solution, the thermodynamics of ligand–substrate interaction must be more favourable than those for the substrate with the solvent.

Optimal complementarity and stability is likely to be found when the substrate co-ordination number and the binding sites upon an electrically neutral ligand are equal. Cram[6] has aptly commented that, 'A host molecule provides an assembly of solvation sites tied together by covalent bonds.' Further, if these sites are covalently tied into rings and cages, at once a sheath of co-operative 'structured solvent' is achieved and the inherent problem of structural divergence is overcome. An example of such optimization is the ligand systems shown in Figure 1.

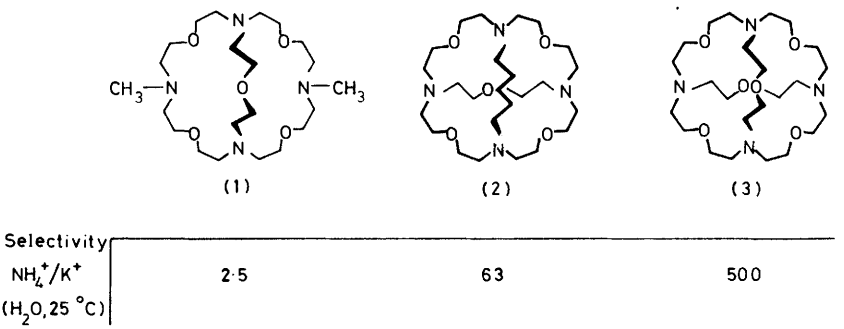


Figure 1 *Optimization of an* NH_4^+/K^+ *selectivity by synthetic manipulation of the receptor-cavity design (ref. 7)*

An ammonium ion is included into the snug, binding-site lined cavity of (3): the four apical, tetrahedral nitrogens are well-placed to hydrogen-bond to the ammonium ion in preference to the similarly sized K^+ ion with its spherical charge distribution.[7] The local environment within a macromolecule may greatly affect the pK_a, for example, of functional groups. It is perhaps no surprise that the apparent pK_a of the complexed ammonium ion in receptor (3) is 15.3.[7]

A cavity can influence significantly the stability of a complex and the physico-chemical properties of the complexed species. Complexes involving bi- or poly-dentate ligands have an enhanced stability as compared with their unidentate counterparts (the chelate effect) and, in turn, as a macrocycle the stability is further enhanced (the macrocyclic effect). Therefore, a receptor of high cyclic order should be a selective complexer in the presence of open-chain, or lower order, analogues.[8]

[6] D. J. Cram, R. C. Helgeson, L. R. Sousa, J. M. Timko, M. Newcomb, P. Moreau, F. De Jong, G. W. Gokel, D. H. Hoffman, L. A. Domeier, S. C. Peacock, K. Madan, and L. Kaplan, *Pure Appl. Chem.*, 1975, **43**, 327.

[7] E. Graf, J.-M. Lehn, and J. Le Moigne, *J. Am. Chem. Soc.*, 1982, **104**, 1672.

[8] The design by Cram of the 'spherands' demonstrates the high complex stability and selectivity possible with a cavity organized during synthesis: D. J. Cram, G. M. Lein, T. Kaneda, R. C. Helgeson, C. B. Knobler, E. Maverick, and K. N. Trueblood, *J. Am. Chem. Soc.*, 1981, **103**, 6228; G. M. Lein and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 1982, 301.

Conceptually, the fundamental recognition process is discrimination amongst monotonically varying spherical entities (spherical recognition). Information sufficient for recognition at this simplest level, could be contained in the receptor as a hole or cavity of relatively precise dimensions (toposelectivity). The difficulties of devising and synthesizing such ligand systems are diminished if the substrate–receptor binding interactions are non-directional. Thus, 'primitive' receptors could be considered those utilizing only the entropic association of complementary non-polar surfaces (hydrophobic interactions) or, the general electrostatic interactions possible to spherically symmetric ions.

An even higher order of molecular behaviour than recognition, catalysis, and transport could be expected if the spatial array of binding sites allowed the binding of several individual substrates or, the co-operative binding of one polyfunctional substrate. The simultaneous or successive participation of several sites in binding allows imitative investigation of the molecular phenomena of co-operativity, allostery, and cascade recognition.[9]

3 Abiotic Receptors for Spherical Ions and Molecules[10]

A. Ion Complexation.—The first model-receptors capable of mimicing the function of selective complexation and transport associated with biological membranes, were the natural acyclic or macrocyclic cation-binding antibiotics. Although capable mimics, these receptors are too complex in structure to allow ready synthetic strategies towards revealing structure–binding relationships. A significant development therefore, was the recognition by Pedersen[11] that macrocyclic polyethers ('crown ethers')[12] he had accidently synthesized possessed the minimal structure and function necessary to show a selective affinity amongst the alkali and alkaline earth cations. The simplicity of both the structure and synthesis of the crowns, finally enabled a coherent discipline to be built for the chemistry of these cations with electrically neutral ligands. The cavities of the macrocyclic crown ethers could be 2- or 3-dimensional in their binding conformation. *X*-Ray structure

[9] Z. Simon, 'Quantum Biochemistry and Specific Interactions', Abacus Press, Tunbridge Wells, 1976, p. 196.

[10] M. Hiraoka, 'Crown Compounds. Their Characteristics and Applications', Elsevier, Amsterdam and New York, 1982; J.-M. Lehn, in IUPAC 'Frontiers of Chemistry', ed. K. J. Laidler, Pergamon Press, Oxford, 1982, p. 265; 'Topics in Current Chemistry, vol. 98: Host Guest Chemistry I', ed. F. Vögtle, Springer Verlag, Berlin, 1981; 'Topics in Current Chemistry, vol. 101: Host Guest Chemistry II', ed. F. Vögtle, Springer Verlag, Berlin, 1982; J.-M. Lehn, *La Recherche*, 1981, **12**, 1213; J. P. Stoddart in 'Enzymic and Non-Enzymic Catalysis', ed. P. Dunnill, A. Wiseman, and N. Blakebrough, Ellis Horwood Ltd., Chichester, 1980, p. 84; J. S. Bradshaw and P. E. Stott, *Tetrahedron*, 1980, **36**, 461; J.-M. Lehn, *Pure Appl. Chem.*, 1980, **52**, 2303, 2441; 1979, **51**, 979; ed. R. M. Izatt and J. J. Christensen, 'Progress in Macrocyclic Chemistry', Wiley, New York, 1979, vol. 1; ed. R. M. Izatt and J. J. Christensen, 'Synthetic Multidentate Macrocyclic Compounds', Academic Press, New York, San Francisco, London, 1978; D. N. Reinhoudt and F. De Jong, *Adv. Phys. Org. Chem.*, 1980, **17**, 279.

[11] C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 16; for a history of the discovery of the crown-ethers, see C. J. Pedersen, *Aldrichim. Acta*, 1971, **4**, 1.

[12] The name 'crown' arises from both the appearance of models of these compounds and their ability to 'crown' cations by complexation. Whilst these compounds can be named explicitly by IUPAC rules, the result is complex and cumbersome. This has been resolved by using incidental names (*e.g.*, 'crown') as the stem. A full account of the nomenclature is found within the reviews of ref. 10.

determinations indicate that many of the crowns include the metal cation within a circular cavity optimal for that ion, with near coplanarity of binding points. With very large rings a 3-dimensional co-ordination of the ion is possible as a result of ring folding. Indeed, in the case of the K^+ complex with dibenzo-[30]-crown-10, the ligand winds the cation within a tri-dimensional embrace.[13]

The bismethylene building unit has been fundamental to the development of abiotic receptors. Each pair of binding points in the repeat unit $(-X-CH_2-CH_2-Y-)_n$ form optimum 5-membered chelate rings with an included cation. Thus, complex stability could well be a function of the number of rings, or the dimensionality of the cavity, when the whole ligand is considered. However, if conformational changes are necessary to bring about or improve binding interactions, the energy and likely entropy changes involved will destabilize the complex relative to one where the optimal arrangement of receptor binding sites exist in a conformational energy minimum. Indeed, despite ten oxygen–cation interactions, the K^+–dibenzo-[30]-crown-10 complex is much less stable than that with a more rigid bicyclic receptor. This contrasts with the findings for the 3-dimensional cryptand ligands.

The relationship between the cryptands and crowns is clear, but the concatenation of chelation possibilities of the former with the cation increases the stability of complexes by several orders of magnitude over monocyclic analogues from both entropic and enthalpic contributions:[14,15] Figure 2.

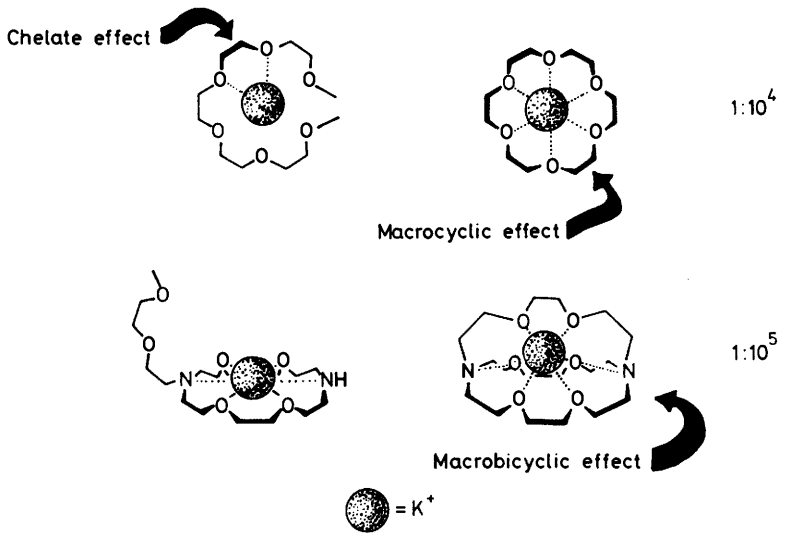


Figure 2 *A stability hierarchy resulting from an increasingly well-defined binding-site lined cavity*

[13] M. A. Bush and M. R. Truter, *J. Chem. Soc., Perkin Trans. 2*, 1972, 345.
[14] J.-M. Lehn and J.-P. Sauvage, *J. Am. Chem. Soc.*, 1975, **97**, 6700.
[15] H. K. Frensdorff, *J. Am. Chem. Soc.*, 1971, **93**, 600.

From the introductory discussion we might expect that the selective complexation of a cation from a series will depend on how the free energy of the complex changes with respect to the solvated cation. The free energy of solvation increases continuously with decreasing cation sizes. However, when included into a cavity, the free energy of complexation will increase as the size of the cation decreases until it matches the cavity. For smaller cations it levels off and indeed, no further increase in interaction energy is expected, because further modification of the cavity to maintain co-ordinative saturation of the cation will incur an energy penalty as the ligand moves away from its equilibrium conformation as shown in Figure 3. A rigid receptor is 'tuned' to cations of a given size and will show a

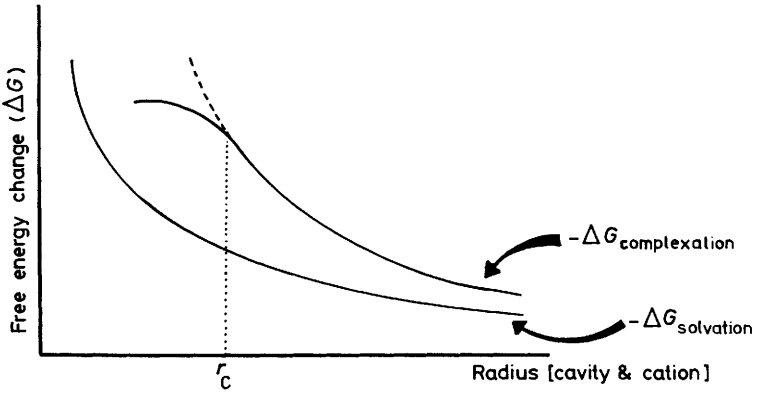


Figure 3 *A schematic representation of the changes in free energy significant upon inclusion of a given cation into its complementary cavity*

selectivity peak at the optimal cation. Conversely, if floppy, conformational adjustments would allow a receptor to mold itself to include similarly sized cations and show a selectivity plateau. For example, although valinomycin shows a high K^+/Na^+ selectivity, it does not distinguish at all well between K^+, Rb^+, and Cs^+. Yet even the most 'rigid' receptor must be sufficiently mobile conformationally to allow stepwise co-ordinative enfolding of the solvated species being complexed.

It seems best, however, to consider that good fit of cation to cavity is merely an empirical and pragmatic criterion for preferred complexation which contains more than just steric effects. Important in any selectivity series are the solvent, shielding of the cation from the counter ion and solvent by the organic ligand, and the nature and number of co-ordinating (binding) atoms.[16,17]

Since both complex stability and selectivity are reflections of free-energy changes between the solvated and ligated states of the cation, the solvent as well as the ligand will be central in the complexation process. A decrease in the solvating power of the solvent relative to the ligand binding sites will enhance complex

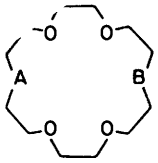
[16] For example, J. Massaux and J. P. Desreux, *J. Am. Chem. Soc.*, 1982, **104**, 2967.

[17] It should be noted that there can be marked differences between enthalpic and free-energy selectivities due to the entropy change on complexation. The latter favours the complexes of small bivalent cations over those of large and monovalent ones.

stability in general. In most cases this effect is grossly proportional to the stability of the complex considered. In addition, for complexes of comparable stabilities, those with small cations often show smaller increases.

The donor atom at the binding sites determines the nature of the ligand–cation interactions and changing the co-ordination atom can lead to quite subtle changes in properties. The replacement of oxygen as the donor atom by nitrogen or sulphur in the classic 18-crown-6 ligand leads to a decrease in stability and selectivity for the alkali and alkaline-earth cations. However, as can be seen in Table 1, desirable complexation properties may emerge for other cations.

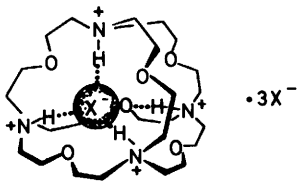
Table 1 *Effect of* N *and* S *substitution on the stabilities of* 18-*crown*-6 *complexes* (ref. 15)



Binding-site atom		log K_s	
A	*B*	K^+(MeOH, 25 °C)	Ag^+(H_2O, 25 °C)
O	O	6.10	1.60
NH	O	3.90	3.3
NH	NH	2.04	7.8
S	S	1.15	4.34

Anionic binding sites preferentially complex small divalent cations.[14] For monodentate ligands (*e.g.* RCO_2^- and $ROPO_3^{2-}$) the binding orders are $Na^+ > K^+$ and $Mg^{2+} > Ca^{2+}$. However, in going from mono- to multi-dentate ligands, the relative affinities remain $Na^+ > K^+$ still, but become $Ca^{2+} > Mg^{2+}$. For example, the polyanionic acyclic ligand EDTA displays a selectivity sequence of $Ca^{2+} > Mg^{2+} > Sr^{2+} > Li^+$. The selectivities of the electrically neutral macrobicyclic ligands are quite different; the stability of M^{2+} complexes are reduced with respect to M^+.

Chemical modification of the more reactive binding sites is of interest for control of complexation. For example, the protonation or alkylation of the atom nitrogens of ligand (3) inverts the co-ordinative polarity of the site from cation into potentially anion binding (4).[18]



(4)

[18] E. Graf and J.-M. Lehn, *J. Am. Chem. Soc.*, 1976, **98**, 6403; *Helv. Chim. Acta*, 1981, **64**, 1040.

However, although halide ions have been included[19] into the cavity of bis-protonated macrobicyclic diamines, $H^+N[(CH_2)_n]_3NH^+$, the apical protonated tertiary amine groups in the above molecule provide a 3-dimensional binding array near ideal for spherical anions. Thus, the stability constants for the Cl^- and Br^- complexes are as given in Figure 4.

The selective binding of anions has been extended to those which are not spherically symmetric and will be considered under a later heading.

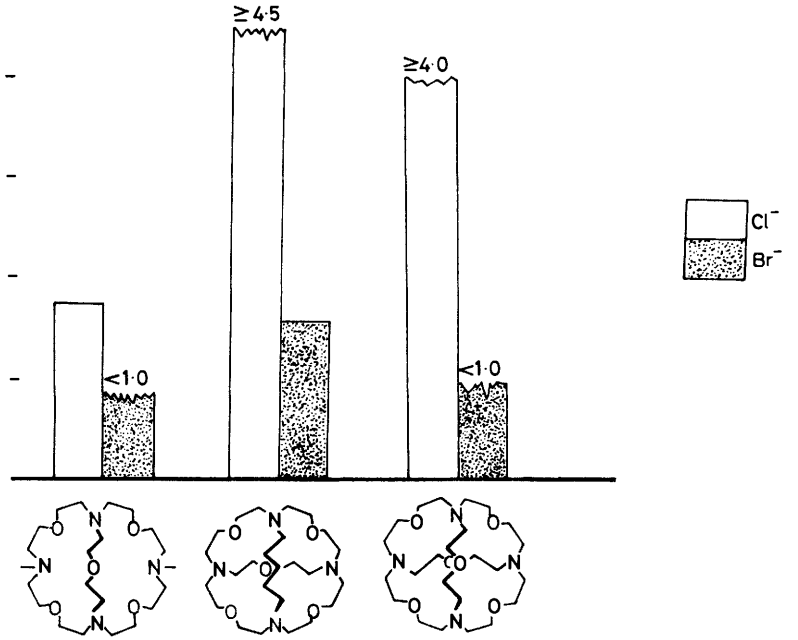


Figure 4 *Halide anion cryptate stabilities* (H_2O; 22 °C) *for three spherical cavities—after protonation* (*ref. 7*)

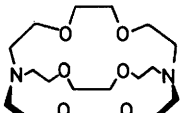
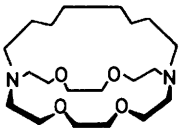
B. Ion Transport.—The isolation of a cation within a lipophilic tunic increases the solubility of a salt in media of low polarity; for example, in lipoidal membranes. The increase in the lipid solubility of complexed salts could ultimately mean their passive diffusion across a membrane. The transport process presents essentially three main steps: complex formation between carrier and substrate; dissolution and diffusion of the complex within the membrane; release of substrate from carrier. Transport selectivity of a carrier will therefore be determined in part by the membrane behaviour of the carrier and in part by the selectivity and kinetics of the complexation process. These two latter parameters apparently mutually exclude

[19] C. H. Park and H. E. Simmons, *J. Am. Chem. Soc.*, 1968, **90**, 2431; R. A. Bell, G. G. Christoph, F. R. Fronczek, and R. E. Marsh, *Science*, 1975, **190**, 151; F. P. Schmidtchen, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 720; *Chem. Ber.*, 1980, **113**, 864.

each other. Rigid ligands do form stable and selective complexes, but due primarily to the slow dissociation of the complex, substrate exchange rates are too slow for receptors to be used as carriers. Therefore, it is necessary to compromise complex stability but, retain the essentials for recognition.

For example, the simple structural modification of removing two binding sites can modify profoundly a sequence of stability constants and transportation rates as shown in Table 2. As both ligands have similarly sized cavities, selectivity of transport will be of functional origin. In the above, the reduced stability of the K^+ complex and a likely increase in lipophilicity apparently places it in the optimum range for efficient transport and converts what had been a specific K^+ receptor into a specific K^+ carrier.

Table 2 *Conversion of a* K^+ *receptor into a* K^+ *transporter*

	Cation	log K_s [l mol^{-1}]	*Initial transport rate* [μ mol h^{-1}]	*Transport selectivity* $K^+ : Na^+$	$Cs^+ : K^+$
	Na^+	7.2	0.6	1 : 20	1 : 0.01
	K^+	9.7	0.03		
	Cs^+	4.4	2.9		
	Na^+	3.5	1.6	1 : 0.45	1 : 50
	K^+	5.2	3.6		
	Cs^+	2.7	0.07		

M. Kirch and J.-M. Lehn, *Angew Chem., Int. Ed. Engl.*, 1975, **14**, 555

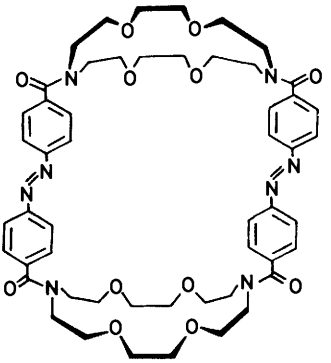
Cation transport *via* facilitated diffusion by natural or synthetic carrier molecules has been extensively investigated in both natural and model systems. Separation of environments by normally impermeable membranes is of considerable interest:

—generation of energy differentials (energy pumping);
—energy process coupling;
—information transfer.

For example, the conceptual potential of a photoresponsive ionophore such as (5)[20] to forerun electrogenic 'pumps' is exciting. Here the coupling of light-controlled binding selectivity with membrane transport could lead to energy 'production'.

An especially fascinating feature is the ability of some membranes to promote cation transport by the formation of trans-membrane channels. There is strong evidence for the existence of essentially ion-specific Na^+, K^+, and Ca^{2+} hydrophilic channels in biological systems.[21] The formation of such channels has been modelled with the linear peptides gramicidin A[22] and alamethicin.[23] Although

[20] S. Shinkai, Y. Honda, Y. Kusano, and O. Manabe, *J. Chem. Soc., Chem. Commun.*, 1982, 848.
[21] M. Klingenberg, *Nature (London)*, 1981, **290**, 449; E. Neher and B. Sakmann, *Nature (London)*, 1976, **260**, 799; G. Ehrenstein, *Physics Today*, 1976, **29** (10), 33.
[22] B. C. Pressman, *Annu. Rev. Biochem.*, 1976, **45**, 501.
[23] U. P. Fringeli and M. Fringeli, *Proc. Natl. Acad. Sci. U.S.A.*, 1979, **76**, 3852.

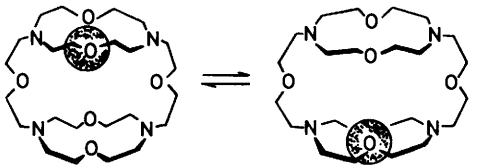


(5)

little is known about the propagation of a cation along chains of binding sites, it has been noted[24] that 'fluctional' behaviour, reminiscent of the elementary jump process between binding sites as might occur in a channel, is shown by alkaline-earth complexes (*e.g.* Ca^{2+}) of the tricyclic ligand (6).

The tetra-substituted crown (7) has a promising architectural style for a covalent molecular channel.[25] Steps to a facially discriminated synthon (8) for the directed construction of such a channel have been reported.[26]

A design for a tunnel or ion-channel molecule might come from long-chain neutral ligands such as (9) or (10). There are only hints at the direction which



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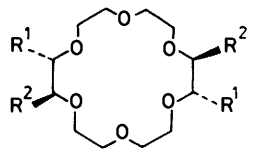
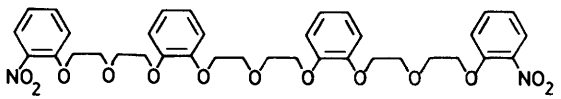


(7) $R^1 = R^2 = -CO{\cdot}N(CH_3)_2$

(8) $R^1 = -CO{\cdot}NHR^3$;
$R^2 = -CO_2^-$



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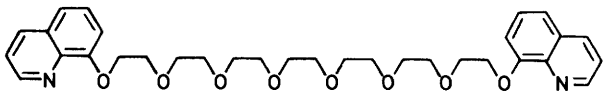


(10)

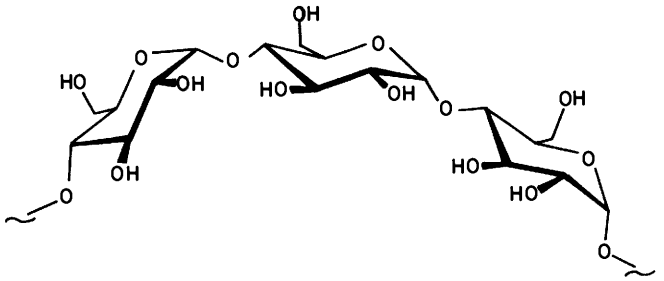
[24] J.-M. Lehn and M. E. Stubbs, *J. Am. Chem. Soc.*, 1974, **96**, 4011.
[25] J.-P. Behr, J.-M. Lehn, A.-C. Dock, and D. Moras, *Nature (London)*, 1982, **295**, 526.
[26] J.-P. Behr, J.-M. Lehn, D. Moras, and J. C. Thierry, *J. Am. Chem. Soc.*, 1981, **103**, 701.

might be taken.[27] The *endo*-hydrophilic–*exo*-lipophilic conformation must be stabilized to disfavour unwinding from a helice-like form. Stabilization by co-ordination to the metal cation is important, but will have to be supplemented by structuring units or by the attachment of associative groups to the spine of the helical channel. The channel-forming biomolecule gramicidin uses the usual hydrogen bonds of peptides to stabilize itself.

4 Molecular Recognition

A. Models for Molecular Recognition and Chiral Recognition.—The step beyond spherical substrates is the design of receptors capable of molecular recognition. In addition to selective complexation, such complexes could display a functional selectivity as proto-enzymes or molecular transporters. Early examples were provided by the cyclic polysaccharides, the cycloamyloses (Table 3). These are known to form well defined inclusion complexes with molecular substrates.

Table 3 *The cycloamyloses*



Cycloamylose	*Number of glucose building blocks*	*Cavity dimensions (Å) Diameter*	*Depth*
Cyclohexa-amylose	6	4.5	6.7
Cycloheptа-amylose	7	7	7
Cyclo-octa-amylose	8	8	7

However, complex stability and selectivity have often been low and in α-cycloamylose, provided the non-polar substrate can fit into the cavity, conformation and hydrogen bonding changes are triggered and a more favourable 'relaxed' form is adopted.[28] However, a functional selectivity can occur in, for example, the base hydrolysis of phenyl esters.[29,30] It is found that the rate for

[27] F. Vögtle and E. Weber, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 753; F. Vögtle and U. Heimann, *Chem. Ber.*, 1978, **111**, 2757; F. Vögtle, *Pure Appl. Chem.*, 1980, **52**, 2405.

[28] W. Saenger, M. Noltemeyer, P. C. Manor, B. Hingerty, and B. Klar, *Bioorg. Chem.*, 1976, **5**, 187. Relaxation as a contribution to binding is unique to α-cycloamylose. In all the cycloamyloses van der Waals forces and hydrophobic interactions probably dominate complex formation: W. Saenger, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 344.

[29] D. W. Griffiths and M. L. Bender, *Adv. Catal.*, 1973, **23**, 209.

[30] M. L. Bender and M. Komiyama, 'Reactivity and Structure; Concepts in Organic Chemistry, Vol. 6: Cyclodextrin Chemistry', Springer Verlag, Berlin, 1978.

Table 4 *A functional differentiation between* meta- *and* para-*substituted esters from substrate inclusion within the cycloamylose cavity*

	Relative rates of catalysed: uncatalysed hydrolysis		
Acetate ester	*Cyclohexa-*	*Cycloheptа-*	*Cyclo-octa-amylose*
m-t-Butylphenyl	226	250	54
p-t-Butylphenyl	1.7	2.2	41
m-Chlorophenyl	113	18	7.8
p-Chlorophenyl	3.0	10	8.8
m-Nitrophenyl	103	54	10.0
p-Nitrophenyl	2.6	6.7	6.2

meta-substituted esters (Table 4) is significantly greater than the *ortho* or *para* analogues. The formation of an inclusion complex when the ester and substituent groupings have a *meta* relationship produces, with a small cavity, optimal interaction distances with the hydroxy-groups of the cycloamylose.

Conceptually, the cycloamyloses as receptors are 'primitive' in that they utilize hydrophobic interactions to associate non-polar surfaces. While a hydrophobic cavity complementary to substrate topology might be expected to discriminate in the formation of inclusion complexes, hydrophobic interactions may serve only to assemble non-polar species.[31] Recognition is perhaps a function of order from other interactions (hydrogen bonds, electrostatic interactions, van der Waals forces ...). However, with more than subtle substrate differences, the selective binding and orientation possibilities achievable with cycloamylose is considerable. The larger amino-acid tryptophan is preferentially formed over alanine in competitive transamination of pyruvic and indole pyruvic acids with pyridoxamine attached to a cycloamylose.[32]

Direction of a reaction along one of two possible pathways has been achieved[33] by offering the transition states two different environments (rate enhancement discrimination). Simple (or spontaneous) hydrolysis of the cyclic phosphate ester gives a mixture of the two possible regio-products as shown in Figure 5. However, when included into bis-imidazole armed cycloamyloses a stereospecific cleavage of the cyclic ester is achieved and its hydrolysis becomes a highly selective process.

As models for covalent catalysis, the utility of the cycloamyloses has suffered from the low nucleophilicity of the hydroxy-groups at near neutral pH and by the relatively slow rates of deacylation of covalent intermediates. Past modifications to introduce a catalytic relay to facilitate deacylation and/or introduce a more reactive nucleophilic system, have had to overcome severe synthetic problems. The difficulties have stemmed primarily from the multiplicity of potentially reactive hydroxy-groups. Recent strategies allow selective activation of either two primary

[31] J. H. Fendler and E. J. Fendler, 'Catalysis in Micellar and Macromolecular Systems', Academic Press, New York, 1975.

[32] R. Breslow, M. Hammond, and M. Lauer, *J. Am. Chem. Soc.*, 1980, **102**, 421.

[33] R. Breslow, J. Doherty, G. Guillot, and C. Lipsey, *J. Am. Chem. Soc.*, 1978, **100**, 3227; R. Breslow, P. Bovy, and C. Lipsey Hersh, *ibid.*, 1980, **102**, 2115.

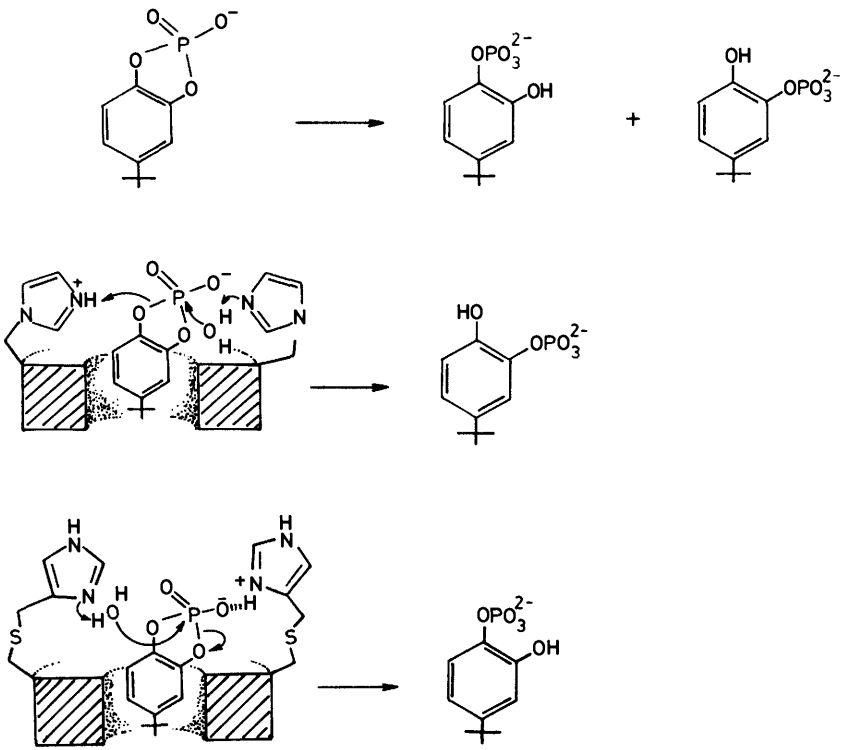


Figure 5 *Direction of a reaction along one of two possible pathways by artificial enzymes derived from a cycloamylose*

hydroxy-groups[34] or a secondary hydroxy-group[35] per molecule as sulphonate esters.

Very significant rate enhancements have now been achieved by Breslow and co-workers by fine-tuning a match between derivatized cycloamyloses, as catalysts, and the substrate.[36] Rate increases of almost 10^8 have been reported[37] for tailored acyl-transfer reactions.

When moving beyond spherical substrates, workers have placed emphasis upon the selective binding (recognition) of protonated amines. While still looking to the co-ordination of a cation, alkylamine salts ($RNH_3^+.X^-$)[38] differ from metal

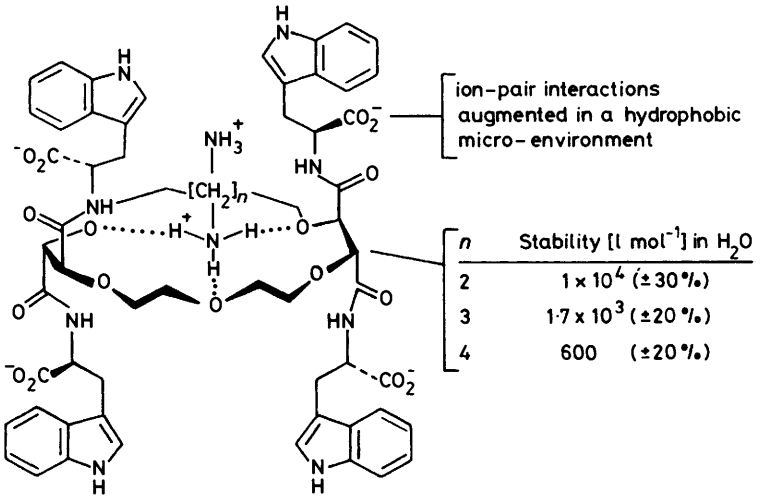
[34] I. Tabushi, K. Shimokawa, N. Shimizu, H. Shirakata, and K. Fujita, *J. Am. Chem. Soc.*, 1976, **98**, 7855.

[35] A. Ueno and R. Breslow, *Tetrahedron Lett.*, 1982, **23**, 3451.

[36] R. Breslow, M. F. Czarnieck, J. Emert, and H. Hamaguchi, *J. Am. Chem. Soc.*, 1980, **102**, 762.

[37] R. Breslow and G. Trainor, *J. Am. Chem. Soc.*, 1981, **103**, 154.

[38] Direct substitution at the N-atom leads to the selectivity sequence $N^+ < NH^+ < NH_2^+ < NH_3^+ < NH_4^+$ with a macrocyclic polyether receptor (ref. 39).



(11)

Figure 6 *Schematic representation of a di-ammonium complex with the receptor molecule* (11). *Complex stability is shown as a complementarity between receptor and substrate*

cations. The binding of the former is principally by hydrogen bonding and so there is interaction between sites of charge density in space; a complementarity is now needed between substrate cation and receptor. Further, anchoring the $-NH_3^+$ groups of an amine salt into say, the macrocyclic receptor (11) [Figure 6], allows further interactions to occur with the hedge of functionalities lining the central cavity. Ion-pair binding to the carboxylate groups by the distal $-NH_3^+$ moiety causes a marked stability of some di-ammonium salt complexes.[39]

Other developments of the theme of distal interaction for the binding of di-ammonium substrates have used the classic crown molecules as receptor synthons. Cram[40] used the convergent relationship afforded by a binaphthyl unit to facilitate the complexation of polyfunctional substrates (12). Synthesis of a cylindrical macrotricycle also provides the facility for binding di-cations in the central cavity.[41,42] Thus, the well dimensioned tricyclic ligand (13) rather selectively binds the cadaverine di-cation.[42]

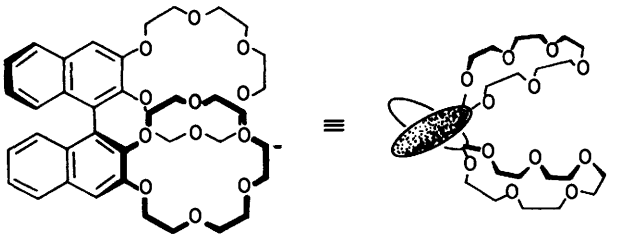
It is true in general that the stability of complexes of alkylammonium salts depends upon the complementarity between the structures of the binding ligand and the amine cations. This relationship is critical to the outcome of chiral dis-

[39] J.-P. Behr, J.-M. Lehn, and P. Vierling, *Helv. Chim. Acta*, 1982, **65**, 1853.

[40] T. L. Tarnowski and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 1976, 661. Crystal structure, I. Goldberg, *Acta Crystallogr.*, 1977, **B33**, 472.

[41] M. R. Johnson, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 309; R. Mageswaran, S. Mageswaran, and I. O. Sutherland, *ibid.*, 1979, 722; N. F. Jones, A. Kumar, and I. O. Sutherland, *ibid.*, 1981, 990.

[42] C. Pascard, C. Riche, M. Cesario, F. Kotzyba-Hibert, and J.-M. Lehn, *J. Chem. Soc., Chem. Commun.*, 1982, 557 and references therein.



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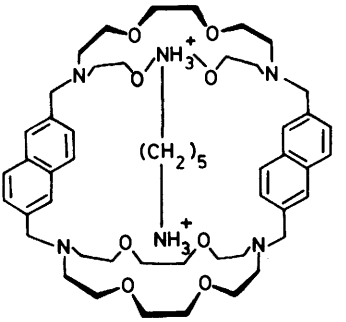


(13)

crimination between the two enantiomers of a racemic salt. As informational units, Cram and co-workers[43] have used substituted binaphthyl systems to advantage. These chiral receptors have been variously successful in the resolution of racemic ammonium salts by discriminative inclusion of the *R* or *S* forms.[44]

In the binaphthyl structured ligands, the information necessary for chiral recognition is a helicoidal arrangement of steric factors. Optimal interactions can occur in only one diastereomeric relationship, Figure 7. The steric com-

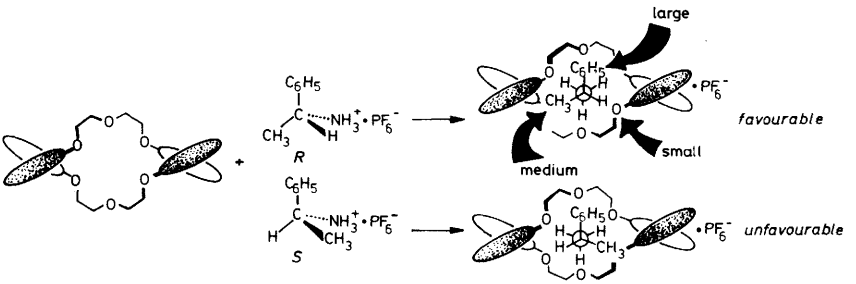
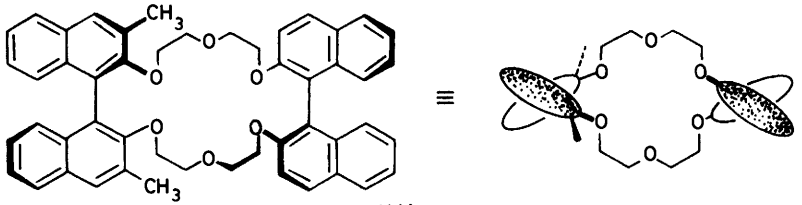


Figure 7 *The helicoidally arranged steric interactions favour one diastereomeric relationship and disfavour the other*

[43] D. J. Cram and J. M. Cram, *Science*, 1974, **183**, 803, *Acc. Chem. Res.*, 1978, **11**, 8; D. J. Cram, in 'Synthetic Host–Guest Chemistry, Application of Biomedical Systems in Chemistry', Part II, ed. Jones, Sih, and Perlman, Wiley, New York, 1976, p. 815.

[44] Carbohydrate-derived chiral structuring units have been used to provide a diastereomeric host–guest environment in receptors: J. F. Stoddart, *Chem. Soc. Rev.*, 1979, **8**, 85.

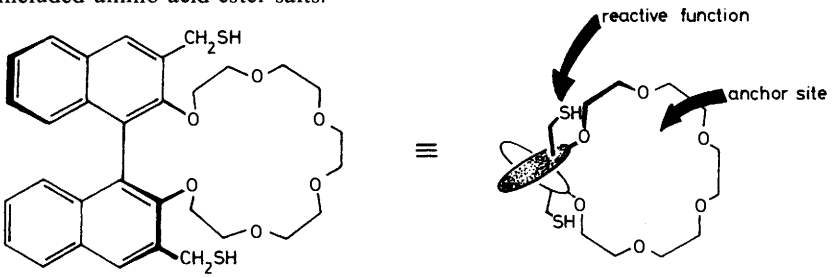
plementarity demanded is that of avoiding to have to 'madly squeeze a right-hand foot into a left-hand shoe'.[45,46] The simple steric model shown in Figure 7 will predict the more stable member of a diastereomeric pair if:
—the medium and large groups differ substantially in size,
—there is minimal interference of binding by the spatial barriers,
—the large and medium sized groups have restricted mobility.
The receptor (14) with two methyl groups as buttresses, has shown an impressively



(14)

high degree of chiral discrimination toward substrates in both simple extraction and transport experiments.[47] Covalent attachment of this receptor to a polymer produces a chromatographic material capable of predictable resolutions on both preparative and analytical scales.[48]

Such buttresses can be used to carry additional sites of binding or, functional groups able to initiate a specific reaction with the bound substrate.[43] The two nucleophilic sulphydryl groups of (15) in Figure 8 cause lysis of complementarity-included amino-acid ester salts.[49]



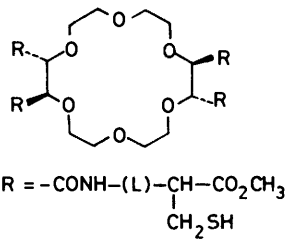
(15)

Figure 8 *An interesting functional receptor molecule carrying within its minimal structure a reactive functional group and a potentially discriminative anchoring site*

[45] Lewis Carroll, from the White Knight's song in 'Alice Through the Looking Glass'.
[46] Data suggests that the more stable diastereomeric complex is due to stronger binding [higher $-\Delta(\Delta H°)$ contribution], but is at the cost of being more highly organized [$-T\Delta(\Delta S°)$ large and positive]. S. C. Peacock, L. A. Domeier, F. C. A. Gaeta, R. C. Helgeson, J. M. Timko, and D. J. Cram, *J. Am. Chem. Soc.*, 1978, **100**, 8190.
[47] E. P. Kyba, K. Koga, L. R. Sousa, M. G. Siegel, and D. J. Cram, *J. Am. Chem. Soc.*, 1973, **95**, 2692; R. C. Helgeson, J. M. Timko, P. Moreau, S. C. Peacock, J. M. Mayer, and D. J. Cram, *ibid.*, 1974, **96**, 6762; S. C. Peacock and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 1976, 282; see also D. S. Lingenfelter, R. C. Helgeson, and D. J. Cram, *J. Org. Chem.*, 1981, **46**, 393.
[48] G. D. Y. Sogah and D. J. Cram, *J. Am. Chem. Soc.*, 1976, **98**, 3038.
[49] Y. Chao, G. R. Weisman, G. D. Y. Sogah, and D. J. Cram, *J. Am. Chem. Soc.*, 1979, **101**, 4948.

Although the restricted rotation of the above binaphthyl unit is useful in receptor construction, the naphthyl species has the serious handicap of sharply reducing the basicity of the attached binding-site oxygens.[50] Functionalized aliphatic crown-ethers promise exciting advances. The receptor (crown) is given a chiral sense by a configurationally stable diol unit chosen from a natural source, *e.g.*, tartaric acid.[51]

Two examples illustrate this potential: the thiolysis (3-nitrophenol displacement from amino-acid and dipeptide esters) by (16) showed a structural selectivity for the dipeptide esters and a sensitive recognition of substrate chiral sense.[52] For the NADH analogues (17), the observed predominant (*S*)-configuration of the product alcohol is predictable if hydride ion transfers to the substrate carbonyl occurred in a close diastereomeric relationship of a bound Mg^{2+} ion, carbonyl, and diethylene glycol bridge.[53]



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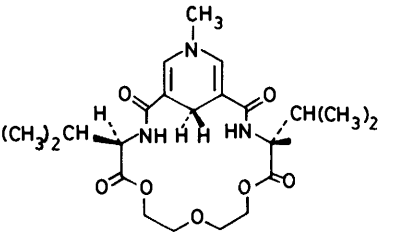


(17)

However, the elaboration of a second generation of 'spherand' receptors[8] by Cram and co-workers[54] has provided the remarkable functional receptor (18).[55] This has a rate factor estimated at about 10^{11} for deacylation of a bound ester. Upon complexation the ammonium cation is firmly bound by the urea oxygen atoms rimming the basket-like receptor. This beautifully proximates the substrate's CO_2R carbonyl electrophile and the pendant oxygen nucleophile of the receptor. Rapid transacylation ensues to give the acylated receptor (19).

[50] Aryl nitrogen sites show a lower basicity and donicity than aryl oxygen sites; aliphatic ether sites are more basic than aryl ether sites: J. C. Lockhart, B. Atkinson, G. Marshall, and B. Davies, *J. Chem. Res.* (*S*), 1979, 32.

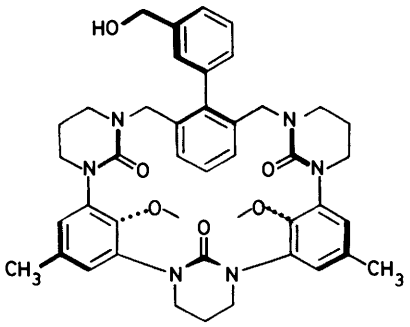
[51] Because carbohydrates can contain several chiral centres, the choice of structuring units is limited to those of C_2 symmetry if more than one such unit is included. The functionality, availability of both enantiomeric isomers, and the C_2 symmetry of tartaric acid make it a valuable shaping unit.

[52] J.-M. Lehn and C. Sirlin, *J. Chem. Soc., Chem. Commun.*, 1978, 949.

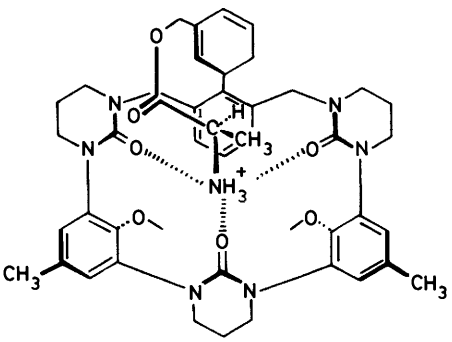
[53] J. G. de Vries and R. M. Kellogg, *J. Am. Chem. Soc.*, 1979, **101**, 2759.

[54] D. J. Cram, I. B. Dicker, C. B. Knobler, and K. N. Trueblood, *J. Am. Chem. Soc.*, 1982, **104**, 6828; see also D. J. Cram, I. B. Dicker, G. M. Lein, C. B. Knobler, and K. N. Trueblood, *ibid.*, 1982, **104**, 6827.

[55] D. J. Cram and H. I. Katz, *J. Am. Chem. Soc.*, 1983, **105**, 135; see also J. L. Fox, *Chem. Eng. News*, 1983, **61**(7), 33.



(18)



(19)

B. The Recognition of Complex Anions.—The selective binding of anions has been extended to those which are not spherically symmetric. Although less well investigated than cation complexation, progress has been made in modelling the requirements for anion recognition and binding.[56]

Anion receptor development has proceeded similarly to that for cations with optimization of the type (principally electrostatic) and spatial distribution of binding sites. For non-spherical anions directionality of the binding interaction is important. Inclusion of the anionic substrate into a macrocycle studded with $^{+}N-H$ hydrogen bonding points, has been a synthetically accessible and efficacious approach.[57]

The strong and selective binding of the azide anion by a hexa-protonated bis-tren receptor, is attributed to the linear N_3^- substrate ideally fitting the molecular cavity and being held by the two arrays of three $N^+-H\cdots N^-$ hydrogen bonds (20).[58] The anion selectivity sequence of ClO_4^-, Cl^-, I^-, $MeCO_2^-$, $Br^- < HCO_2^- < NO_3^-$, $NO_2^- \ll N_3^-$ follows a trend of topology rather than the physico-chemical properties of the anions.

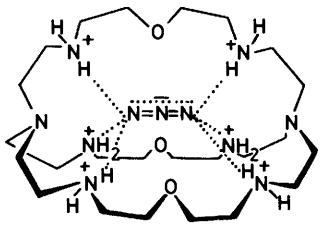
Spatial separation of charge and/or hydrogen bonding sites in other ways (yet retaining co-operativity of binding) will give receptor cavities of different topology. Compounds (21) and (22) form strong complexes with various dicarboxylate salts.[59] Furthermore, they are apparently stoicheiometrically selective toward linear dicarboxylates of the type $^{-}O_2C-(CH_2)_x-CO_2^-$. Selectivity peaks are found at $x = 2$, 3 for (21) and $x = 5$, 6 for (22) as a result of structural complementarity.

[56] J. J. R. Fraústo da Silva, in 'New Trends in Bio-inorganic Chemistry', ed. R. J. P. Williams and J. J. R. Fraústo da Silva, Academic Press, 1978, p. 449; J. J. R. Fraústo da Silva and R. J. P. Williams, *Struct. Bonding (Berlin)*, 1976, **29**, (105).

[57] See for example: E. Kimura, A. Sakonaka, and M. Kodama, *J. Am. Chem. Soc.*, 1982, **104**, 4984, and references therein; B. Dietrich, M. W. Hosseini, J.-M. Lehn and R. B. Sessions, *J. Am. Chem. Soc.*, 1981, **103**, 1282.

[58] J.-M. Lehn, S. H. Pine, E.-I. Watanabe, and A. K. Willard, *J. Am. Chem. Soc.*, 1977, **99**, 6766; J.-M. Lehn, E. Sonveaux, and A. K. Willard, *ibid.*, 1978, **100**, 4914. Confirmed by *X*-ray structure, C. Pascard, J. Guilhem, B. Dietrich, and J.-M. Lehn, unpublished results.

[59] M. W. Hosseini and J.-M. Lehn, *J. Am. Chem. Soc.*, 1982, **104**, 3525.



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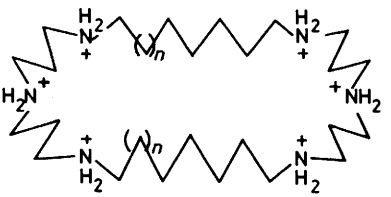
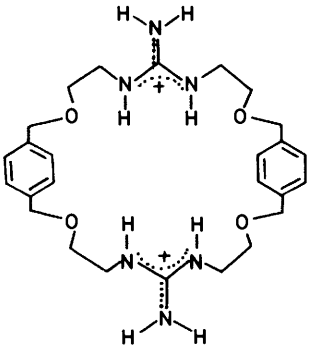


(21) $n = 1$

(22) $n = 4$

The guanidinium ion is well equipped to engage in patterns of hydrogen bonding with such anions as phosphate. In the arginine residue this cation plays, at least, a binding role at the functional sites of proteins.[60] As a structuring and binding unit in the macrocycles (23) and (24) complexes are formed with phosphate anions.[61]



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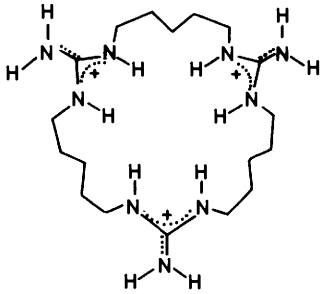


(24)

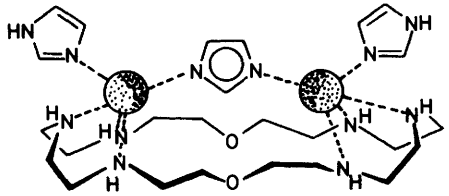
Another, and very different, type of positive centre is provided by metal cations bound to the receptor molecule; inclusion of the anion substrate may only be subsequent to inclusion of the metal centre(s). This represents a new type of selection process—cascade recognition, *e.g.*, (25).[62] The metal cations give centres of high charge-density whose further binding characteristics are a function of the specific cation, oxidation state, and binding ligands.

A remarkable variation in the physico-chemical properties of a series of di-nuclear Cu^{II} azido-bridged complexes has been reported upon variation in binding-

[60] F. A. Cotton, V. W. Day, E. E. Hazen, Jr., and S. Larsen, *J. Am Chem. Soc.*, 1973, **95**, 4834; F. A. Cotton, V. W. Day, E. E. Hazen, Jr., S. Larsen, and S. T. K. Wong, *ibid.*, 1974, **96**, 4471.

[61] B. Dietrich, T. M. Fyles, J.-M. Lehn, L. G. Pease, and D. L. Fyles, *J. Chem. Soc., Chem. Commun.*, 1978, 934. Open chain analogues, B. Dietrich, D. L. Fyles, T. M. Fyles, and J.-M. Lehn, *Helv. Chim. Acta*, 1979, **62**, 2763.

[62] P. K. Coughlin, J. C. Dewan, S. J. Lippard, E.-I. Watanabe, and J.-M. Lehn, *J. Am. Chem. Soc.*, 1979, **101**, 265; K. G. Strothkamp and S. J. Lippard, *Acc. Chem. Res.*, 1982, **15**, 318.



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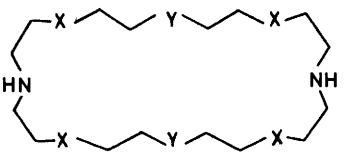
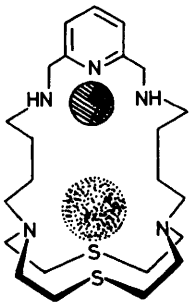


(26) X = Y = O
Y = NH; Y = O
X = S; Y = CH_2

ligand type (26).[63] Subtle changes in the co-ordination environment in which the metal finds itself may influence for example, the electronic and thus the magnetic properties of the complex.

Further flexibility in choice of ligand atom type (and thus selectivity) could result from the attachment of further binding sites to the nitrogens in such macrocycles as (26).[64] Two markedly different co-ordination environments as in ligand (27) could allow the formation of mixed valence or heteronuclear entities with subsequent anion co-ordination (and reaction?).[64]



(27)

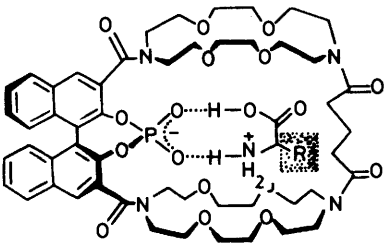
5 On Possible Ways to Organize Molecules

Suggestions have been made that crystalline minerals might have provided concentrating and ordering surfaces in prebiotic chemistry for molecular entities. However, an organic matrix could also have provided functional receptors of low, but existent, substrate specificity.

It is clear that with spatially separate arrays of binding sites considerable complexity can be recognized. The substrate–receptor interactions used have been principally electrostatic or have had a considerable electrostatic component.

[63] J. Comarmond, P. Plumére, J.-M. Lehn, Y. Agnus, R. Louis, R. Weiss, O. Kahn, and I. Morgenstern-Badarau, *J. Am. Chem. Soc.*, 1982, **104**, 6330.

[64] J.-M. Lehn, *Pure Appl. Chem.*, 1980, **52**, 2441; see also S. Gambarotta, F. Arena, C. Floriani, and P. F. Zanazzi, *J. Am. Chem. Soc.*, 1982, **104**, 5082, and references therein.



(28)

Electrostatic co-ordination may not only promote substrate inclusion, but may also cause a receptor site to be more topologically exacting than, for example, hydrophobic interaction.[65] Thus the receptor (28),[66] contrary to what might be expected, preferentially transports the less lipophilic amino-acids. Those with large R groups fitting only with difficulty into the cavity.

Therefore, there is available a methodology for arranging single molecules in a planned way upon some sort of molecular scaffolding (Figure 9). This is essential

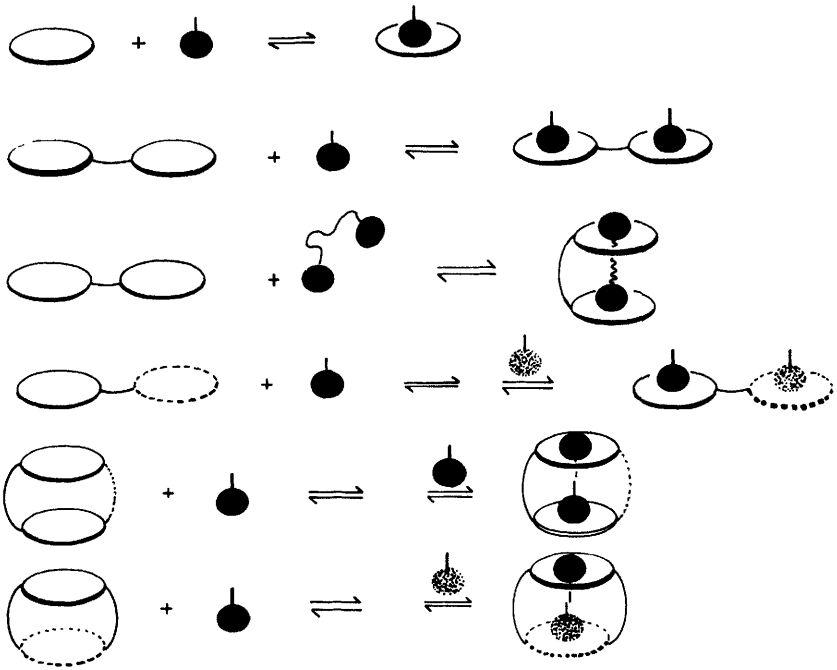
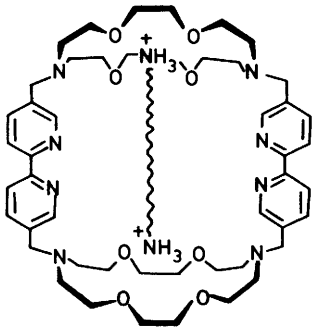
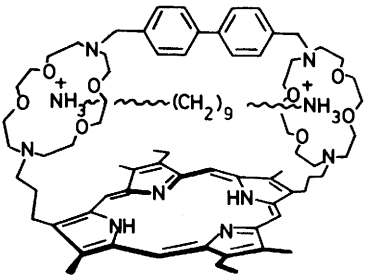


Figure 9 *A schematic view of some molecular assembly surfaces. A significant problem is likely to be the formation of the less desired* exo–endo *or* exo–exo *isomeric species. The solution can only be to make the* endo–endo *binding situation more favourable.*

[65] B. Dietrich, J.-M. Lehn, and J. Simon, *Angew Chem., Int. Ed. Engl.*, 1974, **13**, 406.
[66] J. Simon, Thèse Doctoral d'Etat, Strasbourg, 1976.



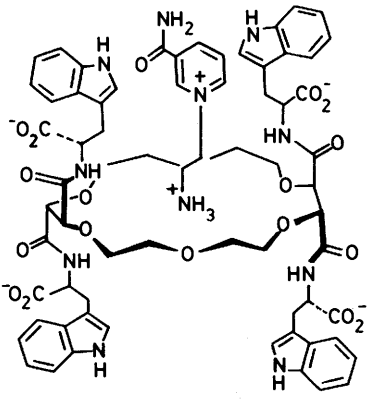
(29)



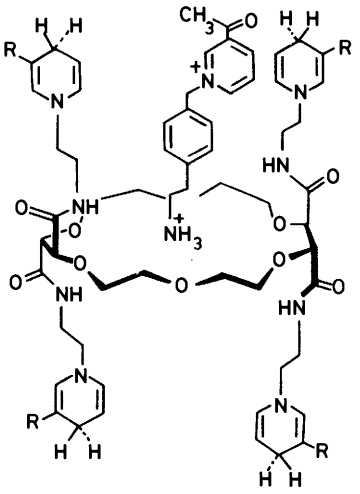
(30)

if primary biological events are to be modelled. The array of co-ordinating sites (or reactive functionality) can be introduced as part of the building blocks. For example, the potential of (29) and (30) to bind a metal cation in addition to the molecular substrate is of interest as it provides a design direction towards model metallo-enzymes.[67] Conceptually, orientation of the bound substrate towards a reaction transition-state is possible by spatially positioned secondary interactions.

Organization by secondary interactions is seen in the complexes (31)[68] and (32).[69] Binding of the substrate primary amino-group to the central crown unit[70] proximates to substrate and side chain.



(31)



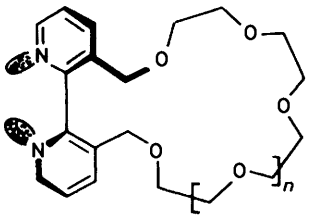
(32) R = CONH•Bu^n

[67] J.-M. Lehn, in IUPAC 'Frontiers of Chemistry', ed. K. J. Laidler, Pergamon Press, Oxford, 1982, p. 265.

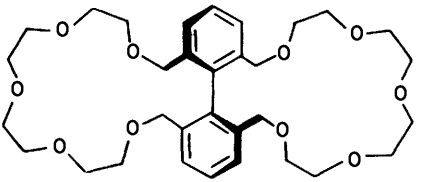
[68] J.-P. Behr and J.-M. Lehn, *Helv. Chim. Acta*, 1980, **63**, 2112.

[69] J.-P. Behr and J.-M. Lehn, *J. Chem. Soc., Chem. Commun.*, 1978, 143.

[70] Crystal structures available for 18-crown-6 receptors with tartaric acid as the shaping unit, show a conformational conservatism and remarkably constant overall shape (ref. 39).



(33) $n = 1, 2$



(34)

Separate binding-site arrays may not just act co-operatively to bind the substrate but may have coupled binding characteristics. Transmission of complexation induced conformation change from one binding array to another (allosteric effect) has been demonstrated in the mobile sytems (33)[71] and (34).[72] For example, with the latter ligand a positive co-operativity is seen; the receptivity toward a second $Hg(CN)_2$ species is enhanced some ten times by the binding of the first one.

The organizational potential of these receptors could be used in an intriguing, albeit rather futuristic area, of membrane transducers (Figure 10) so allowing information treatment at the molecular level.[73] Such an idea is interesting since not only cations, but also uncharged organic molecules containing HN—, HO—, and

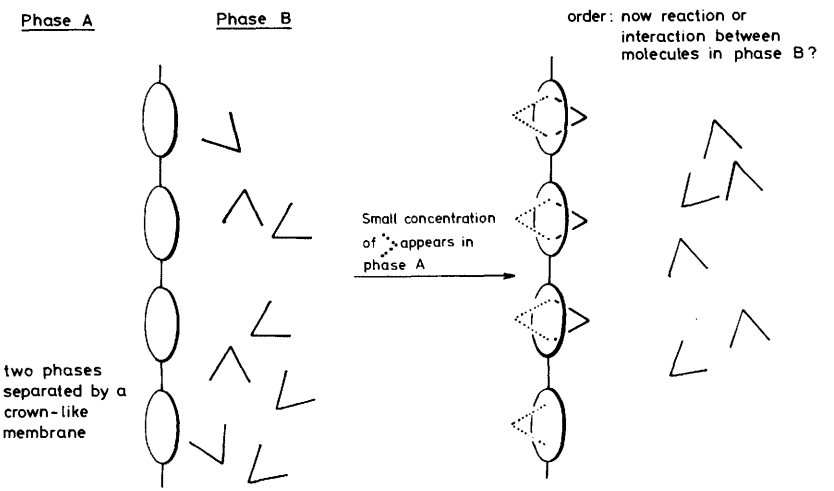


Figure 10 *A futuristic view for an abiotic membrane signal transducer. The effect might be signal transfer, amplification, or system regulation*

[71] J. Rebek, Jr. and R. V. Wattley, *J. Am. Chem. Soc.*, 1980, **102**, 4853.
[72] J. Rebek, Jr., R. V. Wattley, T. Costello, R. Gadwood, and L. Marshall, *Angew Chem., Int. Ed. Engl.*, 1981, **20**, 605; *J. Am. Chem. Soc.*, 1980, **102**, 7398.
[73] J.-M. Lehn, Leçon Inaugurale, College de France, 1980.

HC— acidic groups can be complexed by even simple crown compounds[74] in often a 2 : 1 stoicheiometry.

From its beginnings as the co-ordination chemistry of metal cations, the design and chemistry of organic complexing agents now includes anions as well as cations, charged or neutral molecules as well as metal ions. Yet, perhaps sometimes in the extensive listings of physico-chemical properties a little of the essential excitement has been lost. The first step in specific catalyst design is in hand. It is now possible to synthesize molecules which are capable of quite specifically recognizing and assembling ions and/or molecules. Clues are being gathered to the solution of the cryptogram.

[74] F. Vögtle, H. Sieger, and W. M. Müller, in 'Topics in Current Chemistry, Vol. 98: Host Guest Chemistry I', ed. F. Vögtle. Springer Verlag, Berlin, 1981, p. 107.