

# SUPRAMOLECULAR CHEMISTRY - SCOPE AND PERSPECTIVES MOLECULES - SUPERMOLECULES - MOLECULAR DEVICES

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by

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.

## *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 coreceptors, metallo-receptors, amphiphilic receptors, anion coordination. Supramolecular catalysis by receptors bearing reactive groups effects bond cleavage reactions as well as synthetic, bond formation via cocatalysis. Lipophilic receptor molecules act as selective carriers for various substrates and allow to set up 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 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-assembly occurs with acyclic ligands that form complexes of 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 recogni-

tion, 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-1930's 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  $\sigma$  to its receptor  $Q$  yields the supermolecule and

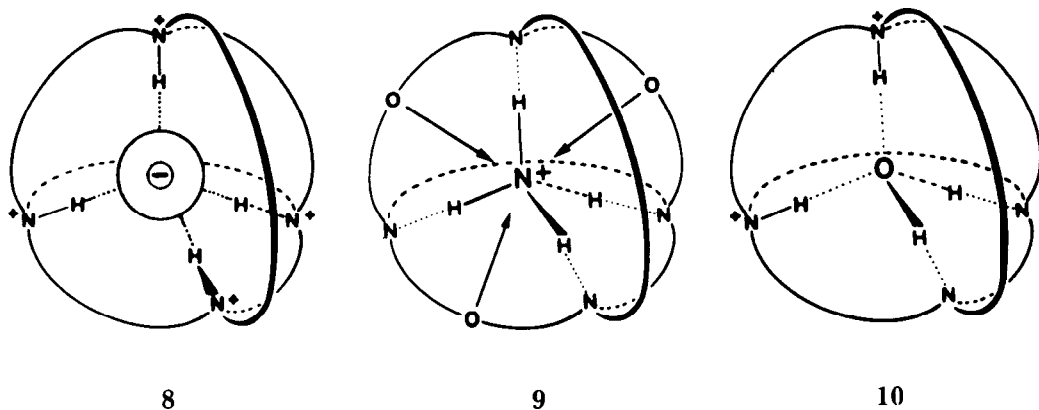












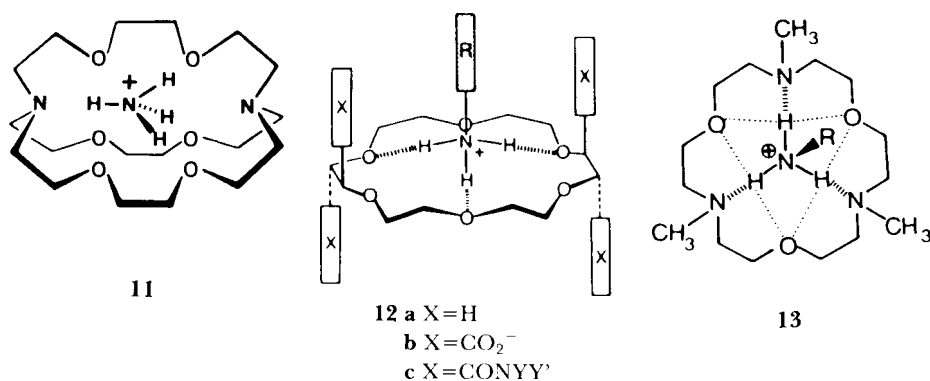
formulation of a water cryptate  $[\text{H}_2\text{O} \subset (5\text{-}2\text{H}^+)]$  **10** with the diprotonated macrotricyclic **5** [2, 6, 40]. The facilitation of the second protonation of **5** represents a *positive cooperativity*, in which the first proton and the effector molecule water set the stage both structurally and energetically for the fixation of a second proton.

Considering together the three cryptates  $[\text{NH}_4^+ \subset 5]$  **9**,  $[\text{H}_2\text{O} \subset (5\text{-}2\text{H}^+)]$  **10** and  $[\text{Cl}^- \subset (5\text{-}4\text{H}^+)]$  **8**, it is seen that the spherical macrotricyclic **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  $\text{NH}_4^+$ , a bent neutral molecule  $\text{H}_2\text{O}$  or a spherical anion  $\text{Cl}^-$  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 macrobicyclic **3** also binds  $\text{NH}_4^+$  forming cryptate **11**. The dynamic properties of **11** with respect to **9** reflect the receptor-substrate binding complementarity: whereas  $\text{NH}_4^+$  is firmly held inside the cavity in **9**, it undergoes internal rotation in **11** [41].

### 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  $-\text{NH}_3^+$  into their circular cavity via three  $^+\text{N-H} \cdots \text{O}$  hydrogen bonds as shown in **12a** [12-15,25,42]; however they complex alkali cations such as  $\text{K}^+$  more strongly. Selective binding of  $\text{R-NH}_3^+$  may be achieved by extending the results obtained for  $\text{NH}_4^+$  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-macrocyclic [18]- $\text{N}_3\text{O}_3$  which forms a complementary array of three  $^+\text{N-H} \cdots \text{N}$  bonds **13**, selects  $\text{R-NH}_3^+$  over  $\text{K}^+$  and is thus a receptor unit for this functional group [43].



A great variety of macrocyclic polyethers have been shown to bind R-NH<sub>3</sub><sup>+</sup> molecules with structural and chiral selectivity [12,13,42]. Particularly strong binding is shown by the tetracarboxylate **12b** which conserves the desirable basic [18]-0<sub>6</sub> 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<sub>3</sub><sup>+</sup> 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<sub>3</sub>)<sub>n</sub><sup>m+</sup> to macrocyclic polyethers via N-H...O interactions with the NH<sub>3</sub> groups, leads to a variety of supramolecular species of "supercomplex type" by second sphere coordination [46]. As with R-NH<sub>3</sub><sup>+</sup> 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 to induce various processes between centrally bound metal-amine species and 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<sub>2</sub>NH<sub>2</sub><sup>+</sup> ions bind to the [12]-N<sub>2</sub>O<sub>2</sub> macrocycle via two hydrogen bonds [48]. The case of quaternary ammonium ions will be considered below.

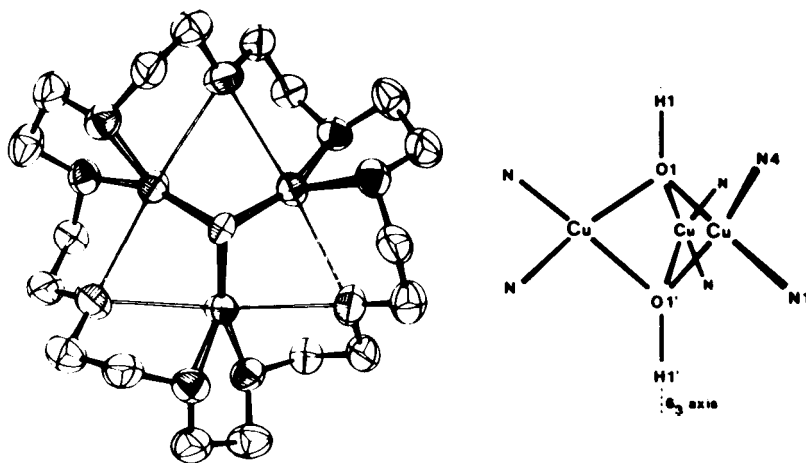
The guanidinium cation binds to [27]-O<sub>6</sub> macrocycles through an array of six H-bonds [49] yielding a particularly stable complex **14** with a hexacarboxylate receptor, that also binds the imidazolium ion [49a].











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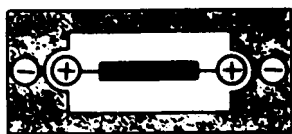
"Cluster cryptates" may be formed by assembling of metal ions and bridging species inside the molecular cavity of polytopic receptors. Thus, in the trinuclear Cu(II) complex **22** (crystal structure **23**) a [tris Cu(II), bis $\mu_3$ -hydroxo] group is bound in the cavity of a tritopic macrocycle [74]. 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.

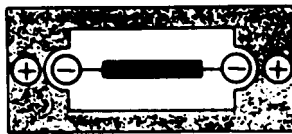
#### 4.2. Linear Recognition of Molecular Length by Ditopic Coreceptors

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**.

Incorporation of macrocyclic subunits that bind  $\text{-NH}_3^+$  groups (see above) into cylindrical macrotricyclic [76] and macrotetra-cyclic [77] structures, yields



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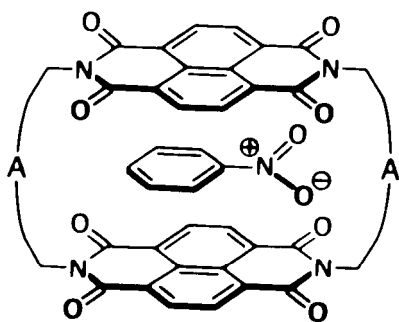
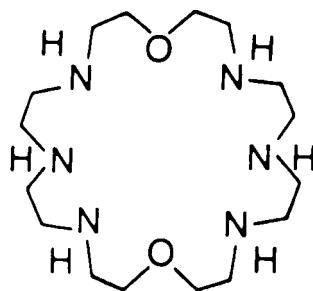


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32 ( $A=(CH_2)_8$ )

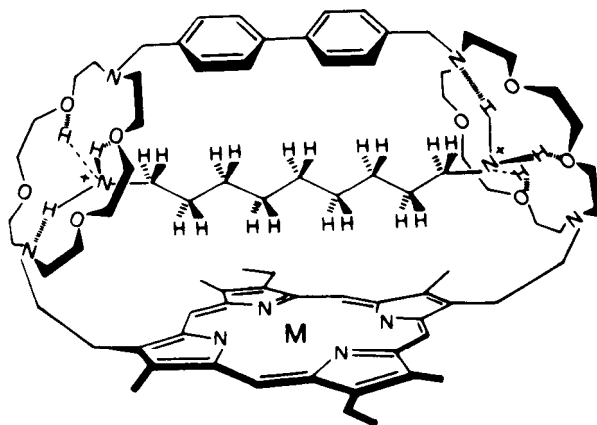
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The spherically shaped *cryptophanes* allow to study recognition between neutral receptors and substrates, and in particular the effect of molecular shape and volume complementarity on selectivity [99].

#### 4.4. Multiple Recognition in Metallo-Receptors

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

Porphyrin and  $\alpha,\alpha'$ -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 the bound, numerous types of metalloreceptors may be imagined which would be of interest as abiotic chemical species or as bioinorganic model systems.

34 ( $M=Zn$ )







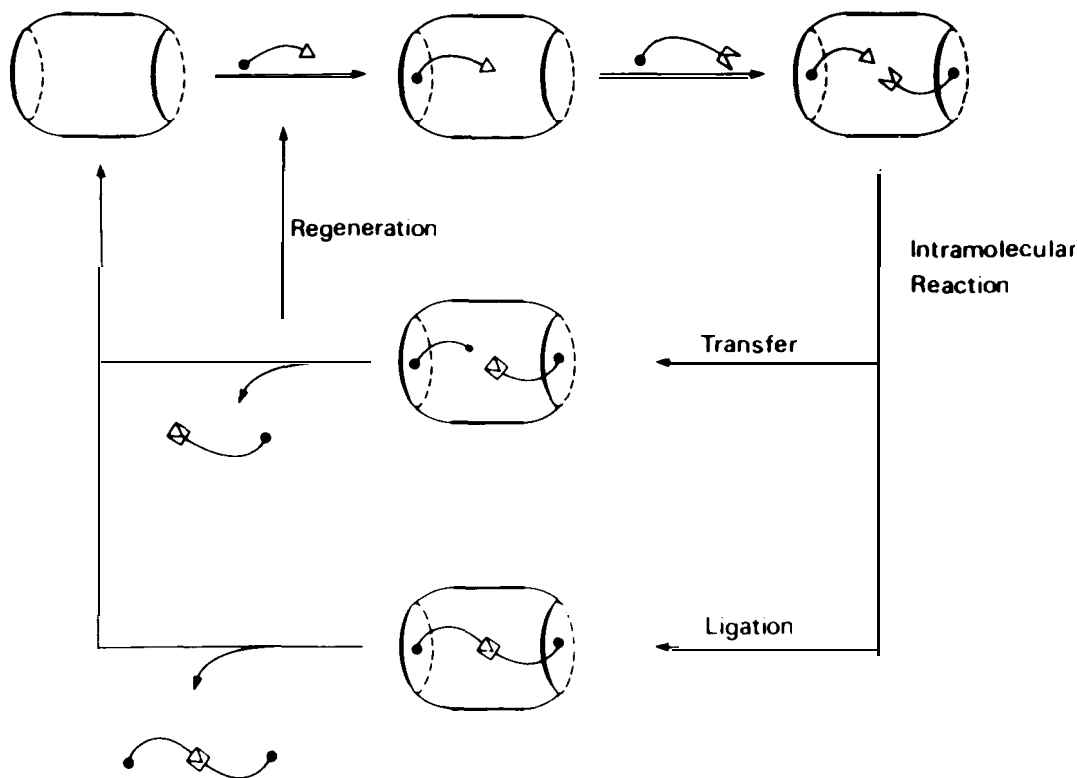


Fig. 4. Schematic illustration of cocatalysis processes: group transfer and ligation reactions occurring within the supramolecular complex formed by the binding of substrates to the two macrocyclic subunits of a macrotricyclic coreceptor molecule.

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 (Fig. 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 presence of divalent metal ions has also been reported [112].

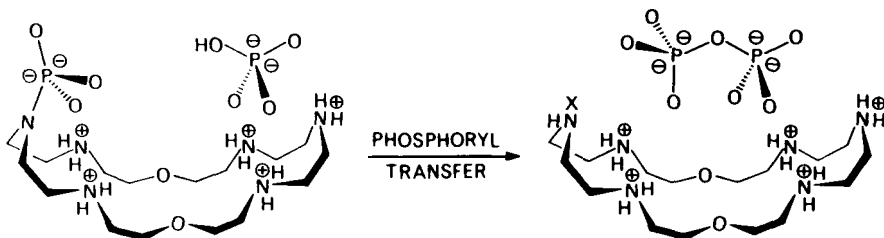


Fig. 5. Cocatalysis: pyrophosphate synthesis by phosphoryl transfer mediated macrocycle **33** via the phosphorylated intermediate **38**.

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, 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 coreceptors open the way to the design of cocatalysts for ligation, metallocatalysis, cofactor 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 effecters, to devise transport processes, to investigate their applications in chemistry and in biology. Selective membrane permeability may be induced either by *carrier molecules* or by *transmembrane channels* (Fig. 6).

### 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) (Fig. 6) is a *physical catalysis* operating a translocation on the substrate like chemical catalysis effects a













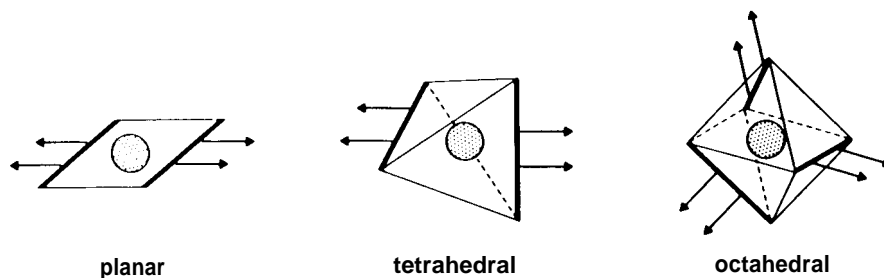


Fig. 9. Schematic representation of the arrangement of external interaction sites (represented by arrows) around a metal ion of given coordination geometry in mononuclear metallo-exoreceptors.

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 (Fig. 9).

As a first approach to receptor design along these lines, specific groups, selected for their information content, have been attached to functionalized  $\alpha, \alpha'$ -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 described 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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