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Supramolecular Chemistry – Scope and Perspectives: Molecules – Supermolecules – Molecular Devices

JEAN-MARIE LEHN
Institut Le Bel, Université Louis Pasteur, 4 rue Blaise Pascal, 67000 Strasbourg and Collège de France, 11 Place Marcelin Berthelot, 75005 Paris.

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Abstract. Supramolecular chemistry is the chemistry of the intermolecular bond, covering the structures and functions of the entities formed by association of two or more chemical species. Molecular recognition in the supermolecules formed by receptor-substrate binding rests on the principles of molecular complementarity, as found in spherical and tetrahedral recognition, linear recognition by co-receptors, metallo-receptors, amphilic receptors and anion coordination. Supramolecular catalysis by receptors bearing reactive groups effects bond cleavage reactions as well as synthetic bond formation via co-catalysis. Lipophilic receptor molecules act as selective carriers for various substrates and allow the setting up of coupled transport processes linked to electron and proton gradients or to light. Whereas endo-receptors bind substrates in molecular cavities by convergent interactions, exo-receptors rely on interactions between the surfaces of the receptor and the substrate; thus new types of receptors such as the metallonucleates may be designed. In combination with polymolecular assemblies, receptors, carriers and catalysts may lead to molecular and supramolecular devices, defined as structurally organized and functionally integrated chemical systems built on supramolecular architectures. Their recognition, transfer and transformation features are analyzed specifically from the point of view of molecular devices that would operate via photons, electrons or ions, thus defining the fields of molecular photonics, electronics and ionics. Introduction of photosensitive groups yields photoactive receptors for the design of light conversion and charge separation centres. Redox active polyolefinic chains represent molecular wires for electron transfer through membranes. Tubular mesophases formed by stacking of suitable macrocyclic receptors may lead to ion channels. Molecular self-assembling occurs with acyclic ligands that form complexes with a double helical structure. Such developments in molecular and supramolecular design and engineering open perspectives towards the realization of molecular photonic, electronic and ionic devices, that would perform highly selective recognition, reaction and transfer operations for signal and information processing at the molecular level.

1. From Molecular to Supramolecular Chemistry

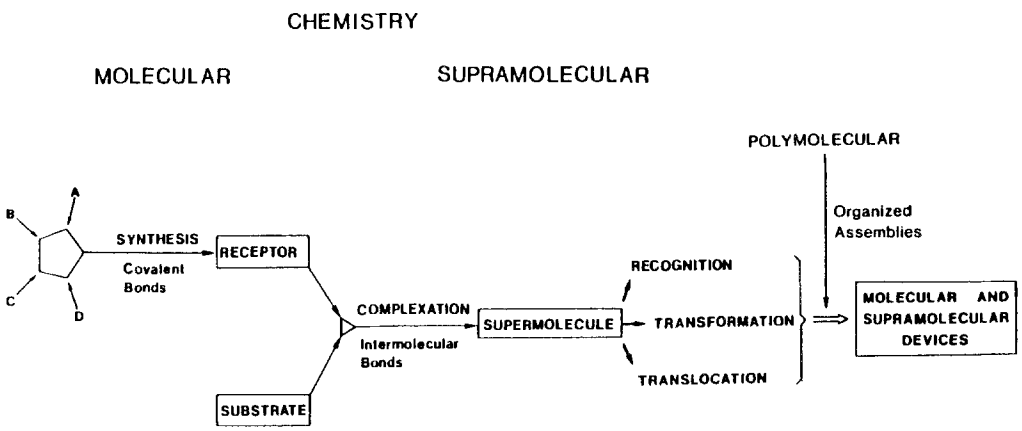
Molecular chemistry, the chemistry of the covalent bond, is concerned with uncovering and mastering the rules that govern the structures, properties and transformations of molecular species.

Supramolecular chemistry may be defined as 'chemistry beyond the molecule,' bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces. Its development requires the use of all resources of molecular chemistry combined with the designed manipulation of non-covalent interactions so as to form supramolecular entities, supermolecules possessing features as well defined as those of molecules themselves. One may say that supermolecules are to molecules and the intermolecular bond what molecules are to atoms and the covalent bond.

Basic concepts, terminology and definitions of supramolecular chemistry were introduced earlier [1–3] and will only be summarized here. Section 2.3 below provides a brief account on the origins and initial developments of our work which led to the formulation of supramolecular chemistry. Molecular associations have been recognized and studied for a long time [4] and the term 'Übermoleküle'. i.e. supermolecules, was introduced already in the mid-1930s to describe entities of higher organization resulting from the association of coordinatively saturated species [5]. The partners of a supramolecular species have been named *molecular receptor* and *substrate* [1, 2, 65], the substrate being usually the smaller component whose binding is being sought. This terminology conveys the relation to biological receptors and substrates for which *Paul Ehrlich* stated that molecules do not act if they are not bound (*"Corpora non agunt nisi fixata"*). The widely employed term of *ligand* seemed less appropriate in view of its many unspecific uses for either partner in a complex.

Molecular interactions form the basis of the highly specific recognition, reaction, transport, regulation etc. processes that occur in biology such as substrate binding to a receptor protein, enzymatic reactions, assembling of protein-protein complexes, immunological antigen-antibody association, intermolecular reading, translation and transcription of the genetic code, signal induction by neurotransmitters, cellular recognition, etc. The design of artificial, abiotic, receptor molecules capable of displaying processes of highest efficiency and selectivity requires the correct manipulation of the energetic and stereochemical features of the non-covalent, intermolecular forces (electrostatic interactions, hydrogen bonding, Van der Waals forces etc.) within a defined molecular architecture. In doing so, the chemist may find inspiration in the ingenuity of biological events and encouragement in their demonstration that such high efficiencies, selectivities and rates can indeed be attained. However chemistry is not limited to systems similar to those found in biology, but is free to invent novel species and processes.

Binding of a substrate σ to its receptor ρ yields the supermolecule and involves a molecular recognition process. If, in addition to binding sites, the receptor also bears reactive functions it may effect a chemical transformation on the bound substrate, thus behaving as a supramolecular reagent or catalyst. A lopophilic, membrane soluble receptor may act as a carrier effecting the translocation of the bound substrate. Thus, *molecular*



Scheme 1. From molecular to supramolecular chemistry: molecules, supermolecules, molecular and supramolecular devices.

recognition, *transformation* and *translocation* represent the basic functions of supramolecular species. More complex functions may result from the interplay of several binding subunits in a polytopic co-receptor. In association with organized polymolecular assemblies and phases (layers, membranes, vesicles, liquid crystals, etc), functional supermolecules may lead to the development of *molecular devices*. The present text describes these various aspects of supramolecular chemistry (diagrammatically shown in Scheme 1) and sketches some lines of future development (for earlier general presentations see [1–3, 6–9]). The results discussed here, taken mainly from our own work, have been completed by references to other studies, in order to draw a broader picture of this rapidly evolving field of research. Emphasis will bear on conceptual framework, classes of compounds and types of processes. Considering the vast literature that has developed, the topics of various meetings and symposia, etc., there is no possibility here to do justice to the numerous results obtained, all the more to provide an exhaustive account of this field of science. Supramolecular chemistry, the designed chemistry of the intermolecular bond, is rapidly expanding at the frontiers of molecular science with physical and biological phenomena.

2. Molecular Recognition

2.1. RECOGNITION – INFORMATION – COMPLEMENTARITY

Molecular recognition has been defined as a process involving both *binding* and *selection* of substrate(s) by a given receptor molecule, as well as possibly a specific *function* [1]. Mere binding is not recognition, although it is often taken as such. One may say that recognition is binding with a purpose, like receptors are ligands with a purpose. It implies a structurally well defined pattern of intermolecular interactions.

Binding of σ to ρ forms a supermolecule characterized by its thermodynamic and kinetic stability and selectivity, i.e. by the amount of energy and of information brought into operation. Molecular recognition thus is a question of *information storage* and *read out* at the supramolecular level. Information may be sorted in the architecture of the ligand, in its binding sites (nature, number, arrangement) and in the ligand layer surrounding bound σ; it is read out at the rate of formation and dissociation of the supermolecule. Molecular recognition thus corresponds to optimal information content of ρ for a given σ [1]. This amounts to a generalized *double complementarity principle* extending over energetical (electronic) as well as geometrical features, the celebrated "lock and key" steric fit concept enunciated by *Emil Fischer* in 1894 [10]. Enhanced recognition beyond that provided by a single equilibrium step may be achieved by multistep recognition and coupling to an irreversible process [11].

The ideas of molecular recognition and of receptor chemistry have been penetrating chemistry more and more over the last fifteen years, namely in view of its bioorganic implications, but more generally for its significance in intermolecular chemistry and in chemical selectivity [1–3, 6–9, 12–21].

2.2. MOLECULAR RECEPTORS – DESIGN PRINCIPLES

Receptor chemistry, the chemistry of artificial receptor molecules may be considered a generalized coordination chemistry, not limited to transition metal ions but extending to all types of substrates: cationic, anionic or neutral species of organic, inorganic or biological nature.

In order to achieve high recognition it is desirable that receptor and substrate be in contact over a large area. This occurs when ρ is able to wrap around its guest so as to establish numerous non covalent binding interactions and to sense its molecular size, shape and architecture. This is the case for receptor molecules that contain intramolecular cavities into which the substrate may fit, thus yielding an inclusion complex, a *cryptate*. In such concave receptors the cavity is lined with binding sites directed towards the bound species; they are endopolarophilic [1] and *convergent*, and may be termed *endo-receptors* (see also below).

Macropolycyclic structures meet the requirements for designing artificial receptors: they are large (macro) and may therefore contain cavities and clefts of appropriate size and shape; they possess numerous branches, bridges and connections (polycyclic) that allow the construction of a given architecture endowed with desired dynamic features; they allow the arrangement of structural groups, binding sites and reactive functions.

The balance between rigidity and flexibility is of particular importance for the dynamic properties of ρ and of σ. Although high recognition may be achieved with rigidly organized receptors, processes of exchange, regulation, cooperativity and allostery require a built-in flexibility so that they may adapt and respond to changes. Flexibility is of great importance in biological receptor-substrate interactions where adaptation is often required for regulation to occur. Such designed dynamics are more difficult to control than mere rigidity and recent developments in molecular design methods allowing the exploration of both structural and dynamical features may greatly help [22]. Receptor design thus covers both static and dynamic features of macropolycyclic structures.

The stability and selectivity of σ binding results from the set of interaction sites in ρ and may be structurally translated into *accumulation* (or collection) + *organization* (or orientation) i.e. bringing together binding sites and arranging them in a suitable pattern. Model computations on $(NH_3)_n$ clusters of different geometries have shown that collection involves appreciably larger energies than changes in orientation [23]. One may note that these intersite repulsions are built into a polydentate ligand in the course of synthesis [1].

We have studied receptors belonging to various classes of macropolycyclic structures (macrocycles, macrobicycles, cylindrical and spherical macrotricycles, etc.) expanding progressively our initial work on macrobicyclic cationic cryptate into the investigation of the structures and functions of supermolecules presenting molecular recognition, catalysis and transport processes.

2.3. INITIAL STUDIES. SPHERICAL RECOGNITION IN CRYPTATE COMPLEXES

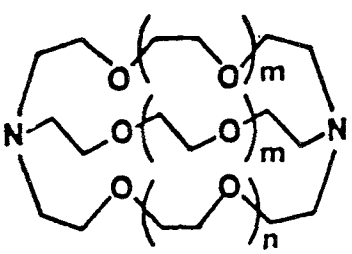
The simplest recognition process is that of spherical substrates; these are either positively charged metal cations (alkali, alkaline-earth, lanthanide ions) or the negative halide anions.

During the last 20 years, the complexation chemistry of alkali cations developed rapidly with the discovery of several classes of more or less powerful and selective ligands: natural [24] or synthetic [25, 26] macrocycles (such as valinomycin, 18-crown-6, spherands) as well as macropolycyclic cryptands and crypto-spherands [1, 6, 9, 26, 27]. It is the design and study of alkali metal cryptates that started our work which developed into supramolecular chemistry.

It may be suitable at this stage to recount briefly the *origins of our work*, trying to trace the initial motivations and the emergence of the first lines of research. In the course of the year 1966, my interest in the processes occurring in the nervous system led me to wonder

how a chemist might contribute to the study of these highest biological functions. The electrical events in nerve cells rest on changes in the distributions of sodium and potassium ions across the membrane. This seemed a possible entry into the field, since it had just been shown that the cyclodepsipeptide valinomycin [24c], whose structure and synthesis had been reported [24d], was able to mediate potassium ion transport in mitochondria [24e]. These results [24d, e] made me think that suitably designed synthetic cyclopeptides or analogues could provide means of monitoring cation distribution and transport across membranes. Such properties were also displayed by other neutral antibiotics [24f] of the enniatin and actin [24g] groups, and were found to be due to selective complex formation with alkali metal cations [24h–l], thus making these substances *ionophores* [24m]. However, since cation complexation might also represent a means of increasing the reactivity of the counteranion (anion activation) [6, 35], it became desirable to envisage molecules which would be chemically less reactive than cyclic peptides[a]. Thus, when the cation binding properties of macrocyclic polyethers (crown ethers) were reported by Charles Pedersen [25a], these substances were perceived as combining the complexing ability of the macrocyclic antibiotics with the chemical stability of ether functions. Meanwhile, it had also become clear that compounds containing a three-dimensional, spheroidal cavity surrounding entirely the bound ion, should form stronger complexes than the rather flat shaped macrocycles; thus emerged the idea of designing macro*bi*cyclic ligands.

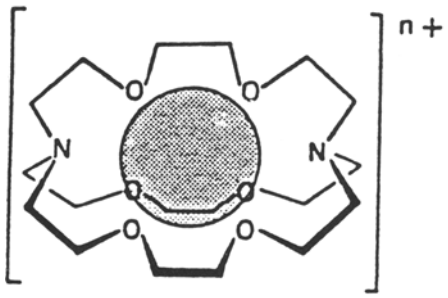
Work started in October 1967 yielded the first such ligand [2.2.2] **3** in the fall of 1968; its very strong binding of potassium ions was noted at once and a cryptate structure was assigned to the complex obtained, allowing us also to envisage its potential use for anion activation and for cation transport [29a][b]. Other ligands such as **1** and **2** and larger ones



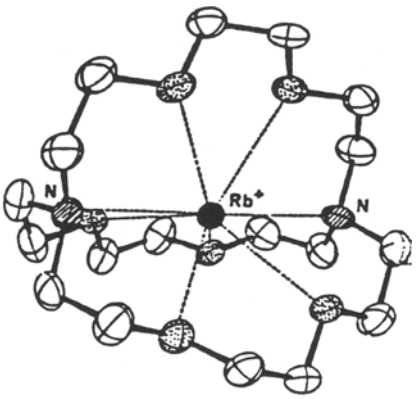
1 [2.1.1] m=0, n=1
2 [2.2.1] m=1, n=0
3 [2.2.2] m=n=1

[a] Earlier observations had suggested that polyethers interact with alkali cations. See for instance in H. C. Brown, E. J. Mead, P. A. Tierney, *J. Am. Chem. Soc.* **79** (1957) 5400; J. L. Down, J. Lewis, B. Moore, G. Wilkinson, *J. Chem. Soc.* 1959, 3767; suggestions had also been made for the design of organic ligands, see R. J. P. Williams, *Analyst* **78** (1953) 586, *Quart. Rev.* **24** (1970) 331.

[b] To name this new class of chemical entities, a term rooted in Greek and Latin, and which would also be equally suggestive in French, English, German and possibly (!) other languages was sought; 'cryptates' appeared particularly suitable for designating a complex in which the cation was contained inside the molecular cavity, the crypt, of the ligand term 'cryptand'.



4a



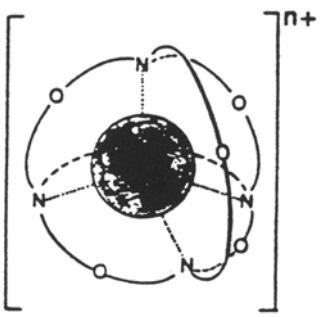
4b

were synthesized and numerous cryptates were obtained [29b]. Their structure was confirmed by crystal structure determinations of a number of complexes, such as the rubidium cryptate of **3**, **4b** [29c] and their stability constants were measured [28].

The problem of *spherical recognition* is that of selecting a given spherical ion among a collection of different spheres of the same charge. Thus, the macrobicyclic cryptands **1–3** form highly stable and selective cryptates [$M^{n+} \subset$ (cryptand)] such as **4**, with the cation whose size is complementary to the size of the cavity i.e., Li^+, Na^+ and K^+ for **1**, **2** and **3** respectively [28a, 29a]. Others display high selectivity for alkali versus alkaline-earth cations [28b]. Thus, recognition features equal to or higher than those of natural macrocyclic ligands may be achieved. The spherical macrotricyclic cryptand **5** binds strongly and selectively the larger spherical cations, giving a strong Cs^+ complex, as in **6** [30].

Anion cryptates are formed by the protonated polyamines **7** [31] and **5** [32] with the spherical halide anions F^- and Cl^- respectively. **5**—$4H^+$ binds Cl^- very strongly and very selectively with respect to Br^- and other types of anions, giving the [$Cl^- \subset$ (**2**—$4H^+$)] cryptate **8**. Quaternary ammonium derivatives of such type of macrotricycles also bind spherical anions [33].

5



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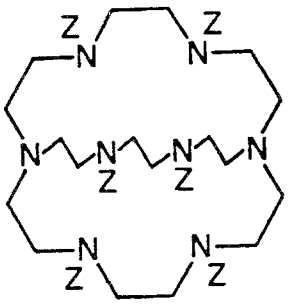
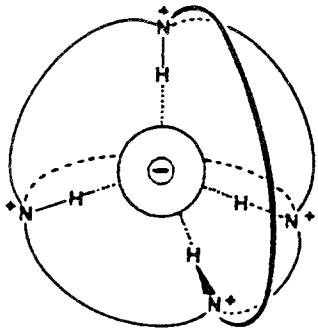


7 (Z=H)



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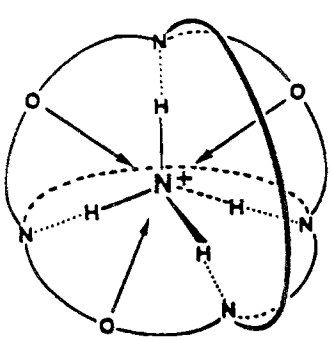
Thus, cryptands **1**–**3** and **5** as well as related compounds display *spherical recognition* of appropriate cations and anions. Their complexation properties result from their macropolycyclic nature and define a *cryptate effect* characterized by high stability and selectivity, slow exchange rates and efficient shielding of the bound substrate from the environment.

As a consequence of these features, cryptate formation strongly influences physical properties and chemical reactivity. Numerous effects have been brought about and studied in detail, such as: stabilization of alkalides and electrides [34], dissociation of ion pairs, anion activation, isotope separation, toxic metal binding, etc. These results will not be described here and reviews may be found elsewhere [6, 35–38].

2.4. TETRAHEDRAL RECOGNITION

Selective binding of a tetrahedral substrate requires the construction of a receptor molecule possessing a tetrahedral recognition site, as realized in the macrotricycle **5** that contains four nitrogen and six oxygen binding sites located respectively at the corners of a tetrahedron and of an octahedron [30]. Indeed, **5** forms an exceptionally stable and selective cryptate [$NH_4^+ \subset$ **5**], **9**, with the tetrahedral NH_4^+ cation, due to the high degree of structural and energetical complementarity. NH_4^+ has the size and shape for fitting into the cavity of **5** and forming a tetrahedral array of $^+N—H\cdots N$ hydrogen bonds with the four



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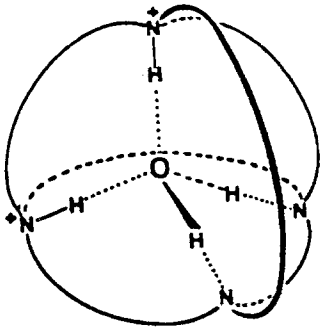

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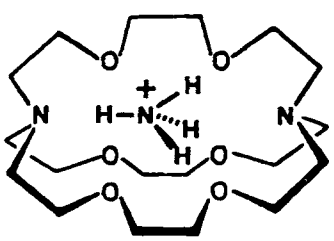
nitrogen sites [39]. As a result of its very strong binding, the pK_a of the NH_4^+ cryptate is about six units higher than that of free NH_4^+ indicating how much strong binding may affect the properties of the substrate. It also indicates that similar effects exist in enzyme active sites and in biological receptor-substrate binding.

The unusual protonation features of **5** in aqueous solution (high pK_a for double protonation, very slow exchange) and ^{17}O-NMR studies led to the formulation of a water cryptate $[H_2O \subset (\mathbf{5}—2H^+)]$ **10** with the diprotonated macrotricycle [2, 6, 40]. The facilitation of the second protonation of **5** represents a *positive cooperativity*, in which the first proton and the effector molecule water set the stage both structurally and energetically for the fixation of a second proton.

Considering together the three cryptates $[NH_4^+ \subset \mathbf{5}]$ **9**, $[H_2O \subset (\mathbf{5}—2H^+)]$ **10** and $[Cl^- \subset (\mathbf{5}—4H^+)]$ **8**, it is seen that the spherical macrotricycle **5** is a molecular receptor possessing a *tetrahedral recognition site* in which the substrates are bound in a tetrahedral array of hydrogen bonds. It represents a state of the art illustration of the molecular engineering involved in abiotic receptor chemistry. Since it binds a tetrahedral cation NH_4^+, a bent neutral molecule H_2O or a spherical anion Cl^- when respectively unprotonated, diprotonated and tetraprotonated, the macrotricyclic cryptand **5** behaves like a sort of molecular chameleon responding to pH changes in the medium!

The macrobicycle **3** also binds NH_4^+ forming cryptate **11**. The dynamic properties of **11** with respect to **9** reflect the receptor-substrate binding complementarity: whereas NH_4^+ is firmly held inside the cavity in **9**, it undergoes internal rotation in **11** [41].



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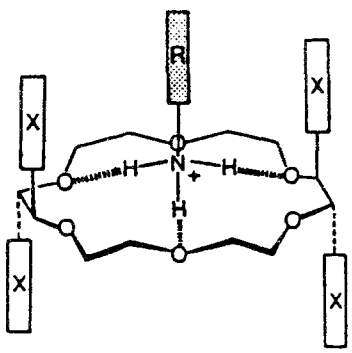
2.5. RECOGNITION OF AMMONIUM IONS AND RELATED SUBSTRATES

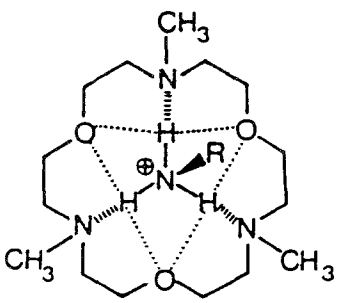
In view of the important role played by substituted ammonium ions in chemistry and in biology, the development of receptor molecules capable of recognizing such substrates is of special interest. Macrocyclic polyethers bind primary ammonium ions by anchoring the $-NH_3^+$ into their circular cavity via three $^+N-H\cdots O$ hydrogen bonds as shown in **12** [12–15, 25, 42]; however they complex alkali cations such as K^+ more strongly. Selective binding of $R-NH_3^+$ may be achieved by extending the results obtained for NH_4^+ complexation by **5** and making use of the aza-oxa macrocycles [15, 43] developed in the course of the synthesis of cryptands. Indeed, the triaza-macrocycle [18]—N_3O_3 which forms a complementary array of three $^+N-H\cdots N$ bonds **13**, selects $R-NH_3^+$ over K^+ and is thus a receptor unit for this functional group [43].



12 a X=H

b $X=CO_2^-$

c X=CONYY'



13

A great variety of macrocyclic polyethers have been shown to bind $R-NH_3^+$ molecules with structural and chiral selectivity [12, 13, 42]. Particularly strong binding is shown by the tetracarboxylate **12b** which conserves the desirable basic [18]—O_6 ring and adds electrostatic interactions, thus forming the most stable metal ion and ammonium complexes of any polyether macrocycle [44]. Very marked *central discrimination* is observed in favour of primary ammonium ions with respect to more highly substituted ones; it allows preferential binding of biologically active ions such as noradrenaline or norephedrine with respect to their N-methylated derivatives adrenaline and ephedrine [44].

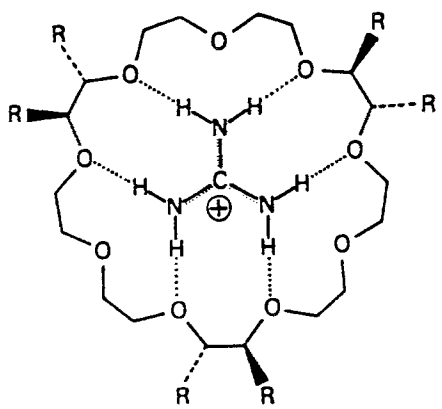
Modulation of the complexation features of **12** by varying the side groups X so as to make use of specific interactions (electrostatic, H-bonding, charge transfer, lipophilic) between X and the R group of the centrally bound $R-NH_3^+$ substrate, brings about *lateral discrimination* effects. This also represents a general way of modeling interactions present in biological receptor-substrate complexes, such as that occurring between nicotinamide and tryptophane [45]. One may thus attach to **12** amino-acid residues, leading to 'parallel peptides' [44] as in **12c**, nucleic bases or nucleosides, saccharides, etc.

Binding of metal–amine complexes $M(NH_3)_n^{m+}$ to macrocyclic polyethers via $N-H\cdots O$ interactions with the NH_3 groups, leads to a variety of supramolecular species

of 'the supercomplex type' by second sphere coordination [46]. As with the $R—NH_3^+$ substrate, binding to aza-oxa or polyaza macrocycles (see **13**) may also be expected. Strong complexation by macrocycles bearing negative charges (such as **12b** or the hexacarboxylate in **14** [47]), should allow the induction of various processes between centrally bound metal–amine species and the lateral groups X in **12** (energy and electron transfer, chemical reaction, etc).

Receptor sites for secondary and tertiary ammonium groups are also of interest. $R_2NH_2^+$ ions bind to the [12]—N_2O_2 macrocycle via two hydrogen bonds [48]. The case of quaternary ammonium ions will be considered below.

The guanidinium cation binds to [27]—O_9 macrocycles through an array of six H—bonds [49] yielding a particularly stable complex **14** with a hexacarboxylate receptor, that also binds the imidazolium ion [49a].



14 $(R\text{-}CO_2^-)$

3. Anion Coordination Chemistry and the Recognition of Anionic Substrates

Although anionic species play a very important role in chemistry and in biology, their complexation chemistry went unrecognised as a specific field of research, while the complexation of metal ions and, more recently, of cationic molecules was extensively studied. The coordination chemistry of anions may be expected to yield a great variety of novel structures and properties of both chemical and biological significance [2, 6, 32]. To this end, anion receptor molecules and binding subunits for anionic functional groups have to be devised. Research has been increasingly active along these lines in recent years and anion coordination chemistry is progressively building up [8, 9, 50].

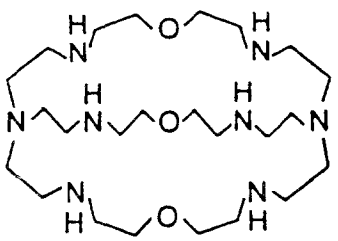
Positively charged or neutral electron deficient groups may serve as interaction sites for anion binding. Ammonium and guanidinium units which form $^+N—H\cdots X^-$ bonds have mainly been used, but neutral polar hydrogen bonds (e.g. with —NHCO— or —COOH functions), electron deficient centres (boron, tin, etc.) or metal ion centres in complexes, also interact with anions.

Polyammonium macrocycles and macropolycycles have been studied most extensively as anion receptor molecules. They bind a variety of anionic species (inorganic anions, car-

boxylates, phosphates, etc.) with stabilities and selectivities resulting from both electrostatic and structural effects.

Strong and selective complexes of the spherical *halide anions* are formed by macrobicyclic and by spherical macrotricyclic polyammonium receptors such as the protonated forms of **5** [32] (see **8**), of bis-tren **15** [51] and of related compounds [50, 52].

The hexaprotonated form of bis-tren, **15**—$6H^+$ complexes various monoatomic and polyatomic anions [51]. The crystal structures of four such anion cryptates provide a unique series of anion coordination patterns [51b]. The spherical halide ions are not complementary to the ellipsoidal receptor cavity and distort the structure, F^- being bound in a tetrahedral array of H-bonds and Cl^- and Br^- having octahedral coordination. The linear triatomic anion N_3^- has a shape and size complementary to the cavity of **15**—$6H^+$ and is bound inside by a pyramidal array of three H-bonds to each terminal nitrogen, forming the cryptate $[N_3^- \subset (\mathbf{15}\text{—}6H^+)]$, **16** (Figure 1). Thus, **15**—$6H^+$ is a molecular receptor recognizing linear triatomic species such as N_3^-, which is indeed bound much more strongly that other singly charged anions.



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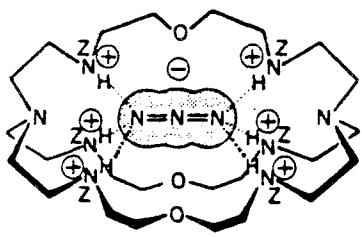


16

Carboxylates and *phosphates* bind to polyammonium macrocycles with stabilities and selectivities determined by the structure and charge of the two partners [50, 51, 53–57]. The design of receptor units for these functional groups is of much interest since they serve as anchoring sites for numerous biological substrates. Thus, strong complexes are obtained with macrobicyclic polyammonium pockets in which carboxylate (formate, acetate, oxalate, etc.) and phosphate groups interact with several ammonium sites [51]. The guanidinium group, which serves as a binding site in biological receptors, may form two

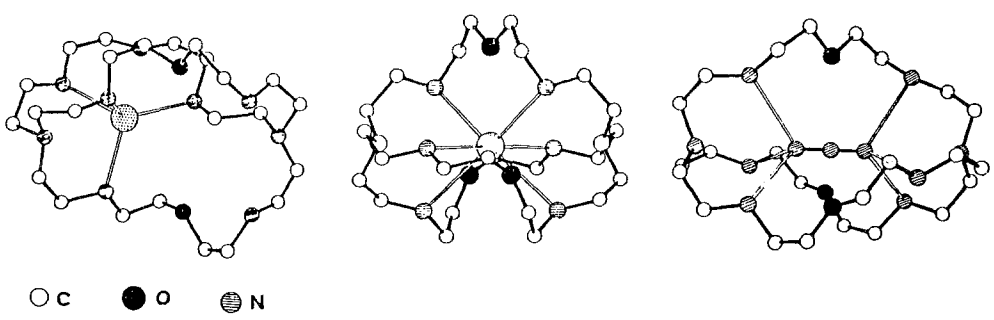


Fig. 1. Crystal structure of the anion cryptates formed by the hexaprontonated receptor molecule **15**—$6H^+$ with fluoride (left), chloride (centre) and azide (right) anions [51b].

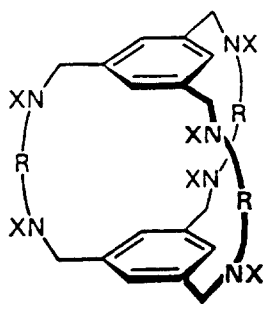
H-bonds with carboxylate and phosphate functions and has been introduced into acyclic [58] and macrocyclic [59] structures. Binding units mimicking the action of vancomycin are being sought [60].

Complexation of complex anions of transition metals such as the hexacyanides $M(CN)_6^{n-}$ yields second coordination sphere complexes, *supercomplexes* [53a] and affects markedly their electrochemical [61, 62] and photochemical [63] properties. Of special interest is the strong binding of adenosine mono-, di- and triphosphate (AMP, ADP and ATP) and related compounds that play a very important biological role [55–57].

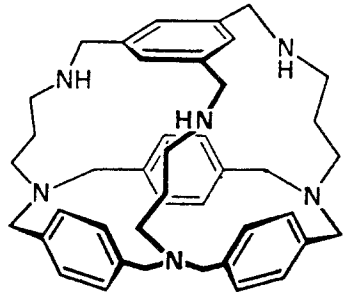
Cascade type binding [64] of anionic species occurs when a ligand first binds metal ions which then serve as interaction sites for an anion. Such processes occur for instance in lipophilic cation/anion pairs [65] and with Cu(II) complexes of bis-tren **15** and of macrocyclic polyamines [66].

Heteronuclear NMR studies give information about the electronic effects induced by anion complexation as found for chloride cryptates [67].

Complexation of various molecular anions by other types of macrocyclic ligands have been reported [50], in particular with cyclophane type compounds. Two such receptors of defined binding geometries are represented by the protonated forms of the macropolycycles **17** [68] and **18** [69].



17 (X=H, R=$(CH_2)_3$)



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Anion coordination chemistry has thus made very significant progress in recent years. The development of other receptor molecules possessing well defined geometrical and binding features will allow us to further refine the requirements for anion recognition, so as to yield highly stable and selective anion complexes with characteristic coordination patterns. Theoretical studies may be of much help in the design of anion receptors and in the *a priori* estimation of binding features, as recently illustrated by the calculation of the relative affinity of **5**—$4H^+$ for chloride and bromide ions [70].

4. Co-receptor Molecules and Multiple Recognition

Once binding units for specific groups have been identified, one may consider combining several of them within the same macropolycyclic architecture. Thus are formed polytopic co-receptor molecules containing several discrete binding subunits which may cooperate for the simultaneous complexation of several substrates or of a multiply bound (polyhapto) polyfunctional species. Suitable modification would yield co-catalysts or co-carriers performing a reaction or a transport on the bound substrate(s). Furthermore, because of their ability to perform multiple recognition and of the mutual effects of binding site

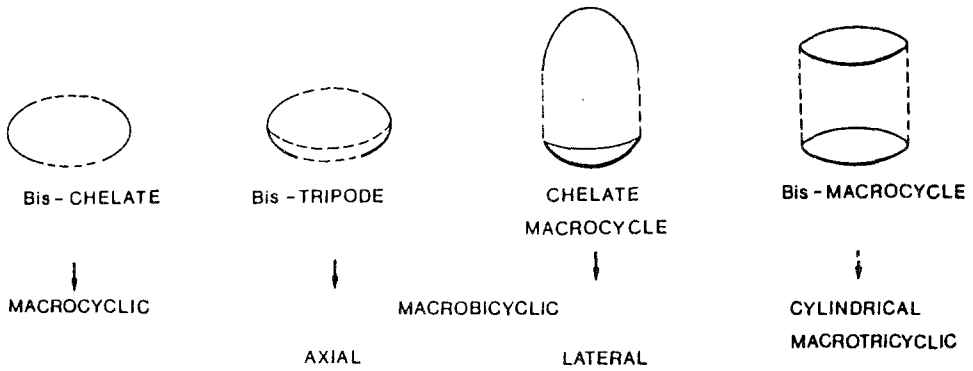


Fig. 2. Combination of chelating, tripodal and cyclic subunits into ditopic co-receptors of macrocyclic, axial and lateral macrobicyclic and cylindrical macrotricyclic types (from left to right).

occupation, such co-receptors provide entries into higher forms of molecular behaviour such as cooperativity, allostery and regulation as well as communication or signal transfer, if a species is released or taken up. Basic ideas and definitions concerning co-receptor molecules have been presented in more detail elsewhere [7].

The simplest class of co-receptors are those containing two binding subunits, ditopic co-receptors, which may belong to different structural types. Combination of chelating, tripodal and macrocyclic fragments yields macrocyclic, axial or lateral, macrobicyclic, or cylindrical macrotricyclic structures (Figure 2). Depending on the nature of these units the resulting coreceptors may bind metal ions, organic molecules or both.

4.1. DINUCLEAR AND POLYNUCLEAR METAL-ION CRYPTATES

Co-receptor molecules containing two or more binding subunits for metal ions form dinuclear or polynuclear cryptates in which the arrangement of the metal ions is determined by the macropolycyclic structure. Such complexes may present a multitude of new properties, such as interactions between cations, electrochemical and photochemical processes, fixation of bridging substrates etc., that are of interest both for bioinorganic modeling and for multicentre-multielectron reactions and catalysis.

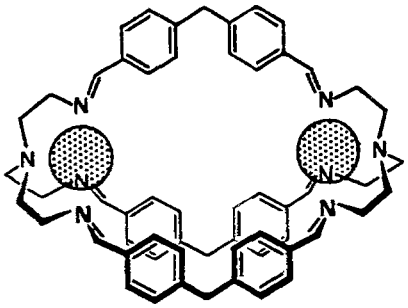
Dinuclear cryptates of ligands belonging to all structural types shown in Figure 2 have been obtained. This vast area will only be illustrated here by a few recent examples (for more details and references see earlier reviews [64, 71]).

Axial macrobicyclic ligands give dinuclear cryptates such as the bis-Cu(I) complex **19** formed by a large hexaimine structure obtained in a one step multiple condensation reaction; its crystal structure is shown in **20** [72].

Lateral macrobicycles are dissymmetric by construction and allow us to arrange metal centres of different properties in the same ligand. Thus, complexes of type **21** combine a redox centre and a Lewis acid centre for activation of a bound substrate [73].

'*Cluster cryptates*' may be formed by assembling metal ions and bridging species inside the molecular cavity of polytopic receptors. Thus, in the trinuclear Cu(II) complex **22** (crystal structure **23**) a [tris Cu(II), bis-μ_3-hydroxo] group is bound in the cavity of a tritopic macrocycle [74]. Modeling of biological iron–sulfur cluster sites may employ inclusion into appropriate macrocyclic cavities [75].

This inorganic aspect of supramolecular species represents in itself a field of research in which many novel structures and reactivities await to be discovered.



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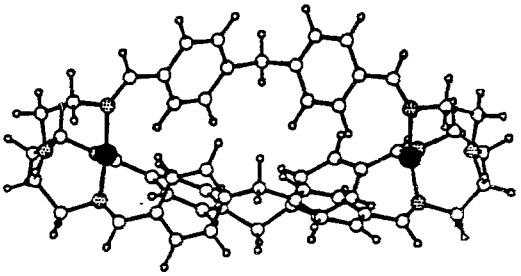

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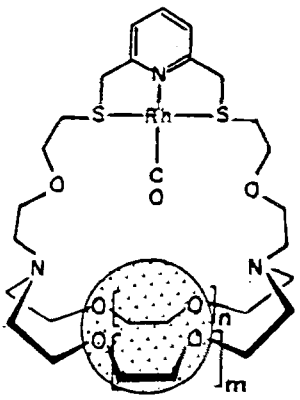
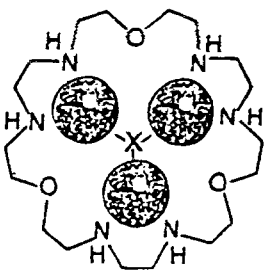


21 (m,n=0,1)



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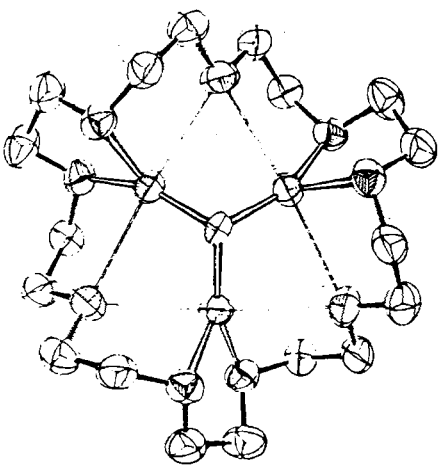

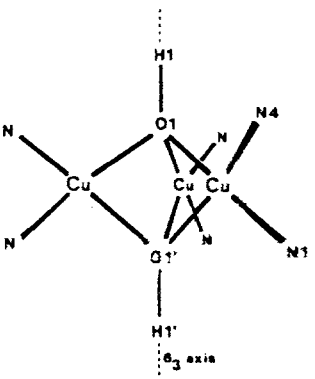

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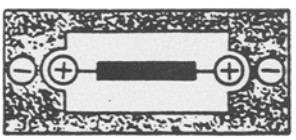
4.2. LINEAR RECOGNITION OF MOLECULAR LENGTH BY DITOPIC CO-RECEPTORS

Receptor molecules possessing two binding subunits located at the two poles of the structure will complex preferentially substrates bearing two appropriate functional groups at a distance compatible with the separation of the subunits. This distance complementarity amounts to a recognition of molecular length of the substrate by the receptor. Such *linear molecular recognition* of dicationic and dianionic substrates corresponds to the binding modes illustrated by **24** and **25**.



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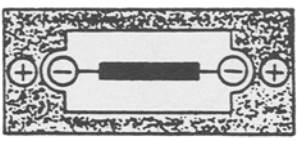

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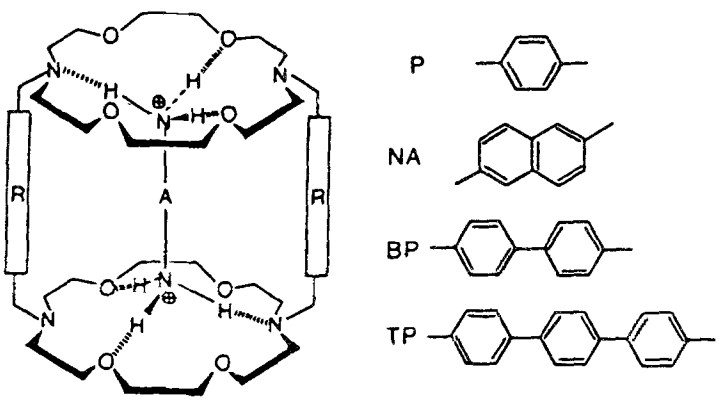
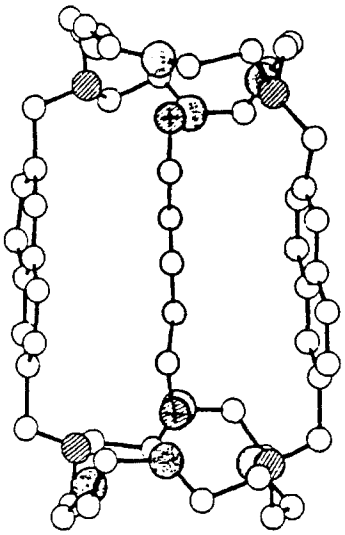
Incorporation of macrocyclic subunits that bind $-NH_3^+$ groups (see above) into cylindrical macrotricyclic [76] and macrotetracyclic [77] structures, yields ditopic co-receptors that form molecular cryptates such as **26** with terminal *diammonium cations* $^+H_3N-(CH_2)_n-NH_3^+$. In the resulting supermolecules the substrate is located in the central molecular cavity and anchored by its two $-NH_3^+$ groups in the macrocyclic binding sites, as shown by the crystal structure **27** (**26** with R = NA and A = $(CH_2)_5$) [78]. Changing the length of the bridges R in **26** modifies the binding selectivity in favour of the substrate of complementary length. NMR relaxation data have also shown that optimal partners present similar molecular motions in the receptor-substrate pair. Thus, complementarity in the supramolecular species expresses itself in both steric *and* dynamic fit [79].



26 (R=P, NA, BP, TP)



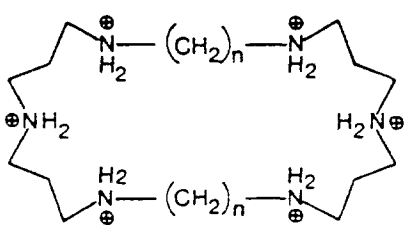
27

Dianionic substrates, the dicarboxylates $^{-}O_2C—(CH_2)_n—CO_2^{-}$, are bound with length discrimination by ditopic macrocycles such as **28**. These receptors contain two triammonium groups as binding subunits interacting with the terminal carboxylate functions, *via* a pattern schematically shown in **29** [80].

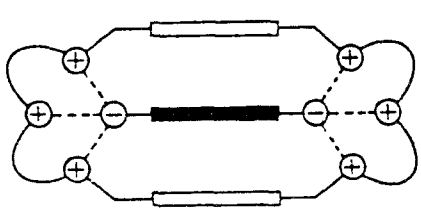
Thus, for both the terminal diammonium and dicarboxylate substrates, selective binding by the appropriate receptors describes a linear recognition process based on length complementarity in a ditopic binding mode. Important biological species such as polyamines, amino-acid and peptide diamines or dicarboxylates, etc. may also be bound selectively.

Numerous variations in the nature of the binding subunits or of the bridges linking them, are conceivable and may be tailored to specific complexation properties (see for instance [15, 81]). The development of *heterotopic receptors* may allow the binding of ion pairs [82] or zwitterionic species [83].

Studies on *dynamic coupling* [79, 84] between a receptor and a substrate are of much interest. Dynamic features of supermolecules correspond on the intermolecular level to the internal conformational motions present in molecules themselves and define molecular recognition processes by their dynamics in addition to their structural aspects.



28 (n=7,10)



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4.3. HETEROTOPIC CO-RECEPTORS. SPELEANDS, AMPHIPHILIC RECEPTORS

Combination of binding subunits of different nature yields heterotopic receptors that may bind substrates by interacting simultaneously with cationic, anionic or neutral sites, making use of electrostatic and Van der Waals forces as well as of solvophobic effects.

The natural cyclodextrins were the first receptor molecules whose binding properties towards organic molecules, yielded a wealth of results on physical and chemical features of molecular complexation [21, 85].

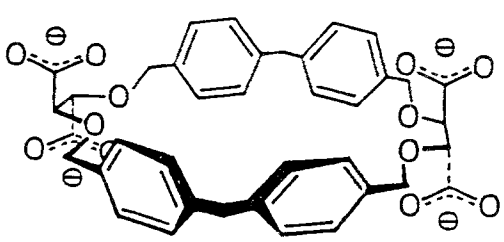
Numerous types of synthetic macrocyclic receptors that contain various organic groups and polar functions, have been developed in recent years. They complex both charged and uncharged organic substrates. Although the results obtained often describe mere binding rather than actual recognition, they have provided a large body of data that allow us to analyze the basic features of molecular complexation and the properties of structural fragments to be used in receptor design. We describe here mainly some of our own results in this area, referring the reader to specific reviews of the subject [20, 86].

Synergetical operation of electrostatic and hydrophobic effects may occur in *amphiphilic receptors* combining charged polar sites with organic residues, which shield the polar sites from solvation and increase electrostatic forces. Such macropolycyclic structures containing polar binding subunits maintained by apolar shaping components, termed *speleands*, yield molecular cryptates, (*speleates*), by substrate binding [87].

Thus, macrocycle **30** incorporating four carboxylate groups and two diphenylmethane units [88], not only forms very stable complexes with primary ammonium ions, but also strongly binds secondary, tertiary and quaternary ammonium substrates. In particular, it complexes *acetylcholine*, giving information about the type of interactions that may play a role in biological acetylcholine receptors, such as the combination of negative charges with hydrophobic walls. Similar effects operate in other anionic receptors complexing quaternary ammonium cations [86a, 89]. Extensive studies have been conducted on the complexation of heterocyclic ammonium ions such as diquat by macrocylic polyether receptors [90].

The $CH_3—NH_3^+$ cation forms a selective speleate **31**, by binding to the [18]—N_3O_3 subunit of a macropolycycle maintained by a cyclotriveratrylene shaping component. The tight intramolecular cavity efficiently excludes larger substrates [87, 91].

Amphiphilic type of binding also occurs for molecular anionic substrates [20, 86, 92]. Charged heterocyclic rings systems such as those derived from the pyridinium group



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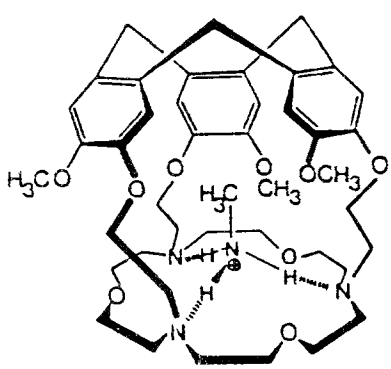
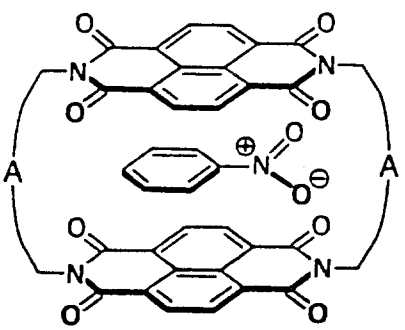


31

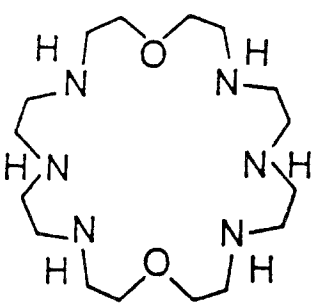
represent an efficient way to introduce simultaneously electrostatic interactions, hydrophobic effects, structure and rigidity in a molecular receptor; in addition they may be electroactive and photoactive [93]. Even single planar units such as diaza-pyrenium dications bind flat organic anions remarkably well in aqueous solution, using electrostatic interactions as well as hydrophobic stacking [93]. A macrocycle containing four pyridinium sites was found to strongly complex organic anions [94].

Receptors of the *cyclointercaland* type, that incorporate intercalating units into a macrocyclic system, are of interest for both the binding of small molecules and their own (selective) interaction with nucleic acids. A *cyclo-bis-intercaland* has been found to form an intercalative molecular cryptate **32** in which a nitrobenzene molecule is inserted between the two planar subunits of the receptor [95]. Such receptors are well suited for the recognition of substrates presenting flat shapes and become of special interest if intercalating dyes are incorporated [96].

Fitting the macrocyclic polyamine **33** with a side chain bearing a 9-aminoacridine group yields a co-receptor that may display both anion binding *via* the polyammonium subunit and stacking interaction by the intercalating dye. It interacts with both the triphosphate and the adenine groups of ATP and provides in addition a catalytic site for its hydrolysis (see below) [97].



32 (A=$(CH_2)_8$)



33

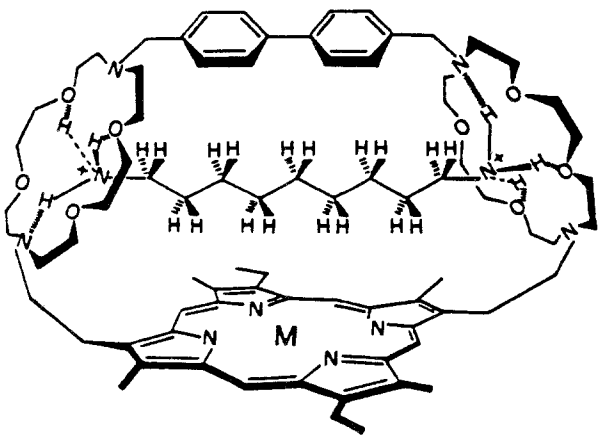
Flat aromatic heterocyclic units bearing lateral acid and amide functional groups, function as receptors that perform size and shape recognition of complementary substrates within their molecular cleft [17b]. Receptor units containing heterocyclic groups such as 2,6-diaminopyridine [98a] or a nucleic base combined with an intercalator [98b] may lead to recognition of nucleotides *via* base pairing [98c].

The spherically shaped *cryptophanes* allow the study of recognition between neutral receptors and substrates, and in particular the effect of molecular shape and volume complementarity on selectivity [99].

4.4. MULTIPLE RECOGNITION IN METALLO-RECEPTORS

Metallo-receptors are heterotopic co-receptors that are able to bind both metal ions and organic molecules by means of substrate-specific units.

Porphyrin and α,α'-bipyridine (bipy) groups have been introduced as metal ion binding units in macropolycyclic coreceptors containing also macrocyclic sites for anchoring $-NH_3^+$groups [64, 71, 100]. These receptors form mixed-substrate supermolecules by simultaneously binding metal ions and diammonium cations as shown in **34** [101]. Metalloreceptors and the supermolecules which they form, thus open up a vast area for the study of interactions and reactions between co-bound organic and inorganic species. In view of the number of metal ion complexes known and of the various potential molecular substrates to be bound, numerous types of metalloreceptors may be imagined which would be of interest as abiotic chemical species or as bioinorganic model systems.



34 (M=Zn)

5. Supramolecular Reactivity and Catalysis

Reactivity and catalysis represent major features of the functional properties of supramolecular systems. Molecular receptors bearing appropriate reactive groups in addition to binding sites, may complex a substrate (with given stability, selectivity and kinetic features), react with it (with given rate, selectivity and turnover) and release the products, thus regenerating the reagent for a new cycle (Figure 3).

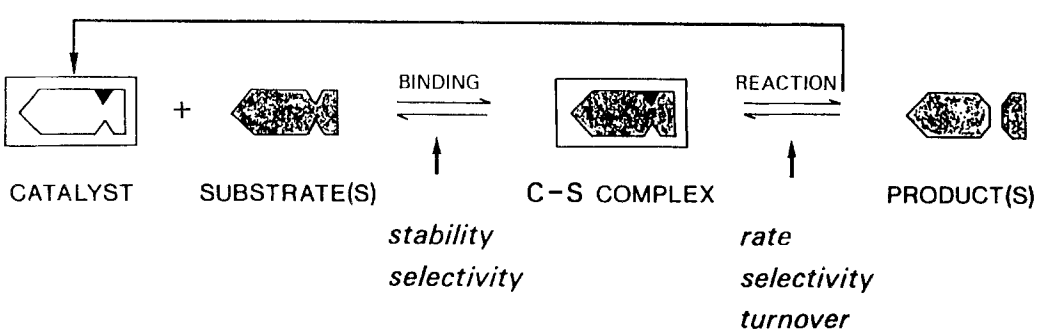


Fig. 3. Schematic representation of the supramolecular catalysis process.

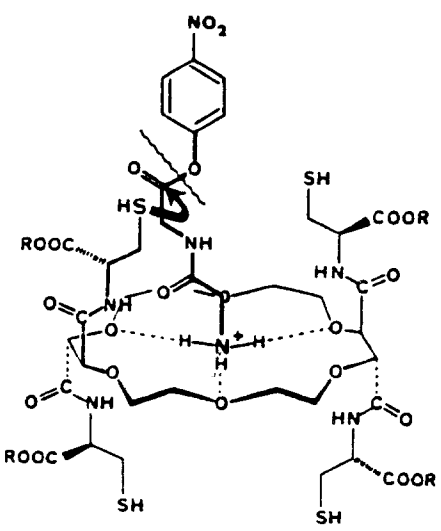
Supramolecular reactivity and catalysis thus involve two main steps: – *binding* which selects the substrate, followed by transformation of the bound species into products within the supermolecule formed. Both steps take part in the molecular *recognition* of the *productive* substrate and require the correct molecular information in the reactive receptor [1]. Compared to molecular catalysis, a binding step is involved that selects the substrate and precedes the reaction itself.

The design of efficient and selective supramolecular reagents and catalysts may give mechanistic insight into the elementary steps of catalysis, provide new types of chemical reagents and effect reactions that reveal factors contributing to enzymatic catalysis. This led to numerous investigations that made use mainly of reagents based on functionalized α-cyclodextrin, macrocyclic polyethers and cyclophanes [84, 85, 102, 103].

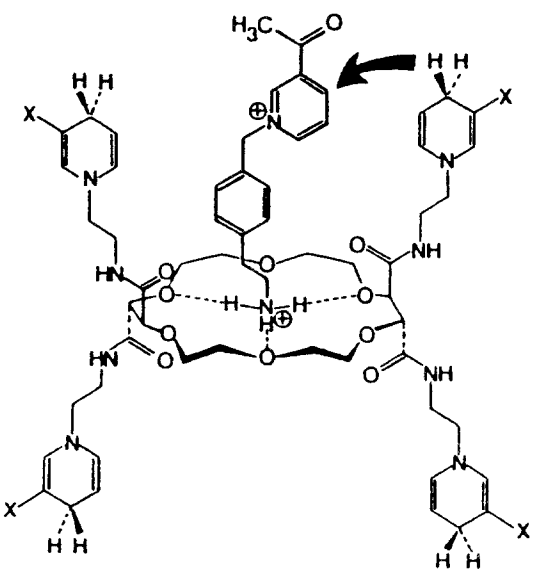
5.1. CATALYSIS BY REACTIVE CATION RECEPTOR MOLECULES

Ester cleavage processes have been most frequently investigated in enzyme model studies. Macrocyclic polyethers fitted with side chains bearing thiol groups cleave activated esters with marked rate enhancements and chiral discrimination between optically active substrates [104–106]. The tetra-(*L*)-cysteinyl derivative of macrocycle **12c** binds *p*-nitrophenyl (PNP) esters of amino-acids and peptides, and reacts with the bound species, releasing *p*-nitrophenol as shown in **35** [105]. The reaction displays (i) substrate selectivity with (ii) marked rate enhancements in favour of dipeptide ester substrates, (iii) inhibition by complexable metal cations that displace the bound substrate, (iv) high chiral recognition between enantiomeric dipeptide esters, (v) slow but definite catalytic turnover.

Binding of pyridinium substrates to a macrocycle of type **12c** bearing 1,4-dihydropyridyl side chains led to enhanced rates of *hydrogen transfer* from dihydropyridine to pyridinium within the supramolecular species **36** formed. The first order intracomplex reaction was inhibited and became bimolecular on displacement of the bound substrate by complexable cations [107].



35 (R=CH_3)



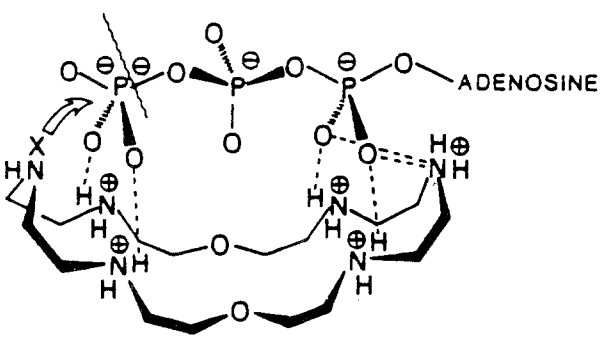
36 (X=CONHnBu)

Activation and orientation by binding was observed for the hydrolysis of *O*-acetylhydroxylamine. $CH_3COONH_3^+$ forms such a stable complex with the macrocyclic tetracarboxylate **12b** [44], that it remains protonated and bound even at neutral pH, despite the low pK_a of the free species (~ 2.15). As a consequence, its hydrolysis is accelerated and exclusively gives acetate and hydroxylamine, whereas in the presence of K^+ ions, which displace the substrate, the latter rearranges to acetylhydroxamic acid $CH_3CONH—OH$ ($\sim 50\%$) [108]. Thus, strong binding may be sufficient for markedly accelerating a reaction and affecting its course, a result that also bears on enzyme catalyzed reactions.

5.2. CATALYSIS BY REACTIVE ANION RECEPTOR MOLECULES

The development of anion coordination chemistry and of anion receptor molecules has made it possible to perform molecular catalysis on anionic substrates of chemical and biochemical interest [50], such as adenosine triphosphate (ATP).

ATP hydrolysis was found to be catalyzed by a number of protonated macrocyclic polyamines. In particular [24]—N_6O_2, **33**, strongly binds ATP and markedly accelerates its hydrolysis to ADP and inorganic phosphate over a wide pH range [109]. The reaction presents first-order kinetics and is catalytic with turnover. It proceeds *via* initial formation of a complex between ATP and protonated **33**, followed by an intracomplex reaction which may involve a combination of acid, electrostatic, and nucleophilic catalysis. Structure **37** represents one possible binding mode of the ATP-**33** complex and indicates how cleavage of the terminal phosphoryl groups might take place. A transient intermediate identified as phosphoramidate **38**, is formed by phosphorylation of the macrocycle by ATP and is subsequently hydrolyzed. Studies with analogues of ATP indicated that the mechanism was dissociative in character within a pre-associative scheme resulting from receptor-substrate binding [110]. In this process catalyst **33** presents prototypical ATPase activity, i.e. it behaves as a proto-ATPase.



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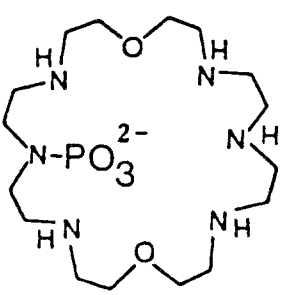

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5.3. CO-CATALYSIS: CATALYSIS OF SYNTHETIC REACTIONS

A further step lies in the design of systems capable of inducing *bond formation* rather than bond cleavage, thus effecting *synthetic* reactions as compared to degradative ones. To this end, the presence of several binding and reactive groups is essential. Such is the case for

coreceptor molecules in which subunits may cooperate for substrate binding and transformation [7]. They should be able to perform *cocatalysis* by bringing together substrate(s) and cofactor(s) and mediating reactions between them within the supramolecular structure (Figure 4).

A process of this type has been realized recently [111]. Indeed, when the same macrocycle **33** used in the studies of ATP hydrolysis was employed as catalyst for the hydrolysis of acetylphosphate (AcP = $CH_3COOPO_3^{2-}$), it was found to mediate the *synthesis of pyrophosphate* from AcP. Substrate consumption was accelerated and catalytic with turnover. The results obtained agree with a catalytic cycle involving the following steps: (i) substrate AcP binding by the protonated molecular catalyst **33**; (ii) phosphorylation of **33** within the supramolecular complex, giving the phosphorylated intermediate PN 38; (iii) binding of the substrate HPO_4^{2-} (P); (iv) phosphoryl transfer from PN to P with formation of pyrophosphate PP (Figure 5); (v) release of the product and of the free catalyst for a new cycle.

The fact that **33** is a ditopic coreceptor containing two diethylenetriamine subunits is of special significance for both PN and PP formation. These subunits may cooperate in binding AcP and activating it for phosphoryl transfer *via* the ammonium sites, in providing an unprotonated nitrogen site for PN formation, as well as in mediating phosphoryl transfer from PN to P. Thus **33** would combine electrostatic and nucleophilic catalysis in a defined structural arrangement suitable for PP synthesis *via* two successive phosphoryl transfers, displaying protokinase type activity (Figure 5). This bond-making process extends supramolecular reactivity to cocatalysis, mediating *synthetic reactions* within the supramolecular entities formed by coreceptor molecules. The formation of PP when ATP is hydrolyzed by **33** in the presence of divalent metal ions has also been reported [112].

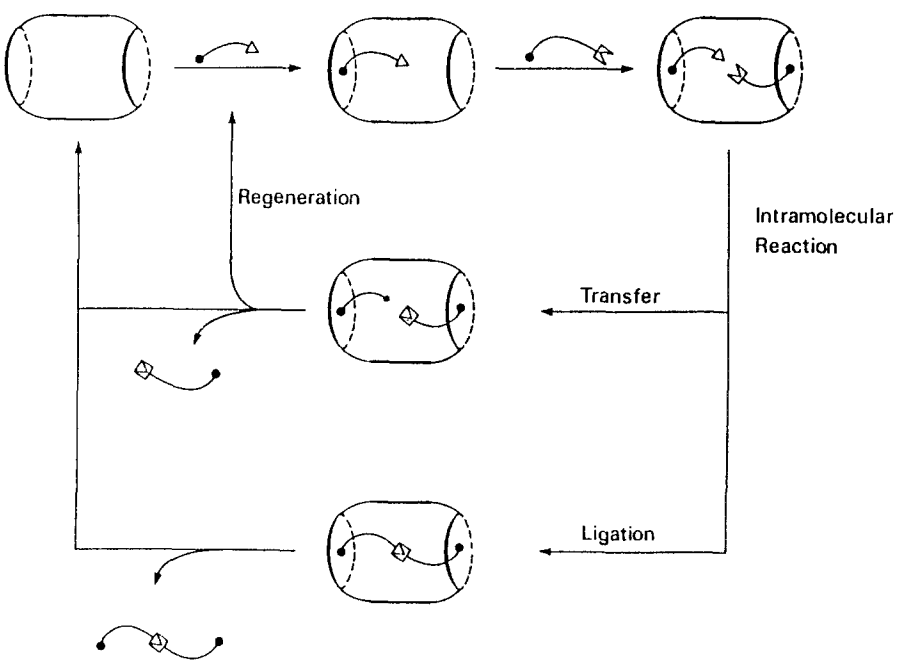


Fig. 4. Schematic illustration of co-catalysis processes: group transfer and ligation reactions occurring within the supramolecular complex formed by the binding of substrates to the two macrocyclic subunits of a macrotricyclic co-receptor molecule.

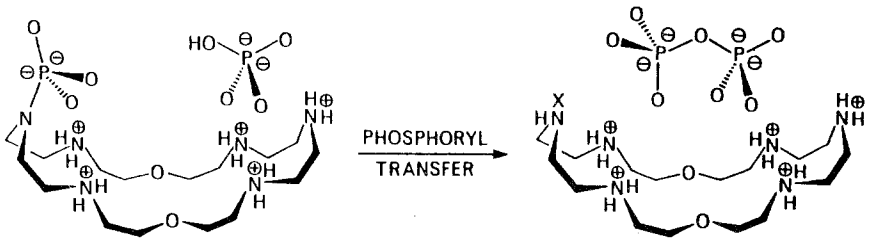


Fig. 5. Co-catalysis: pyrophosphate synthesis by phosphoryl transfer mediated by macrocycle **33** *via* the phosphorylated intermediate **38**.

Functionalized macrocyclic polyethers were used for peptide bond formation in two successive intra-complex steps [113] and a thiazolium bearing macrobicyclic cyclophane was shown to effect supramolecular catalysis of the benzoin condensation of two benzaldehyde molecules [114].

The systems described above possess the properties that define supramolecular reactivity and catalysis: substrate recognition, reaction within the supermolecule, rate acceleration, inhibition by competitively bound species, structural and chiral selectivity and catalytic turnover. Many other types of processes may be imagined. Thus, supramolecular catalysis of the hydrolysis of unactivated esters and of amides presents a challenge [115] that chemistry has met in natural enzymatic reagents but not yet in abiotic catalysts. Designing modified enzymes by chemical mutation [116], or by protein engineering [117] and producing catalytic proteins by antibody induction [118] represent biochemical approaches to artificial catalysts. Of particular interest is the development of supramolecular catalysts performing synthetic reactions that create new bonds rather than cleave them. By virtue of their multiple binding features co-receptors open the way to the design of co-catalysts for ligation, metallo-catalysis or co-factor reactions, that act on two or more co-bound and spatially oriented substrates.

Supramolecular catalysts are by nature *abiotic* reagents, chemical catalysts that may perform the same *overall* processes as enzymes, without following the detailed way in which the enzymes actually realize them. This chemistry may develop reagents that effect highly efficient and selective processes that enzymes do not perform or realize enzymatic ones in conditions in which enzymes do not operate.

6. Transport Processes and Carrier Design

The organic chemistry of membrane transport processes and of carrier molecules has only recently been developed, although the physico-chemical features and the biological importance of transport processes have long been recognized. The design and synthesis of receptor molecules binding selectively organic and inorganic substrates made available a range of compounds which, if made membrane soluble, could become carrier molecules and induce selective transport by rendering membranes permeable to the bound species. Thus, transport represents one of the basic functional features of supramolecular species together with recognition and catalysis [2, 103].

The chemistry of transport systems comprises three main aspects: to design transport effectors, to devise transport processes and to investigate their applications in chemistry and in biology. Selective membrane permeability may be induced either by *carrier molecules* or by *transmembrane channels* (Figure 6).

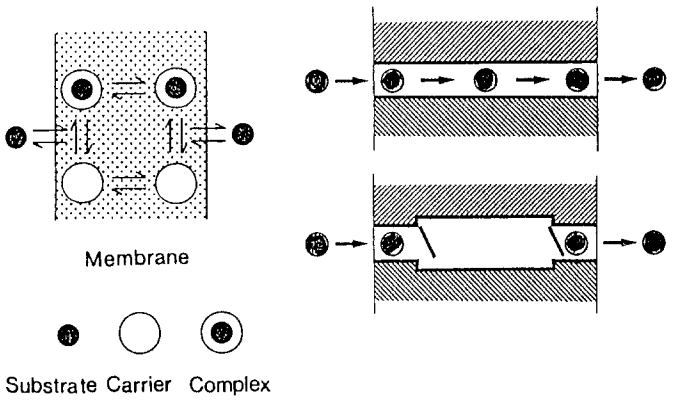


Fig. 6. Transport processes: carrier mediated (left), channel (top right), gated channel (bottom right).

6.1. CARRIER-MEDIATED TRANSPORT

Carrier-mediated transport consists in the transfer of a substrate across a membrane, facilitated by a carrier molecule. The four step cyclic process (association, dissociation, forward and back-diffusion) (Figure 6) is a *physical catalysis* operating a translocation on the substrate just as chemical catalysis effects a transformation into products. The carrier is the transport catalyst and the active species is the carrier-substrate supermolecule. Transport is a three-phase process, whereas homogeneous chemical and phase-transfer catalyses are respectively single phase and two-phase processes.

Carrier design is the major feature of the organic chemistry of membrane transport since the carrier determines the nature of the substrate, the physico-chemical features (rate, selectivity) and the type of process (facilitated diffusion, coupling to gradients and flows of other species, active transport). The carrier must be highly selective, present appropriate exchange rates and lipophilic/hydrophilic balance and bear functional groups suitable for flow coupling. The transport process depends also on the nature of the membrane, the concentrations in the three phases and the other species present. More detailed considerations on these internal and external factors that affect transport processes may be found in earlier reports [1, 103, 120, 121].

Our initial work on the *transport of amino-acids*, dipeptides and acetylcholine through a liquid membrane employed simple lipophilic surfactant type carriers. It was aimed at the physical organic chemistry of transport processes, exploring various situations of transport coupled to flows of protons, cations or anions in concentration and pH gradients [122].

Selective *transport of metal cations*, mainly of alkali cations, has been a major field of investigation, spurred by the numerous cation receptors of natural or synthetic origin that are able to function as cation carriers [24, 103, 120, 121, 123, 124].

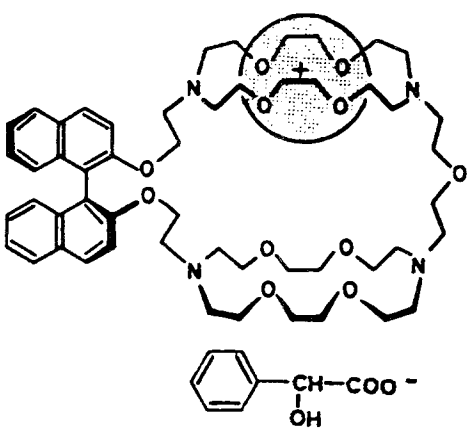
Cryptands of type **1**–**3** and their derivatives carry alkali cations [125], even under conditions in which natural or synthetic macrocycles are inefficient. The selectivities observed depend on the structure of the ligand, the nature of the cation and the type of co-transported counter anion. Designed structural changes allow us to transform a cation receptor into a cation carrier [120, 125]. The results obtained with cryptands indicated that there was an optimal complex stability and phase transfer equilibrium for highest transport rates [125]. Combined with data for various other carriers and cations, they gave a bell-shaped

dependence of transport rates on extraction equilibrium (see Figure 3 in [120]), with low rates for very small or very large (carrier saturation) extraction and highest rates for half-filled carriers [120, 125]. Kinetic analyses allowed us to relate the experimental results to the dependence of transport rates and selectivities on carrier properties [124, 126, 127]. Detailed studies of the transport of K^+ and Na^+ by lipophilic derivatives of **2** and **3** in vesicles centred on the efficiency, the selectivity and the mechanism of the processes [128].

Modifying the nature of the binding sites allows the selective transport of other cations such as toxic metal ions. Macrocyclic polyethers carry organic primary ammonium cations, in particular physiologically active ones [129]. The nature of the counterion and the concentrations of species strongly influence rates of transport and may affect the selectivity [120, 125].

Anion transport may be effected by lipophilic ammonium ions or by metal complexes [130] acting as anion receptors. Progress in anion coordination chemistry should provide a range of anion carriers that will help to develop this area of transport chemistry. The selective transport of carboxylates and phosphates is of great interest. Some results, references and suggestions have been given earlier [120].

Cation-anion co-transport was effected by a chiral macrotricyclic cryptand that carried simultaneously an alkali cation and a mandelate anion, see **39** [82]. Employing a cation and an anion carrier together should give rise to *synergetic transport* with double selection, by facilitating the flow of both components of a salt (see the electron-cation symport, below).



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Selective transport of *amino-acids* occurs with a macrotricycle containing an internal phosphoric acid group [83b] and with a convergent dicarboxylic acid receptor [83c]. *Neutral* molecules are carried between two organic phases through a water layer by water soluble receptors containing a lipophilic cavity [132].

It is clear that numerous facilitated transport processes may still be set up, especially for anions, salts or neutral molecules and that the active research in receptor chemistry will make available a variety of carrier molecules. Of special interest are those transport effectors derived from coreceptors, that allow coupled transport, *co-transport*, to be performed.

6.2. COUPLED TRANSPORT PROCESSES

A major goal in transport chemistry is to design carriers and processes that involve the coupled flow of two (or more) species either in the same (symport) or in opposite (antiport) direction. Such parallel or antiparallel vectorial processes would allow the setting up of pumped systems in which a species is carried in the potential created by physico-chemical gradients of electrons (redox gradient), protons (pH gradient) or other species (concentration gradient). To this end, either two or more individual carriers for different species may be used simultaneously or the appropriate subunits may be introduced into a single species, a *co-carrier*.

6.2.1. *Electron Coupled Transport in a Redox Gradient*

Electron-cation symport has been realized in a double carrier process where the coupled parallel transport of electrons and metal cations was mediated by an electron carrier and a selective cation carrier [133]. The transport of electrons by a nickel complex in a redox gradient was the electron pump for driving the selective transport of K^+ ions by a macrocyclic polyether (Figure 7). The process has the following features: – active K^+ transport and coupled electron flow; two cooperating carriers acting synergetically; – a redox pump; –a selection process by the cation carrier and regulation by the cation/carrier pair. This system represents a prototype for the design of other multicarrier coupled transport processes. Electron transport with quinone carriers involves a ($2e^-$, $2H^+$) symport [134, 135].

Electron-anion antiport has been realized for instance with carriers such as ferrocene or alkylviologens [136]. The latter have been used extensively in light driven systems and in studies on solar energy conversion.

6.2.2. *Proton Coupled Transport in a pH Gradient*

Carriers bearing negatively charged groups may effect cation antiport across membranes so that if one cation is a proton, a proton pump may be set up in a pH gradient. This has been realised for alkali cations with natural or synthetic carboxylate bearing ionophores [137].

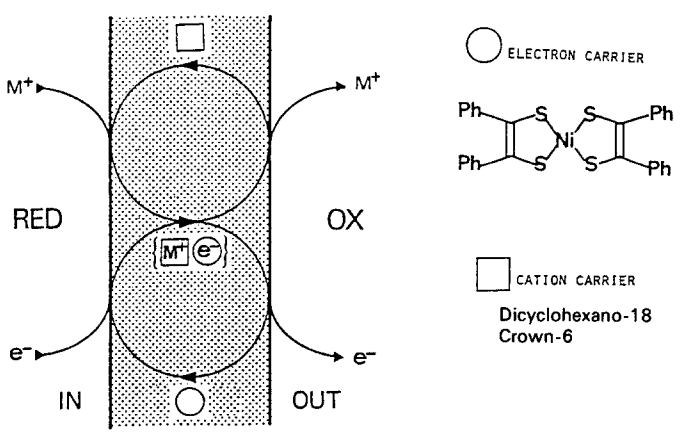
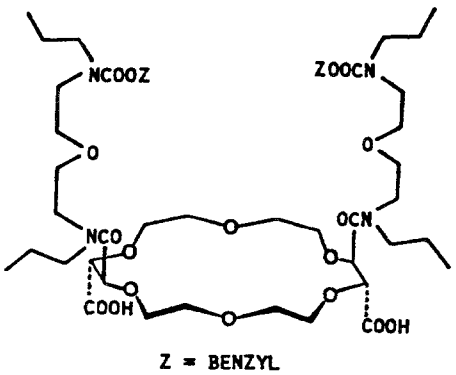


Fig. 7. Electron-cation coupled transport: redox driven electron-cation symport via an electron carrier (nickel complex) and a selective cation carrier (macrocyclic polyether) RED: potassium dithionite, OX: potassium ferricyanide [133].

A case of special interest is that of the transport of divalent ions such as calcium, versus monovalent ones. The lipophilic carrier **40** containing a *single* cation receptor site and *two* ionizable carboxylic acid groups, was found to transport selectively Ca^{2+} in the dicarboxylate form and K^+ when monoionized, thus allowing pH control of the process. This striking change in transport features involves *pH regulation* of Ca^{2+}/K^+ selectivity in a competitive (Ca^{2+}, K^+) symport coupled to a (Ca^{2+}, $2H^+$) and (K^+, H^+) antiport in a pH gradient, which provides a proton pump (Figure 8) [138].



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This system demonstrates how carrier design allows us to endow transport processes with regulation of rates and selectivity as well as coupling to energy sources, for transport of a species against its own concentration gradient.

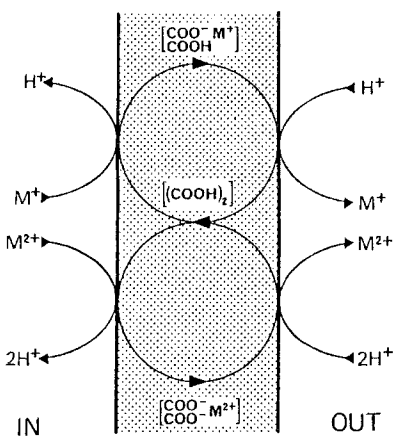


Fig. 8. Competitive divalent/monovalent cation symport coupled to a $M^{2+}/2H^+$ and M^+/H^+ antiport in a pH gradient by a macrocyclic carrier such as **40**; the state of the carrier is indicated as diprotonated $[(CO_2H)_2]$ or complexed $[(CO_2^-)_2, M^{2+}]$ and $[(CO_2H)(CO_2^-), M^+]$.

6.2.3. *Light Coupled Transport Processes*

Light driven transport may be brought about by photogeneration of a species that will induce the process or perturb it.

This has been achieved in a *light induced electron transport* process involving the proflavine sensitized photogeneration of reduced methylviologen MV^+ which transfers electrons to a quinone type carrier contained in the membrane [135]. Light driven (electron, cation) symport occurs when combining this system with the (nickel complex, macrocycle) process described above [139]. The increased lipophilicity of reduced viologens facilitates electron and phase transfer [140]. Such processes are also of interest for solar energy storage systems where electron permeable membranes separate the reductive and oxidation components. Photocontrol of ion extraction and transport has been realized with macrocyclic ligands undergoing a structural change under irradiation, between two forms having different ion affinities [141].

The results obtained on coupled transport processes stress the role of co-carrier systems capable of transporting several substrates with coupling to physical and chemical energy sources.

6.3. TRANSFER VIA TRANSMEMBRANE CHANNELS

Transmembrane channels represent a special type of multiple-unit effector allowing the passage of ions or of molecules through membranes by a flow or site-to-site hopping mechanism. They play an important role in biological transport. Natural and synthetic peptide channels (gramicidine A, alamethicin) for cations have been studied [142, 143].

Artificial *cation channels* would provide fundamental information on the mechanism of cation flow and channel conduction. A solid state model of cation transfer inside a channel is provided by the crystal structure of the KBr complex of **12c** ($Y = Y' = CH_3$) which contains stacks of macrocycles with cations located alternatively inside and above a macrocyclic unit, like a frozen picture of cation propagation through the 'channel' defined by the stack [144].

A polymeric stack of macrocycles has been synthesized [145] and a cyclodextrin based model of a half-channel has been reported [146]. A derivative of monensin, an acyclic polyether ionophore, forms lithium channels in vesicles [147] which may be sealed by diammonium salts [148].

Cylindrical macrotricycles such as **26** (substrate removed) represent the basic unit of a cation channel based on stacks of linked macrocycles; they bind alkali cations [149] and cation jumping processes between the top and bottom rings have been observed [150]. Theoretical studies give insight into the molecular dynamics [151] of ion transport and the energy profiles [152] in cation channels.

Electron channels, as transmembrane wires, represent the channel type counterpart to the mobile electron carriers discussed above and will be considered below. *Anion channels* may also be envisaged.

Thus, several types of studies directed towards the development of artificial ion channels and the understanding of ion motion in channels are in progress. These effectors deserve and will receive increased attention, in view also of their potential role in molecular ionics (see below).

A further step in channel design must involve the introduction of (proton, ion, redox or light activated) *gates and control elements* for regulating opening and closing, rates and

selectivity. In this respect, one may note that ionizable groups on mobile carriers (as in **40**, see above) are, for these effectors, the counterpart of gating mechanisms in channels.

In conclusion, transport studies open ways to numerous developments of this chemically and biologically most important function: effector design, analysis of elementary steps and mechanisms, coupling to chemical potentials, energy and signal transduction, models of biological transport processes, construction of vesicular microreactors and artificial cells, etc., with a variety of possible applications, for instance in separation and purification or in batteries and systems for artificial photosynthesis.

By the introduction of polytopic features, which may include selective binding subunits as well as gating components for flow regulation, the design of co-carriers and of artificial molecular channels should add another dimension to the chemistry of the effectors and mechanisms of transport processes.

7. From Endo-receptors to Exo-receptors. Exo-Supramolecular Chemistry

The design of receptor molecules has mainly relied on macrocyclic or macropolycyclic architectures (see above) and/or on rigid spacers or templates (see for instance [17b, 26, 76–79, 81b, 83b]) that allow us to position binding sites on the walls of molecular cavities or clefts in such a way that they converge towards the bound substrate. The latter is more or less completely surrounded by the receptor, forming an *inclusion* complex. This widely used principle of *convergence* defines a convergent or *endo-supramolecular chemistry* with endo-receptors effecting endo-recognition. Biological analogies are found in the active sites of enzymes where a small substrate binds inside a cavity of a large protein molecule.

The opposite point of view would be to make use of an external *surface* with protuberances and depressions, rather than an internal cavity, as the substrate receiving site. This would correspond to the change from a convergent to a *divergent* or *exo-supramolecular chemistry* and from endo- to *exo-receptors*. Receptor-substrate binding then occurs by surface-to-surface interaction, that may be termed *affixion* and symbolized by $\|$ or by the mathematical symbol of intersection (if there is notable interpenetration of the surfaces) [153], $[\rho \,\|\, \sigma]$ and $[\rho \cap \sigma]$ respectively. *Exo-recognition* with strong and selective binding requires a large enough contact area and a sufficient number of interactions as well as geometrical and site (electronic) complementarity between the surfaces of ρ and σ. Such a mode of binding finds biological analogies in protein-protein interactions, for instance at the antibody-antigen interface where the immunological recognition processes occur [154].

One may note that exo-recognition includes recognition between (rather large) bodies of similar size as well as recognition at interfaces with monolayers, films, membranes, cell walls, etc.

7.1. METALLO-EXORECEPTORS. METALLONUCLEATES

In order to reinforce the binding strength one may think of introducing one or more interaction *poles*, for instance electrical charges, generating strong electrostatic forces. Such could be the case for a metal complex whose central cation would be the electrostatic pole and whose external surface could bear functional groups containing the molecular information required for recognizing the partner. In addition, the metal cation provides a further way of organizing the structure by virtue of its coordination geometry (tetrahedral, square-planar, octahedral, etc.) which leads to a given arrangement of the external interaction sites (Figure 9).

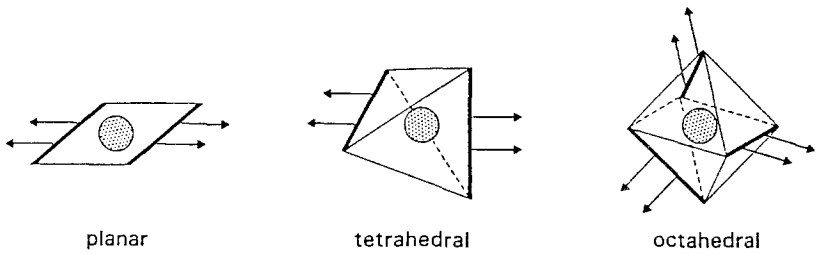
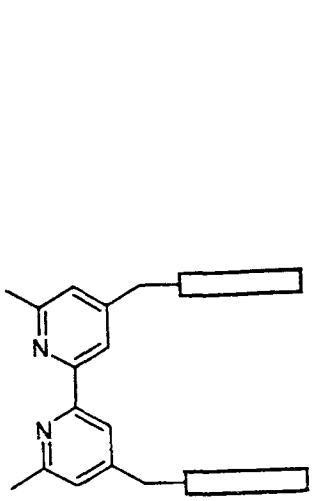


Fig. 9. Schematic representation of the arrangement of external interaction sites (represented by arrows) around a metal ion of given coordination geometry in mononuclear metallo-exoreceptors.

As a first approach to receptor design along these lines, specific groups, selected for their information content, have been attached to functionalized α,α'-bipyridines, giving ligands of type **41** that form metal complexes of defined geometry and physico-chemical properties. With nucleosides, species such as the bis-adenosine derivative **42** are obtained [155]. The resulting positively charged, *metallonucleate* complexes should interact strongly and selectively with the negatively charged oligonucleotides and nucleic acids, the fixation site depending on the nature and disposition of the external nucleosides. Double helical metallonucleates [155] may be derived from the helicates describes below. Numerous variations may be imagined for the external groups (intercalators, amino-acids, oligo-peptides, reactive functions) so as to yield metal complexes displaying selective fixation and reactivity (chemical, photochemical) determined by the nature of the attached sites.



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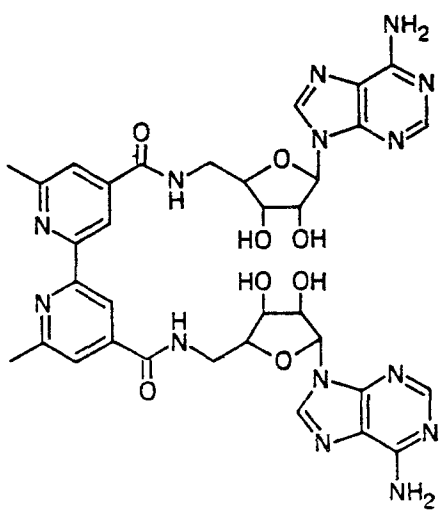

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7.2. MOLECULAR MORPHOGENESIS

The design of exo-receptors requires means of generating defined external molecular shapes. This may be achieved in a number of ways, namely by stepwise synthesis of

molecular architectures or by assembling on metal templates that impose a given coordination geometry, as noted above.

Another approach to such controlled molecular morphogenesis, is provided by the generation of globular molecules such as the 'starburst dendrimers' [156] and the 'arborols' [157], based on branched structures formed *via* cascade processes. Starting from a given core, it may be possible to produce a molecule of given size and external shape. On the polymolecular level, this may be related to the generation of shapes and structures in two-dimensional lipid monolayers [158] and in aggregates of amphiphilic molecules [159] (see also below).

8. From Supermolecules to Polymolecular Assemblies

Molecular chemistry is the domain of (more or less) independent *single* molecules. *Supramolecular chemistry* may be divided into two broad, partially overlapping areas; – supermolecules are well-defined *oligo*molecular species that result from the intermolecular association of a few components (a receptor and its substrate (s following a built-in Aufbau scheme based on the principles of molecular recognition; – *molecular assemblies* are polymolecular systems that result from the spontaneous association of a non-defined number of components into a specific phase having more or less well-defined microscopic organization and macroscopic characteristics depending on its nature (layers, membranes, vesicles, micelles, mesomorphic phases etc. [160]).

Continuous progress is being made in the design of synthetic molecular assemblies, based on a growing understanding of the relations between the features of the molecular components (structure, sites for intermolecular binding, etc.), the characteristics of the processes which lead to their association and the supramolecular properties of the resulting polymolecular assembly.

Molecular organization, self-assembling and cooperation, construction of multilayer films [161–164], generation of defined aggregate morphologies [159], etc. allow us to build up supramolecular architectures. The polymerization of the molecular subunits has been a major step in increasing control over the structural properties of the polymolecular system [165, 166]. Incorporating suitable groups or components may yield functional assemblies capable of performing operations such as energy, electron or ion transfer, information storage, signal transduction, etc. [160, 162, 167, 168]. The combination of receptors, carriers and catalysts, handling electrons and ions as discussed above, with polymolecular organized assemblies, opens the way to the design of what may be termed *molecular* and *supramolecular devices*, and to the elaboration of chemical microreactors and artificial cells.

One may also note that polymolecular assemblies define *surfaces* on which and through which processes occur, a feature that again stresses the interest of designing exoreceptors operating at the interfaces, in addition to endo-receptors embedded in the bulk of the membranes.

9. Molecular and Supramolecular Devices

Molecular devices may be defined as structurally organized and functionally integrated chemical systems built into supramolecular architectures. The development of such devices requires the design of molecular components (effectors) performing a given function and suitable for incorporation into an organized array such as that provided by the different types of polymolecular assemblies (see above). The components may be photo-, electro-,

iono-, magneto-, thermo-, mechano-, or chemo-active depending on whether they handle photons, electrons or ions, respond to magnetic fields or to heat, undergo changes in mechanical properties or perform a chemical reaction. A major requirement would be that these components and the devices that they bring about, perform their function(s) at the *molecular* and *supramolecular* levels as distinct from the bulk material.

Molecular receptors, reagents, catalysts, carriers and channels are potential effectors that may generate, detect, process and transfer signals by making use of the three-dimensional information storage and read-out capacity operating in molecular recognition and of the substrate transformation and translocation processes conveyed by reactivity and transport. Coupling and regulation may occur if the effectors contain several subunits that can interact, influence each other and respond to external stimuli such as light, electricity, heat, pressure, etc.

The nature of the mediator (substrate) on which molecular devices operate defines the fields of molecular photonics, molecular electronics and molecular ionics. Their development requires the design of effectors that handle these mediators and to examine their potential use as components of molecular devices. We shall now analyse specific features of molecular receptors, carriers and reagents from this point of view.

9.1. SUPRAMOLECULAR PHOTOCHEMISTRY AND MOLECULAR PHOTONICS

The formation of supramolecular entities from photoactive and/or electroactive components may be expected to perturb the ground state and excited state properties of the individual species, giving rise to novel properties that define a *supramolecular photochemistry* and *electrochemistry*.

Thus, a number of processes may take place within supramolecular systems, modulated by the arrangement of the bound units as determined by the organizing receptor: photoinduced energy migration, charge separation by electron or proton transfer, perturbation of optical transitions and polarisabilities, modification of redox potentials in ground or excited states, photoregulation of binding properties, selective photochemical reactions, etc.

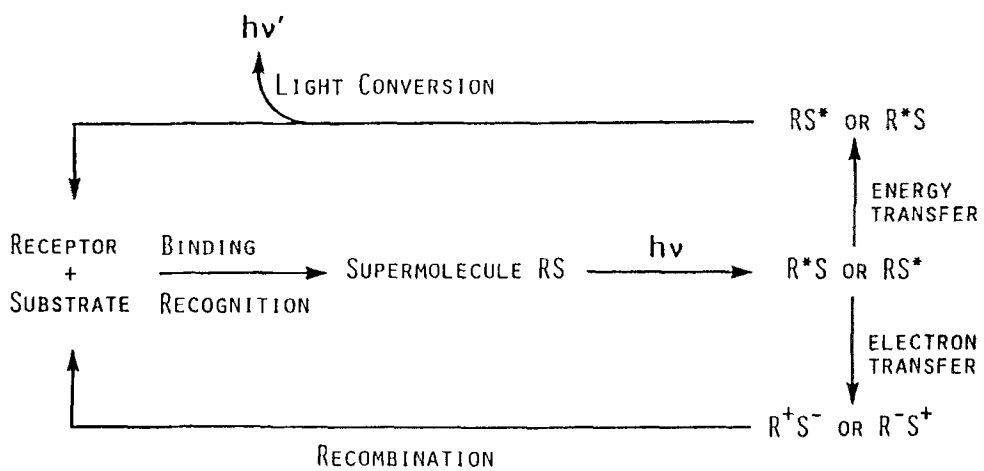
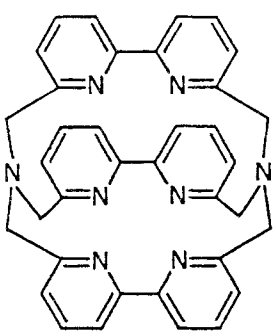


Fig. 10. Representation of the processes involved in supramolecular photochemistry. R*S, RS*, R^+S^- or R^-S^+ may be followed by a chemical reaction.

Supramolecular photochemistry, like catalysis, may involve three steps: binding of substrate and receptor, mediating a photochemical process followed by restoration of the initial state for a new cycle or by a chemical reaction [169] (Figure 10). The photophysical and photochemical features of supramolecular entities form a vast area of investigation into processes occurring at a level of intermolecular organization.

9.1.1. *Light Conversion by Energy Transfer*

A light conversion molecular device may be realized by an Absorption–Energy Transfer–Emission (*A–ET–E*) process in which light absorption by a receptor molecule is followed by intramolecular energy transfer to a bound substrate which then emits. This occurs in the europium(III) and terbium(III) cryptates of the macrobicyclic ligand [bipy·bipy·bipy] **43** [170]. UV light absorbed by the bipy groups is transferred to the lanthanide cation bound in the molecular cavity, and released in the form of visible lanthanide emission *via* an A–ET–E process, as shown in **44** [171]. These Eu(III) and Tb(III) complexes display a bright luminescence in aqueous solution, whereas the free ions do not emit under the same conditions. Numerous applications may be envisaged for such substances, in particular as luminescent probes for monoclonal antibodies, nucleic acids, membranes, etc.



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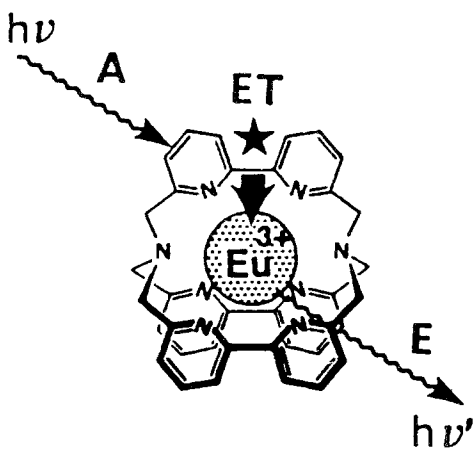

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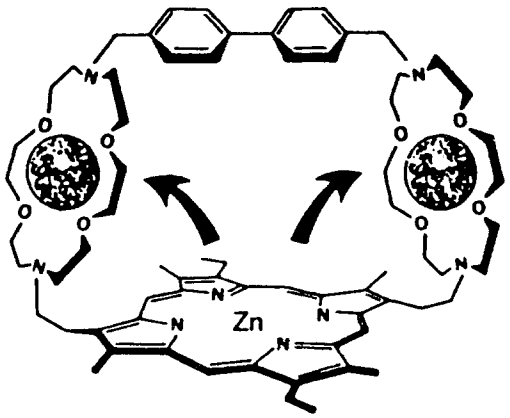
Photophysical processes occuring in macrocyclic [172], cryptate [173] and molecular [174, 175] complexes have been investigated.

9.1.2. *Photoinduced Electron Transfer in Photoactive Co-receptor Molecules*

The photogeneration of charge separated states is of interest both for inducing photocatalytic reactions (e.g. for artificial photosynthesis) and for the transfer of photo-signals, for instance through a membrane. It may be realized in D–PS–A systems in which excitation of a photosensitizer PS, followed by two electron transfers from a donor D to an acceptor A, yields D^+–PS–A^-. Numerous systems of this type are being studied in many laboratories from the standpoint of modelling photosynthetic centres.

The D and A units may be metal coordination centres. Thus, binding of silver ions to the lateral macrocycles of co-receptors containing porphyrin groups as photosensitizers, introduces electron acceptor sites, as shown in **45**. This results in quenching of the singlet excited state of the Zn-porphyrin centre by an efficient intra-complex electron transfer, leading to charge separation and generating a porphyrinium cation of long half-life [176].



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Systems performing photoinduced electron transfer processes represent components for *light to electron conversion devices*. The light activated electron transport mentioned above [135] also belongs to this general type.

9.1.3. *Photoinduced Reactions in Supramolecular Species*

The binding of a substrate to a receptor molecule may affect the photochemical reactivity of either or both species, orienting the course of a reaction or giving rise to novel transformations.

Complexation of coordination compounds may allow the control of their photochemical behaviour via the structure of the supramolecular species formed. Thus, the photoaquation of the $Co(CN)_6^{3-}$ anion is markedly affected by binding to polyammonium macrocycles. The results agree with the formation of supramolecular species, in which binding to the receptor hinders some CN^- groups from escaping when the Co—CN bonds are temporarily broken following light excitation [63]. It thus appears possible to orient the photosubstitution reactions of transition metal complexes by using appropriate receptor molecules. Such effects may be general, applying to complex cations as well as to complex anions, and providing an approach to the control of photochemical reactions via formation of defined supramolecular structures [169, 177, 178].

Structural or conformational changes photoproduced in receptor molecules affect their binding properties thus causing release or uptake of a species, as occurs in macrocyclic ligands containing light sensitive groups [141, 172]. Such effects may be used to generate protonic or ionic photosignals in *light-to-ion conversion* devices.

9.1.4. *Non-linear Optical Properties of Supramolecular Species*

Substances presenting a large electronic polarisability are likely to yield materials displaying large macroscopic optical non-linearities. This is the case for push-pull compounds possessing electron donor and acceptor units. The potential non-linear optical (NLO) properties of materials based on metal complexes and supramolecular species has been pointed out recently [179a]. The D–PS–A system investigated for their ability to yield charge separated states possess such features; they may be metallic or molecular complexes.

Ion dependent optical changes produced by indicator ligands [180] might lead to cation control of non-linear optical properties.

Molecular electron–donor–acceptor complexes could present NLO effects since they possess polarized ground states and undergo (partial) intermolecular charge separation on excitation. It is possible to more or less finely tune their polarization, polarizability, extent of charge transfer, absorption bands, etc. by many variations in basic structural types as well as in substituents (see for instance [174, 179b]).

The results discussed above provide illustrations and incentives for further studies of photo-effects brought about by the formation of supramolecular species.

In a broader perspective, such investigations may lead to the development of *photoactive molecular devices*, based on photoinduced energy migration, electron transfer, substrate release or chemical transformation in supermolecules. Thus would be brought together molecular design, intermolecular bonding and supramolecular architectures with photophysical, photochemical and optical properties, building up a kind of *molecular photonics*.

9.2. MOLECULAR ELECTRONIC DEVICES

More and more attention is being given to *molecular electronics* and to the possibility of developing electronic devices that would operate at the molecular level [3, 181]. Molecular rectifiers, transistors and photodiodes have been envisaged, the latter requiring features such as those of charge transfer states in organic molecules, in metal complexes and in D–PS–A systems discussed above (see refs. in [182]).

Among the basic components of electronic circuitry at the molecular level, a unit of fundamental importance is a connector or junction allowing electron flow to take place between different parts of the system, i.e., a *molecular wire*.

An approach to such a unit is represented by the *caroviologens*, vinylogous derivatives of methylviologen that combine the features of the carotenoids and of the viologens [182]. They present features required for a molecular wire: a conjugated polyene chain for electron conduction; terminal electroactive and hydrosoluble pyridinium groups for reversible electron exchange and a length sufficient for spanning typical molecular supporting elements such as a monolayer or bilayer membrane.

Caroviologens have been incorporated into sodium dihexadecyl phosphate vesicles. The data obtained agree with a structural model in which the caroviologens of sufficient length span the bilayer membrane, the pyridinium sites being close to the negatively charged outer and inner surfaces of the vesicles and the polyene chain crossing the lipidic interior of the membrane (Figure 11). These and other functionalized membranes are being tested in processes in which the caroviologen would function as a continuous, transmembrane electron channel, i.e., a genuine molecular wire. With respect to electron transport by means of redox active mobile carrier molecules (see above), the caroviologens represent electron channels, similar to the cation channels and cation carriers. They portray a first

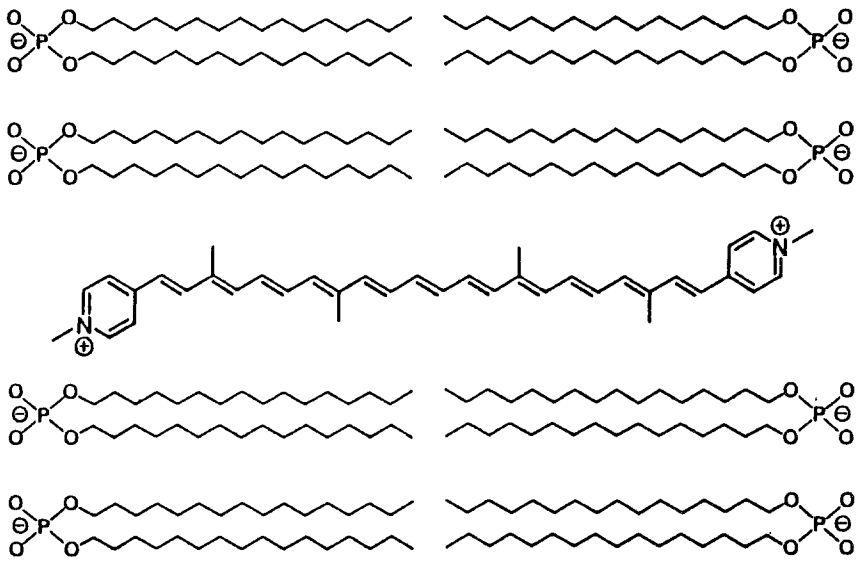


Fig. 11. Transmembrane incorporation of a caroviologen into sodium dihexadecylphosphate vesicles.

approach to molecular wires and several modifications concerning the end-groups and the chain may be envisaged [183a]. For instance, coupling with photoactive groups could yield photoresponsive electron channels, as well as charge separation and signal transfer devices [183b]. Combination with other polymolecular supports, such as polymeric layers or mesomorphic phases, and with other components, might allow the assembly of nanocircuits and more complex molecular electronic systems.

Redox modification of an electroactive receptor or carrier molecule leads to changes in bonding and transport properties, thus causing release or uptake of the substrate, in a way analogous to the photo-effects discussed above. To this end redox couples such as disulfide/dithiol [184, 185a] and quinone/hydroquinone [185] have been introduced into receptor molecules and shown to modify their substrate binding features. Complexation of metal hexacyanides $M(CN)_6^{n-}$ by polyammonium macrocycles markedly perturbs their redox properties [61]. These electrochemical features resulting from receptor-substrate association define a *supramolecular electrochemistry*. The mutual effects between redox changes and binding strength in a receptor-substrate pair, may allow us to achieve electrocontrol of complexation and, conversely, to modify redox properties by binding (see also below).

9.3. MOLECULAR IONIC DEVICES

The numerous receptor, reagent and carrier molecules capable of handling inorganic and organic ions are potential components of molecular and supramolecular *ionic devices* that would function *via* highly selective recognition, reaction and transport processes with coupling to external factors and regulation. Such components and the devices that they may build up form the basis of a field of *molecular ionics*, the field of systems operating with ionic species as support for signal and information storage, processing and transfer. In view of the size and mass of ions, ionic devices may be expected to perform more slowly than electronic devices. However ions have a very high information content by virtue of their multiple molecular (charge, size, shape, structure) and supramolecular (binding geometry,

strength and selectivity) features. Molecular ionics appears a promising field of research which may already draw from a vast amount of knowledge and data on ion processing by natural and synthetic receptors and carriers.

Selective ion receptors represent basic units for ionic transmitters or detectors, selective ion carriers corespond to ionic transducers. These units may be fitted with triggers and switches sensitive to external physical (light, electricity, electric or magnetic field, heat, pressure) or chemical (other binding species, regulating sites) stimuli for connection and activation.

Binding or transport and triggering may be performed by separate species each having a specific function, as in multiple carrier transport systems (see above) [133]. This allows a variety of combinations between photo- or electro-active components and different receptors or carriers. On the other hand, light and redox sensitive groups have been incorporated into receptors and carriers and shown to affect binding and transport properties (see [141, 172, 184, 185] and references therein). Coreceptors and cocarriers provide means for regulation via cofactors, co-bound species that modulate the interaction with the substrate. Thus, a simple ionizable group such as a carboxylic acid function represents a *proton switch* and leads to gated receptors and carriers responding to pH changes, as seen for instance in the regulation of transport selectivity by **40** [138].

The main problem is the generally insufficient changes brought about in most systems by the switching process. It is worth stressing that proton triggered yes/no or +/− switches are potentially contained in the ability of polyamine receptors and carriers to bind and transport cations when unprotonated and anions when protonated, also zwitterions such as amino-acids may change from bound to unbound or conversely when they undergo charge inversion as a function of pH. Molecular *protonic devices* thus represent a particularly interesting special case of ionic devices. A proton conducting channel would be a *proton wire*.

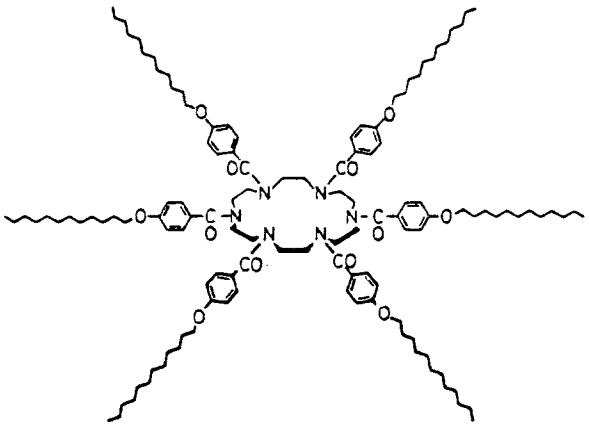
Functional molecular assemblies provide ways of organizing molecular devices and of introducing regulation and cooperative processes which may induce a much steeper response of the system to the stimuli. Vesicles have been fitted with functional units [168], for instance with a Li^+ ion channel that may be sealed [147, 148]. Liquid crystals consisting of macrocyclic molecules bearing mesogenic groups, such as **46**, form *tubular mesophases*, composed of stacked rings as in **47**, that lead to the development of phase dependent ion conducting channels [186, 187]. Cooperativity and self-assembly may also be designed directly into the molecular components (see below).

Biological information and signals are carried by ionic and molecular species (Na^+, K^+, Ca^{2+}, acetylcholine, cyclic AMP, etc.). Polytopic metalloproteins such as calcium binding proteins [188] perform complicated tasks of detecting, processing and transferring ionic signals. These biological functions give confidence and inspiration for the development of molecular ionics.

One may note that ion receptors, channels, switches and gates have been considered within a potential European research programme on 'Ionic Adaptative Computers' (EURIAC). Applications such as selective chemical sensors based on molecular recognition are already well advanced [121].

9.4. MOLECULAR SELF-ASSEMBLY

Self-assembling and multiple binding with positive cooperativity are processes of spontaneous molecular organization that also allow us to envisage *amplification molecular devices*.



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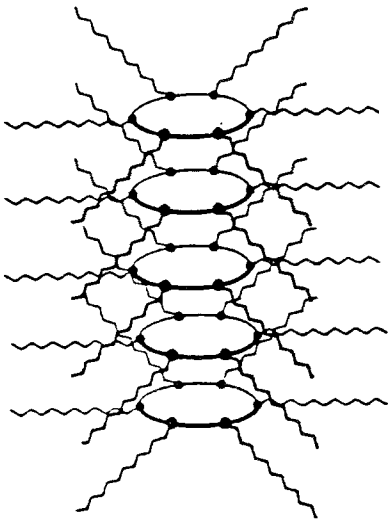

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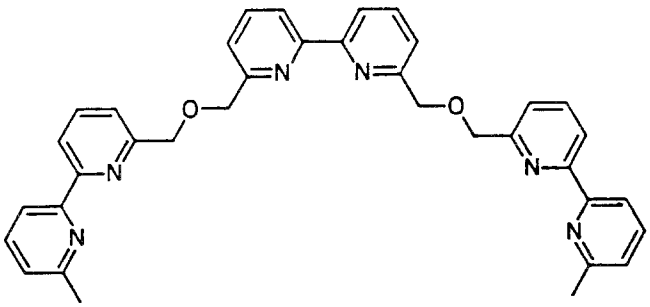
Such phenomena are well documented in biology, but much less so in chemistry. By virtue of their multiple binding subunits, polytopic co-receptors may display self-assembling if substrate binding to one receptor molecule generates binding sites that induce association with another one.

Positive cooperativity in substrate binding is more difficult to set up than negative cooperativity. However, both effects are of interest for regulation processes. Cooperativity is found in the unusual facilitation of the second protonation of **5** by a water effector molecule as in **10** (see above) [40]. Allosteric effects on cation binding to macrocyclic polyethers have been studied by inducing conformational changes *via* a remote site [17a] and subunit cooperativity occurs in a dimeric porphyrin [189].

The spontaneous formation of the double helix of nucleic acids represents the self-assembling of a supramolecular structure induced by the pattern of intermolecular interactions provided by the complementary nucleic bases. It involves recognition and positive cooperativity in base pairing [190].

Such self-assembling has recently been shown to occur in repetitive chain ligands, acyclic co-receptors containing several identical binding sites arranged linearly. Based on earlier work with a quaternary pyridine ligand, oligo-bipyridine chain ligands incorporating two to five bipy groups were designed. By treatment with Cu(I) ions they underwent a spontaneous assembling into *double stranded helicates* containing two ligand molecules and one Cu(I) ion per bipy site of each ligand, the two receptor strands being wrapped around the metal ions which hold them together. Thus, the tris-bipy ligand **48** forms the trinuclear complex **49** whose crystal structure has been determined, confirming that it is indeed an *inorganic double helix* [191]. The results obtained indicate that the process occurs probably with positive cooperativity, binding of a Cu(I) ion with two ligands facilitating complexation of the next one. Furthermore, it appears that in a mixture of ligands containing different numbers of bipy units, pairing occurs preferentially between the *same* ligands, thus performing *self-self recognition.* This spontaneous formation of an organized



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structure of the intermolecular type opens ways to the design and study of self-assembling systems presenting cooperativity, regulation and amplification features. Catalytic reactions, gated channels and phases changes represent other processes that might be used for inducing amplification effects.

Various further developments may be envisaged along organic, inorganic and biochemical lines. Thus, if substituents are introduced at the *para* positions of the six pyridine units in **48**, treatment with Cu(I), should form an inorganic double helix bearing twelve outside directed functional groups [155].

Designed self-assembling rests on the elaboration of molecular components that will spontaneously undergo organization into a desired supramolecular architecture. Such control of self-organization at the molecular level is a field of major interest in molecular design and engineering, that may be expected to become a subject of increasing activity.

9.5. CHEMIONICS

Components and molecular devices such as molecular wires, channels, resistors, rectifiers, diodes, photosensitive elements, etc. might be assembled into nanocircuits and combined with organized polymolecular assemblies to yield systems capable ultimately of performing functions of detection, storage, processing, amplification and transfer of signals and information by means of various mediators (photons, electrons, protons, metal cations, anions, molecules) with coupling and regulation [3, 8, 181, 182, 192].

Molecular photonics, electronics and ionics represent three areas of this intriguing and rather futuristic field of chemistry which may be termed '*chemionics*' [3, 8] – the design and operation of photonic, electronic and ionic components, devices, circuitry and systems for signal and information treatment at the molecular level. Such perspectives lie, of course, in the long range [193], but along the way they could yield numerous spin-offs and they do represent ultimate goals towards which work may already be planned and realized.

10. Conclusion

The present text was aimed at presenting the scope, providing illustration and exploring perspectives of supramolecular chemistry. Its conceptual framework has been progressively laid down and the very active research on molecular recognition, catalysis and transport, together with extension to molecular surfaces and polymolecular assemblies, is building up a vast body of knowledge on molecular behaviour at the supramolecular level. It is clear that much basic chemistry remains to be done on the design and realization of numerous other systems and processes that await to be imagined. The results obtained may also be analyzed with the view of developing components for molecular devices that would perform highly selective functions of recognition, transformation, transfer, regulation and communication, and allow signal and information processing. This implies operation *via* intermolecular interactions and incorporation of the *time* dimension into recognition events. One may note that such functions have analogies with features of expert systems, thus linking processes of artificial intelligence and molecular behaviour.

These developments in molecular and supramolecular science and engineering offer exciting perspectives at the frontiers of chemistry with physics and biology. Of course, even with past achievements and present activities, extrapolations and predictions can only be tentative; yet, on such an occasion for the celebration of chemistry, it appears justified to try looking out into the future for "He (or she) who sits at the bottom of a well to contemplate the sky, will find it small" (*Han Yu*, 768–824).

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References

1. J.-M. Lehn: *Struct. Bonding* (Berlin) **16**, 1 (1973).
2. J.-M. Lehn: *Pure Appl. Chem.* **50**, 871 (1978).
3. J.-M. Lehn: Leçon Inaugurale, Collège de France, Paris 1980.
4. R. Pfeiffer: *Organische Molekülerverbindungen*, Stuttgart, 1927.
5. K. L. Wolf, F. Frahm and H. Harms: *Z. Phys. Chem. Abt. B* **36**, 17 (1937); K. L. Wolf, H. Dunken and K. Merked: ibid. **46**, 287 (1940); K. L. Wolf and R. Wolff: *Angew. Chem.* **61**, 191 (1949).
6. J.-M. Lehn: *Acc. Chem. Res.* **11**, 49 (1978).
7. J.-M. Lehn: in Z. I. Yoshida and N. Ise (Eds.): *Biomimetic Chemistry*, Kodansha, Tokyo and Elsevier, Amsterdam 1983, p. 163.
8. J.-M. Lehn: *Science* **277**, 849 (1985).
8. P. G. Potvin and J.-M. Lehn: in R. M. Izatt and J. J. Christensen (Eds.): *Synthesis of Macrocycles: The Design of Selective Complexing Agents* (Progress in Macrocyclic Chemistry vol. 3), Wiley, New York, 1987, p. 167.

10. E. Fischer: *Ber. Deutsch. Chem. Gesell.* **27**, 2985 (1894).
11. F. Cramer and W. Freist: *Acc. Chem. Res.* **20**, 79 (1987).
12. J. F. Stoddart: *Chem. Soc. Rev.* **8**, 85 (1979); *Annual Reports B, Roy. Soc. Chem.* (1983) p. 353.
13. D. J. Cram and J. M. Cram: *Acc. Chem. Res.* **11**, 8 (1978).
14. R. C. Hayward: *Chem. Soc. Rev.* **12**, 285 (1983).
15. I. O. Sutherland: *Chem. Soc. Rev.* **15**, 63 (1986).
16. G. van Binst (Ed.): *Design and Synthesis of Organic Molecules Based on Molecular Recognition*, Springer, Berlin 1986.
17. (a) J. Rebek, Jr.: *Acc. Chem. Res.* **17**, 258 (1984); (b) *Science* **235**, 1478 (1987).
18. (a) P. B. Dervan, R. S. Youngquist and J. P. Sluka: in W. Bartmann and K. B. Sharpless (Eds.) *Stereochemistry of Organic and Bioorganic Transformations*, Verlag Chemie, Heidelberg 1987, p. 221; (b) W. C. Still: *ibid.* p. 235.
19. R. M. Izatt, J. J. Christensen (Eds.): *Progress in Macrocyclic Chemistry*, Wiley, New York, vol. 1 (1979), vol. 2 (1981), vol. 3 (1987).
20. F. Vögtle (Ed.): *Host Guest Chemistry* (*Topics Curr. Chem.* **98**) (1981), **101** (1982); F. Vögtle and E. Weber (Eds.), *ibid.*, **121** (1984).
21. J. L. Atwood, J. E. D. Davies and D. D. MacNicol: *Inclusion Compounds*, Academic Press, London, vols. 1, 2, 3 (1984).
22. G. Wipff, P. K. Kollman and J.-M. Lehn: *J. Mol. Struct.* **93**, 153 (1983); G. Ranghino, S. Romano, J.-M. Lehn and G. Wipff: *J. Am. Chem. Soc.* **107**, 7873 (1985); G. Wipff and P. Kollman: *Nouv. J. Chim.* **9**, 457 (1985); 'Structure and Dynamics of Macromolecules', S. Lifson, M. Levitt (Eds.) *Isr. J. Chem.* **27** (1986) No. 2.
23. An idea about the respective role of collection and orientation may be gained from examining the energies calculated for a series of $Li(NH_3)_n^+$ complexes and of the corresponding $(NH_3)_n$ units in the indentical geometry. In the presence of Li^+ the formation energies of the complexes are obtained at the optimized $Li^+ \cdots NH_3$ distances. When Li^+ is removed and the NH_3 molecules are kept at the same position the energies calculated are for the formation of the coordination shell alone. These energies represent the repulsion between the NH_3 groups; they are a measure of the intersite repulsive energy for bringing together two, three or four amine binding sites into a polydentate ligand of the same coordination geometry. *Results*, $(NH_3)_n$, geometry (repulsive energy, kcal/mole): $(NH_3)_2$, linear (−2.4), bent (−3.8); $(NH_3)_3$, trigonal (−9.1), pyramidal (−10.8); $(NH_3)_4$, tetrahedral (−20.8). Thus, the total collection energies are appreciably larger than the organization energies represented by the changes from one geometry to another, linear to bent (1.4 kcal/mole) or trigonal to pyramidal (1.7 kcal/mole). *Ab initio* computations performed with a set of Gaussian type basis functions, contracted into a double set with polarisation; J.-M. Lehn, R. Ventavoli, unpublished results; see also: R. Ventavoli, 3è Cycle Thesis, Université Louis Pasteur, Strasbourg, 1972.
24. (a) Yu. A. Ovchinnikov, V. T. Ivanov and A. M. Skrob: *Membrane Active Complexones*, Elsevier, New York (1974); (b) B. C. Pressman: *Ann. Rev. Biochem.* **45**, 501 (1976); (c) H. Brockmann and H. Gerren: *Annalen* **603**, 217 (1957); (d) M. M. Shemyakin, N. A. Aldanova, E. I. Vinogradova and M. Yu. Feigina, *Tetrahedron Lett.* 1963, 1921; (e) C. Moore and B. C. Pressman: *Biochem. Biophys. Res. Commun.* **15**, 562 (1964); (f) B. C. Pressman: *Proc. Natl. Acad. Sci. USA* **53**, 1077 (1965); (g) J. Beck, H. Gerlach, V. Prelog and W. Voser: *Helv. Chim. Acta* **74**, 620 (1962); (h) Z. Stefanac and W. Simon: *Chimia* **20**, 436 (1966) and *Microchem. J.* **12**, 125 (1967); (i) K. T. Kilbourn, J. D. Dunitz, L. A. R. Pioda and W. Simon: *J. Mol. Biol.* **30**, 559 (1967); (j) P. Mueller and D. O. Rudin: *Biochem. Biophys. Res. Commun.* **26**, 398 (1967); (k) T. E. Andreoli, M. Tieffenberg and D. C. Tosteson: *J. Gen. Biol.* **50**, 2527 (1967); (l) M. M. Shemyakin, Yu. A. Ovchinnikov, V. T. Ivanov, V. K. Antonov, A. M. Skrob, I. I. Mikhaleva, A. V. Evstratov and G. G. Malenkov: *ibid.* **29**, 834 (1967); (m) B. C. Pressman, E. J. Harris, W. S. Jagger and J. H. Johnson: *Proc. Natl. Acad. Sci. USA* **58**, 1949 (1967).
25. (a) C. J. Pedersen: *J. Am. Chem. Soc.* **89**, 7017 (1967); (b) C. J. Pedersen and H. K. Frensdorff: *Agnew. Chem. Int. Ed. Engl.* **11**, 16 (1972).
26. D. J. Cram: *Angew. Chem. Int. Ed. Engl.* **25**, 1039 (1986).
27. D. Parker: *Adv. Inorg. Chem. Radiochem.* **27**, 1 (1983); B. Dietrich: *J. Chem. Ed.* **62**, 954 (1985). For the sepulchrate type of encapsulated metal ions, see A. M. Sargeson: *Pure Appl. Chem.* **56**, 1603 (1984).
28. (a) J.-M. Lehn and J.-P. Sauvage: *J. Am. Chem. Soc.* **97**, 6700 (1975); (b) B. Dietrich, J.-M. Lehn and J.-P. Sauvage: *J. Chem. Soc., Chem. Commun.* 1973, 15.
29. (a) B. Dietrich, J.-M. Lehn and J.-P. Sauvage: *Tetrahedron Lett.* 1969, 2885 and 2889; (b) B. Dietrich, J.-M. Lehn, J.-P. Sauvage and J. Blanzat, Tetrahedron **29**, 1629 (1973); B. Dietrich, J.-M. Lehn and J.-P. Sauvage: *ibid.* **29**, 1647 (1973); (c) B. Metz, D. Moras and R. Weiss: *J. Chem. Soc., Chem. Commun.* 1970, 217; F. Mathieu, B. Metz, D. Moras and R. Weiss: *J. Am. Chem. Soc.* **100**, 4412 (1978) and references therein.

30. E. Graf and J.-M. Lehn: *J. Am. Chem. Soc.* **97**, 5022 (1975); *Helv. Chim. Acta* **64**, 1040 (1981).
31. B. Dietrich and J.-M. Lehn: unpublished results.
32. E. Graf and J.-M. Lehn: *J. Am. Chem. Soc.* **98**, 6403 (1976).
33. F. Schmidtchen and G. Muller: *J. Chem. Soc., Chem. Commun.* 1984, 11115.
34. J. L. Dye: *Angew. Chem. Int. Ed. Engl.* **18**, 587 (1979); J. L. Dye and M. G. DeBacker: *Ann. Rev. Phys. Chem.* **38**, 271 (1987).
35. J.-M. Lehn: *Pure Appl. Chem.* **52**, 2303 (1980).
36. A. I. Popov and J.-M. Lehn: in G. A. Melson (Ed.): *Coordination Chemistry of Macrocyclic Compounds* Plenum Press, New York, 1979.
37. I. M. Kolthoff: *Anal. Chem.* **51**, 1R (1979).
38. F. Montanari, D. Landini and F. Rolla: *Topics Curr. Chem.* **101**, 203 (1982); E. Blasius and K.-P. Janzen: *ibid.* **98**, 163 (1981).
39. E. Graf, J.-M. Lehn and J. LeMoigne: *J. Am. Chem. Soc.* **104**, 1672 (1982).
40. E. Graf. J.-P. Kintzinger and J.-M. Lehn: unpublished results.
41. B. Dietrich, J.-P. Kintzinger, J.-M. Lehn, B. Metz and A. Zahidi: *J. Phys. Chem.* in press.
42. (a) D. J. Cram and K. N. Trueblood: *Topics Curr. Chem.* **98**, 43 (1981); (b) F. De Jong and D. N. Reinhoudt: in V. Gold and D. Bethell (Eds.): *Adv. Phys. Org. Chem.* **17**, 219 (1980), Academic Press, New York.
43. J.-M. Lehn and P. Vierling: *Tetrahedron Lett.* 1980, 1323.
44. J.-P. Behr, J.-M. Lehn and P. Vierling: *J. Chem. Soc., Chem. Commun.* 1976, 621; *Helv. Chim. Acta* **65**, 1853 (1982).
45. J.-P. Behr and J.-M. Lehn: *Helv. Chim. Acta* **63**, 2112 (1980).
46. H. M. Colquhoun, J. F. Stoddart and D. J. Williams: *Angew. Chem. Int. Ed. Engl.* **25**, 487 (1986).
47. Stability constants of about 800 and 10^5 L mol^{-1} have been obtained for binding of $Ru(NH_3)_6^{3+}$ to **12b** and to the hexacarboxylate in **14**, respectively (aqueous solution, pH = 7.3); J.-M. Lehn and P. Vierling, unpublished results.
48. J. C. Metcalfe, J. F. Stoddart and G. Jones: *J. Am. Chem. Soc.* **99**, 8317 (1977); J. Krane and O. Aune: *Acta Chem. Scand.* **B34**, 397 (1980).
49. (a) J.-M. Lehn, P. Vierling and R. C. Hayward: *J. Chem. Soc., Chem. Commun.* 1979, 296; (b) see also: K. Madan and D. J. Cram: *ibid.* 1975, 427; J. W. H. M. Uiterwijk, S. Harkema, J. Geevers and D. N. Reinhoudt: *ibid* 1982, 200.
50. (a) F. Vögtle, H. Sieger and W. M. Muller: *Topics Curr. Chem.* **98**, 107 (1981); (b) K. Saigo: *Kagaku to Kogyo* **35**, 90 (1982); (c) J.-L. Pierre and P. Baret: *Bull. Soc. Chim. Fr.* **II** 1983, 367; (d) E. Kimura: *Topics Curr. Chem.* **128**, 113 (1985); (e) F. P. Schmidtchen: *ibid.* **132**, 101 (1986).
51. (a) J.-M. Lehn, E. Sonveaux and A. K. Willard: *J. Am. Chem. Soc.* **100**, 4914 (1978); (b) B. Dietrich, J. Guilhem, J.-M. Lehn, C. Pascard and E. Sonveaux: *Helv. Chim. Acta* **67**, 91 (1984); (c) for other macrobicyclic receptors see also M. W. Hosseini, Thèse de Doctorat-ès-Sciences, Université Louis Pasteur, Strasbourg 1983.
52. C. H. Park and H. Simmons: *J. Am. Chem. Soc.* **90**, 2431 (1968).
53. (a) B. Dietrich, M. W. Hosseini, J.-M. Lehn and R. B. Sessions: *J. Am. Chem. Soc.* **103**, 1282 (1981); (b) *Helv. Chim. Acta* **68**, 289 (1985).
54. J. Cullinane, R. I. Gelb, T. N. Margulis and L. J. Zompa: *J. Am. Chem. Soc.* **104**, 3048 (1982); E. Suet and H. Handel: *Tetrahedron Lett.* 1984, 645.
55. M. W. Hosseini, J.-M. Lehn and M. P. Mertes: *Helv. Chim. Acta* **66**, 2454 (1983).
56. E. Kimura, M. Kodama and T. Yatsunami: *J. Am. Chem. Soc.* **104**, 3182 (1982); J. F. Marecek and C. J. Burrows: *Tetrahedron Lett.* 1986, 5943.
57. M. W. Hosseini and J.-M. Lehn: *Helv. Chim. Acta* **70**, 1312 (1987); see also H. R. Wilson and R. J. P. Williams: *J. Chem. Soc., Faraday Trans. I* **83**, 1885 (1987).
58. B. Dietrich, D. L. Fyles, T. M. Fyles and J.-M. Lehn: *Helv. Chim. Acta* **62**, 2763 (1979).
59. B. Dietrich, T. M. Fyles, J.-M. Lehn, L. G. Pease and D. L. Fyles: *J. Chem. Soc., Chem. Commun.* 1978, 934.
60. M. J. Mann, N. Pant and A. D. Hamilton: *J. Chem. Soc., Chem. Commun.* 1986, 158.
61. F. Peter, M. Gross, M. W. Hosseini and J.-M. Lehn: *J. Electroanal. Chem.* **144**, 279 (1983).
62. E. Garcia-Espana, M. Micheloni, P. Paoletti and A. Bianchi: *Inorg. Chim. Acta* **102**, L9 (1985); A. Bianchi, E. Garcia-Espana, S. Mangani, M. Micheloni, P. Orioli and P. Paoletti: *J. Chem. Soc., Chem. Commun.* 1987, 729.
63. M. F. Manfrin, L. Moggi, V. Castelvetro, V. Balzani, N. W. Hosseini and J.-M. Lehn: *J. Am. Chem. Soc.* **107**, 6888 (1985).
64. J.-M. Lehn: *Pure Appl. Chem.* **52**, 2441 (1980).

65. J.-M. Lehn, J. Simon and J. Wagner: *Angew. Chem. Int. Ed. Engl.* **12**, 578, 579 (1973).
66. R. J. Motekaitis, A. E. Martell, B. Dietrich and J.-M. Lehn: *Inorg. Chem.* **23**, 1588 (1984); R. J. Motekaitis, A. E. Martell and I. Murase: *ibid.* **25**, 938 (1986); A. Evers, R. D. Hancock and I. Murase: *ibid.* **25**, 2160 (1986); D. E. Whitmoyer, D. P. Rillema and G. Gerraudi: *J. Chem. Soc., Chem. Commun.* 1986, 677.
67. J.-P. Kintzinger, J.-M. Lehn, E. Kauffmann, J. L. Dye and A. I. Popov: *J. Am. Chem. Soc.* **105**, 7549 (1983).
68. D. Heyer and J.-M. Lehn: *Tetrahedron Lett.* 1986, 5869.
69. T. Fujita and J.-M. Lehn: unpublished work.
70. T. P. Lybrand, J. A. McCammon and G. Wipff: *Proc. Natl. Acad. Sci. USA* **83**, 833 (1986).
71. J.-M. Lehn: in K. J. Laidler (Ed.): *IUPAC Frontiers of Chemistry*, Pergamon Press, Oxford 1982, p. 265.
72. J. Jazwinski, J.-M. Lehn, D. Lilienbaum, R. Ziessel, J. Guilhem and C. Pascard: *J. Chem. Soc., Chem. Commun.* 1987, 1691.
73. A. Carroy and J.-M. Lehn: *J. Chem. Soc., Chem. Commun.* 1986, 1232.
74. J. Comarmond, B. Dietrich, J.-M. Lehn and R. Louis: *J. Chem. Soc., Chem. Commun.* 1985, 74.
75. Y. Okuno, K. Uoto, O. Yonemitsu and T. Tomohiro: *J. Chem. Soc., Chem. Commun.* 1987, 1018; J. R. Holmes and J.-M. Lehn: work in progress.
76. F. Kotzyba-Hibert, J.-M. Lehn and P. Vierling: *Tetrahedron Lett.* 1980, 941.
77. F. Kotzyba-Hibert, J.-M. Lehn and K. Saigo: *J. Am. Chem. Soc.* **103**, 4266 (1981).
78. C. Pascard, C. Riche, M. Cesario, F. Kotzyba-Hibert and J.-M. Lehn: *J. Chem. Soc., Chem. Commun.* 1982, 557.
79. J.-P. Kintzinger, F. Kotzyba-Hibert, J.-M. Lehn, A. Pagelot and K. Saigo: *J. Chem. Soc., Chem. Commun.* 1981, 833.
80. M. W. Hosseini and J.-M. Lehn: *J. Am. Chem. Soc.* **104**, 3525 (1982); *Helv. Chim. Acta* **69**, 587 (1986).
81. (a) F. P. Schmidtchen: *J. Am. Chem. Soc.* **108**, 8249 (1986); (b) J. Rebek, Jr. D. Nemeth, P. Ballester and F.-T. Lin: *ibid.* **109**, 3474 (1987).
82. J.-M. Lehn, J. Simon and A. Moradpour: *Helv. Chim. Acta* **61**, 2407 (1978).
83. (a) F. P. Schmidtchen: *J. Org. Chem.* **51**, 5161 (1986); (b) J. Simon: Thèse de Doctorat d'Etat, Université Louis Pasteur, Strasbourg 1976; see also structure **28** in ref. [14] p. 305; (c) J. Rebek, Jr., B. Askew, O. Nemeth and K. Parris: *J. Am. Chem. Soc.* **109**, 2432 (1987).
84. J.-P. Behr and J.-M. Lehn: *J. Am. Chem. Soc.* **98**, 1743 (1976).
85. F. Cramer: *Einschlussverbindungen*, Springer Verlag, Berlin 1954; M. L. Bender and M. Komiyama: *Cyclodextrin Chemistry*, Springer Verlag, Berlin 1978.
86. (a) J. Franke and F. Vögtle: *Topics Curr. Chem.* **132**, 137 (1986); (b) F. Vögtle, W. M. Müller and W. H. Watson: *ibid.* **125**, 131 (1984); (c) for calixarenes, see C. D. Gutsche: *ibid* **123**, 1 (1984); *Acc. Chem. Res.* **16**, 161 (1983); (d) for cavitands, see D. J. Cram: *Science* **219**, 1177 (1983).
87. J. Canceill, A. Collet, J. Gabard, F. Kotzyba-Hibert and J.-M. Lehn: *Helv. Chim. Acta* **65**, 1894 (1982).
88. M. Dhaenens, L. Lacombe, J.-M. Lehn and J.-P. Vigneron: *J. Chem. Soc., Chem. Commun.* 1984, 1097.
89. H.-J. Schneider, D. Guttes and U. Schneider: *Angew. Chem. Int. Ed. Engl.* **25**, 647 (1986).
90. B. L. Atwood, F. H. Kohnke, J. F. Stoddart and D. J. Williams: *Angew. Chem. Int. Ed. Engl.* **24**, 581 (1985).
91. For dissymmetric cylindrical macrotricyclic co-receptors that bind ammonium ions, see A. D. Hamilton and P. Kazanjian: *Tetrahedron Lett.* 1985, 5735; K. Saigo, R.-J. Lin, M. Kubo, A. Youda and M. Hasegawa: *Chem. Lett.* 1986, 519.
92. For macrocyclic cyclophane type receptors see also K. Odashima, T. Soga and K. Koga: *Tetrahedron Lett.* 1980, 5311; F. Diederich and K. Dick: *ibid.* **106**, 8024 (1984) and references therein.
93. A. J. Blacker, J. Jazwinski and J.-M. Lehn: *Helv. Chim. Acta* **70**, 1 (1987).
94. I. Bidd, B. Dilworth and J.-M. Lehn: unpublished work.
95. J. Jazwinski, A. J. Blacker, J.-M. Lehn, M. Cesario, J. Guilhem and C. Pascard: *Tetrahedron Lett.* 1987, in press.
96. J.-M. Lehn, F. Schmidt and J.-P. Vigneron: work in progress.
97. A. J. Blacker, M. W. Hosseini and J.-M. Lehn: unpublished work.
98. (a) J.-P. Behr and J.-M. Lehn: unpublished work; (b) J.-M. Lehn and I. Stibor: work in progress; (c) for recent examples see J. Rebek, Jr., B. Askew, P. Ballester, C. Buhr, S. Jones, D. Nemeth and K. Williams: *J. Am. Chem. Soc.* **109**, 5033 (1987); A. D. Hamilton and D. Van Engen: *ibid.* **109**, 5035 (1987).
99. J. Canceill, M. Cesario, A. Collet, C. Riche and C. Pascard: *J. Chem. Soc., Chem. Commun.* 1986, 339; J. Canceill, L. Lacombe and A. Collet: *C.R. Acad. Sc. Paris* **304**, II, 815 (1987).
100. A. D. Hamilton, J.-M. Lehn and J. L. Sessler: *J. Chem. Soc., Chem. Commun.* 1984, 311; *J. Am. Chem. Soc.* **108**, 5158 (1986).
101. For other metalloreceptor type species see for instance references in [15]; N. M. Richards, I. O. Sutherland, P. Camilleri and J. A. Pape: *Tetrahedron Lett.* 1985, 3739; M. C. Gonzalez and A. C. Weedon: *Can. J. Chem.*

63, 602 (1985); D. H. Busch and C. Cairns, in [9] p. 1; V. Thanabal and V. Krishnan: *J. Am. Chem. Soc.* **104**, 3643 (1982); G. B. Maiya and V. Krishnan: *Inorg. Chem.* **24**, 3253 (1985).
102. (a) R. Breslow: *Science* **218**, 532 (1982) and in ref. [21] vol. 3, p. 473; (b) R. M. Kellogg: *Topics Curr. Chem.* **101**, 111 (1982); (c) I. Tabushi and K. Yamamura: *ibid.* **113**, 145 (1983); (d) Y. Murakami: *ibid.* **115**, 107 (1983); (e) C. Sirlin: *Bull. Soc. Chim. France* **II**, 5 (1984); (f) R. M. Kellogg: *Angew. Chem. Int. Ed. Engl.* **23**, 782 (1984); (g) V. T. D'Souza and M. Bender: *Acc. Chem. Res.* **20**, 146 (1987).
103. J.-M. Lehn: *Pure Appl. Chem.* **51**, 979 (1979); *Ann. N.Y. Acad. Sci.* **471**, 41 (1986).
104. Y. Chao, G. R. Weisman, G. D. Y. Sogah and D. J. Cram: *J. Am. Chem. Soc.* **101**, 4948 (1979).
105. J.-M. Lehn and C. Sirlin: *J. Chem. Soc., Chem. Commun.* 1978, 949; *Nouv. J. Chim.* **11**, 693 (1987).
106. S. Sasaki and K. Koga: *Heterocycles* **12**, 1305 (1979).
107. J.-P. Behr and J.-M. Lehn: *J. Chem. Soc., Chem. Commun.* 1978, 143.
108. J.-M. Lehn and T. Nishiya: *Chem. Lett.* 1987, 215.
109. M. W. Hosseini, J.-M. Lehn and M. P. Mertes: *Helv. Chim. Acta* **66**, 2454 (1983); M. W. Hosseini, J.-M. Lehn, L. Maggiora, K. B. Mertes and M. P. Mertes: *J. Am. Chem. Soc.* **109**, 537 (1987).
110. G. M. Blackburn, G. R. J. Thatcher, M. W. Hosseini and J.-M. Lehn: *Tetrahedron Lett.* 1987, 2779.
111. M. W. Hosseini and J.-M. Lehn: *J. Chem. Soc., Chem. Commun.* 1985, 1155; *J. Am. Chem. Soc.* **109**, 7047 (1987).
112. P. G. Yohannes, M. P. Mertes and K. B. Mertes: *J. Am. Chem. Soc.* **107**, 8288 (1985).
113. S. Sasaki, M. Shionoya and K. Koga: *J. Am. Chem. Soc.* **107**, 3371 (1985).
114. H.-D. Lutter and F. Diederich: *Angew. Chem. Int. Ed. Engl.* **25**, 1125 (1986).
115. F. M. Menger and M. Ladika: *J. Am. Chem. Soc.* **109**, 3145 (1987).
116. E. T. Kaiser and D. S. Lawrence: *Science* **226**, 505 (1984).
117. See, for instance, J. A. Gerlt: *Chem. Rev.* **87**, 1079 (1987); A. J. Russell and A. R. Fersht: *Nature* **328**, 496 (1987).
118. A. Tramontano, K. D. Janda and R. A. Lerner: *Science* **234**, 1566 (1986); S. J. Pollack, J. W. Jacobs and P. G. Schultz: *ibid.* **234**, 1570 (1986); R. A. Lerner and A. Tramontano: *TIBS* **12**, 427 (1987).
119. B.Dietrich, J.-M. Lehn and J.-P. Sauvage: *Tetrahedron Lett.* 1969, 2889.
120. J.-M. Lehn: in G. Spach (Ed.), *Physical Chemistry of Transmembrame Ion Motions*, Elsevier, Amsterdam, 1983, p. 181.
121. W. Simon, W. E. Morf and P. Ch. Meier: *Structure and Bonding* **16**, 113 (1973); W. E. Morf, D. Amman, R. Bissig, E. Prestsch and W. Simon, in ref. [19], vol. 1, p. 1.
122. J.-P. Behr and J.-M. Lehn: *J. Am. Chem. Soc.* **95**, 6108 (1973).
123. B. C. Pressman: *Ann. Rev. Biochem.* **45**, 501 (1976).
124. J. D. Lamb and J. J. Christensen: in ref. [21] vol 3, p. 571.
125. M. Kirch and J.-M. Lehn: *Angew. Chem. Int. Ed. Engl.* **14**, 555 (1975); M. Kirsch: Thèse de Doctorat-ès-Sciences, Université Louis Pasteur, Strasbourg, 1980.
126. J.-P. Behr, M. Kirch and J.-M. Lehn: *J. Am. Chem. Soc.* **107**, 241 (1985).
127. T. M. Fyles: *Can. J. Chem.* **65**, 884 (1987).
128. M. Castaing, F. Morel and J.-M. Lehn: *J. Membrane Biol.* **89**, 251 (1986); M. Castaing and J.-M. Lehn: *ibid.* **97**, 79 (1987).
129. E. Bacon, L. Jung and J.-M. Lehn: *J. Chem. Res. (S)* 1980, 136.
130. H. Tsukube: *Angew. Chem. Int. Ed. Engl.* **21**, 304 (1982).
131. Anion transport with anion cryptands has been observed recently: T. M. Fyles and J.-M. Lehn, unpublished results.
132. F. Diederich and K. Dick: *J. Am. Chem. Soc.* **106**, 8024 (1984); A. Harada and S. Takahashi: *J. Chem. Soc., Chem. Commun.* 1987, 527.
133. J. J. Grimaldi and J.-M. Lehn: *J. Am. Chem. Soc.* **101**, 1333 (1979).
134. S. S. Anderson, I. G. Lyle and R. Paterson: *Nature* **259**, 147 (1976).
135. J. J. Grimaldi, S. Boileau and J.-M. Lehn: *Nature* **265**, 229 (1977).
136. J. K. Hurst and D. H. P. Thompson: *J. Membrane Sci.* **28** (1986) and references therein; I. Tabushi and S.-i. Kugimiya: *Tetrahedron Lett.* 1984, 3723.
137. M. Okahara and Y. Nakatsuji: *Topics Curr. Chem.* **128**, 37 (1985).
138. A. Hriciga and J.-M. Lehn: *Proc. Natl. Acad. Sci. USA* **80**, 6426 (1983).
139. R. Frank and H. Rau: *Z. Naturforsch.* **37A**, 1253 (1982).
140. I. Tabushi and S.-i. Kugimiya: *J. Am. Chem. Soc.* **107**, 1859 (1985).
141. S. Shinkai and O. Manabe: *Topics Curr. Chem.* **121**, 67 (1984).
142. D. W. Urry: *Topics Curr. Chem.* **128**, 175 (1985).

143. R. Nagaraj and P. Balaram: *Acc. Chem. Res.* **14**, 356 (1981); R. O. Fox, Jr. and F. M. Richards: *Nature* **300**, 325 (1982).
144. J.-P. Behr, J.-M. Lehn, A.-C. Dock and D. Moras: *Nature* **295**, 526 (1982).
145. U. F. Kragten, M. F. M. Roks and R. J. M. Nolte: *J. Chem. Soc., Chem. Commun.* 1985, 1275.
146. I. Tabushi, Y. Kuroda and K. Yokota: *Tetrahedron Lett.* 1982, 4601.
147. J.-H. Fuhrhop and U. Liman: *J. Am. Chem. Soc.* **106**, 4643 (1984).
148. J.-H. Fufrhop, U. Liman and H. H. David: *Angew. Chem. Int. Ed. Engl.* **24**, 339 (1985).
149. J.-M. Lehn and J. Simon: *Helv. Chim. Acta* **60**, 141 (1977).
150. J.-M. Lehn and M. E. Stubbs: *J. Am. Chem. Soc.* **96**, 4011 (1974).
151. W. Fischer, J. Brickmann and P. Lauger: *Biophys. Chem.* **13**, 105 (1981).
152. C. Etchebest, S. Ranganathan and A. Pullman: *FEBS Letters* **173**, 301 (1984).
153. For an earlier use of the intersection sign, see: E. Kauffmann, J. L. Dye, J.-M. Lehn and A. I. Popov: *J. Am. Chem. Soc.* **102**, 2274 (1980).
154. A. G. Amit, R. A. Mariuzza, S. E. V. Phillips and R. J. Poljak: *Science* **233**, 747 (1986); H. M. Geysen, J. A. Tainer, S. J. Rodda, T. J. Mason, H. Alexander, E. D. Getzoff and R. A. Lerner: *ibid.* **235**, 1184 (1987).
155. M. M. Harding and J.-M. Lehn: unpublished work.
156. D. A. Tomalia, M. Hall and D. M. Hedstrand: *J. Am. Chem. Soc.* **109**, 1601 (1987) and references therein.
157. G. R. Newkome, Z.-q. Yao, G. R. Baker, V. K. Gupta, P. S. Russo and M. J. Saunders: *J. Am. Chem. Soc.* **108**, 849 (1986); G. R. Newkome, G. R. Baker, M. J. Saunders, P. S. Russo, V. K. Gupta, Z.-q. Yao, J. E. Miller and K. Bouillion: *J. Chem. Soc., Chem. Commun.* 1986, 752.
158. H. M. McConnell, L. K. Tamm and R. M. Weiss: *Proc. Natl. Acad. Sci. USA* **81**, 3249 (1984); R. M. Weiss and H. M. McConnell: *Nature* **310**, 47 (1984).
159. T. Kunitake, Y. Okahata, M. Shimomura, S.-i. Yasunami and K. Takarabe: *J. Am. Chem. Soc.* **103**, 5401 (1981); N. Nakashima, S. Asakuma and T. Kunitake: *ibid.* **107** (1985) 509.
160. J. H. Fendler: *Membrane Mimetic Chemistry*, Wiley, New York, 1982.
161. H. Kuhn and D. Moebius: *Angew. Chem. Int. Ed. Engl.* **10**, 620 (1971).
162. D. Moebius: *Acc. Chem. Res.* **14**, 63 (1981); *Ber. Bunsenges Phys. Chem.* **82**, 848 (1978); *Z. Physik. Chem. Neue Folge* **154**, 121 (1987).
163. J. A. Hayward (Ed.): *New Technological Applications of Phospholipid Bilayers, Thin Films and Vesicles*, Tenerife, January 6–9, 1986, Plenum Press.
164. J. Sagiv: in [163]; L. Netzer and J. Sagiv: *J. Am. Chem. Soc.* **105**, 674 (1983).
165. H.-H. Hub, B. Hupfer, H. Koch and H. Ringsdorf: *Angew. Chem. Int. Ed. Engl.* **19**, 938 (1980); L. Gros, H. Ringsdorf and H. Schupp: *ibid.* **20**, 305 (1981).
166. G. Wegner: *Chimia* **36**, 63 (1982); C. M. Paleos: *Chem. Soc. Rev.* **14**, 45 (1985).
167. H. Kuhn: *Pure Appl. Chem.* **53**, 2105 (1981).
168. (a) J.-H. Fufrhop and J. Mathieu: *Angew. Chem. Int. Ed. Engl.* **23**, 100 (1984); (b) J.-H. Fuhrhop and D. Fritsch: *Acc. Chem. Res.* **19**, 130 (1986); (c) Y. Okahata: *Acc. Chem. Res.* **19**, 57 (1986).
169. (a) B. Balzani (Ed.): *Supramolecular Photochemistry*, D. Reidel Publ. Co., Dordrecht, Holland, 1987; (b) J.-M. Lehn: p. 29 therein.
170. J.-C. Rodriguez-Ubis, B. Alpha, D. Plancherel and J.-M. Lehn: *Helv. Chim. Acta* **67**, 2264 (1984).
171. B. Alpha, J.-M. Lehn and G. Mathis: *Angew. Chem. Int. Ed. Engl.* **26**, 266 (1987); B. Alpha, V. Balzani, J.-M. Lehn, S. Perathoner and N. Sabbatini: *Angew. Chem. Int. Ed. Engl.* **26** (1987), in press; N. Sabbatini, S. Perathoner, V. Balzani, B. Alpha and J.-M. Lehn, in ref. [169a], p. 187.
172. (a) H. Bouas-Laurent, A. Castellan and J.-P. Desvergne: *Pure Appl. Chem.* **52**, 2633 (1980); (b) H. Bouas-Laurent, A. Castellan, M. Daney, J.-P. Desvergne, G. Guinand, P. Marsau and M.-H. Riffaud: *J. Am. Chem. Soc.* **108**, 315 (1986).
173. J. P. Konopelski, F. Kotzyba-Hibert, J.-M. Lehn, J.-P. Desvergne, F. Fagès, A. Castellan and H. Bouas-Laurent: *J. Chem. Soc., Chem. Commun.* **1985**, 433.
174. D. F. Eaton: *Tetrahedron* **43**, 1551 (1987) and references therein.
175. A. Guarino: *J. Photochem.* **35**, 1 (1986).
176. M. Gubelmann, J.-M. Lehn, J. L. Sessler and A. Harriman: to be published.
177. V. Balzani, N. Sabbatini and F. Scandola: *Chem. Rev.* **86**, 319 (1986).
178. Photoactive units may photooxidise complexed substrates [93] and effect DNA photocleavage: A. J. Blacker, J. Jazwinski, J.-M. Lehn and F.-X. Wilhelm: *J. Chem. Soc., Chem. Commun.* 1986, 1035.
179. (a) J.-M. Lehn, in D. S. Chemla and J. Zyss (Eds.): *Non-Linear Optical Properties of Organic Molecules and Crystals*, Academic Press, New York, vol. 1987, p. 215; (b) J. F. Nicoud and R. J. Twieg: *ibid.* p. 221.

180. M. Takagi and K. Ueno: *Topics Curr. Chem.* **121**, 39 (1984); H.-G. Lohr and F. Vögtle: *Acc. Chem. Res.* **18**, 65 (1985); R. Klink, D. Bodart, J.-M. Lehn, B. Helfert and R. Bitsch: Merck GmbH, Eur. Patent Appl. 83100281.1 (14.01.1983).
181. R. C. Haddon and A. A. Lamola: *Proc. Natl. Acad. Sci. USA* **82**, 1874 (1985); R. W. Munn: *Chem. Br.* 1984, 518; J. Simon, J.-J. André and A. Skoulios: *Nouv. J. Chim.* **10**, 295 (1986); J. Simon, F. Tournilhac and J.-J. André: *ibid* **11**, 383 (1987) and references therein.
182. T. S. Arrhenius, M. Blanchard-Desce, M. Dvolaitzky, J.-M. Lehn and J. Malthete: *Proc. Natl. Acad. Sci. USA* **83** 5355 (1986).
183. (a) Biological effectors may also be sought: I. Tabushi, T. Nishiya, M. Shimomura, T. Kunitake, H. Inokuchi and T. Yagi: *J. Am. Chem. Soc.* **106**, 219 (1984); (b) for other related work see for instance: J. K. Nagle, J. S. Bernstein, R. C. Young and T. J. Meyer: *Inorg. Chem* **20**, 1760 (1981); E. T. T. Jones, O. M. Chyan and M. S. Wrighton: *J. Am. Chem. Soc.* **109**, 5526 (1987).
184. R. Schwyzer, A. Tun-Kyi, M. Caviezel and P. Moser: *Helv. Chim. Acta* **53**, 15 (1970); *Experientia* **26**, 577 (1970); see also ref. [1] p. 19.
185. (a) S. Shinkai: *Pure Appl. Chem.* **59**, 425 (1987); (b) D. A. Gustowski, M. Delgado, V. J. Gatto, L. Echegoyen and G. W. Gokel: *J. Am. Chem. Soc.* **108**, 7553 (1986) and references therein.
186. J.-M. Lehn, J. Malthête and A.-M. Levelut: *J. Chem. Soc., Chem. Commun.* 1985, 1794.
187. For phthalocyanine derived columnar mesophases see D. Masurel, C. Sirlin and J. Simon: *New J. Chem.* **11**, 455 (1987) and references therein.
188. E. Carafoli and J. T. Penniston: *Sci. Amer.* November 50 (1985); T. Hiraoki and H. J. Vogel: *J. Cardiovasc. Pharm.* **10**, (Suppl. 1), S14 (1987).
189. I. Tabushi, S.-i. Kugimiya and T. Sasaki: *J. Am. Chem. Soc.* **107**, 5159 (1985) and references therein.
190. D. Pörschke and M. Eigen: *J. Mol. Biol.* **62**, 361 (1971) and references therein.
191. J.-M. Lehn, A. Rigault, J. Siegel, J. Harrowfield, B. Chevrier and D. Moras: *Proc. Natl. Acad. Sci. USA* **84**, (1987) 2565; J.-M. Lehn and A. Rigault, unpublished results.
192. K. E. Drexler: *Proc. Natl. Acad. Sci. USA* **78**, 5275 (1981); C. Joachim and J.-P. Launay: *Nouv. J. Chim.* **8**, 723 (1984).
193. G. C. Pimentel, Chairman: *Opportunities in Chemistry*, Natl. Acad. Sci., Washington, DC, pp. 219–220.