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Template Synthesis of Macrocyclic Compounds

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Preface

The synthesis of substances or creation of molecules by means of chemical transformations is the basis of progress in almost all domains of chemistry. The level of chemical understanding in any epoch, as well as practical scientific achievements, depend on what substances can be obtained and what properties they have. The modern facilities available to science, including apparatus, instruments, devices and methods of studying matter and its properties, tend to overshadow the importance of synthesis. Moreover, obtaining compounds and materials with predefined properties depends significantly on the power of the synthetic tools deployed.

Since the mid 1960s the employment of template processes (reactions on matrices) has been of great significance. They allow us to obtain compounds that are difficult or even impossible to synthesise from their components by traditional methods. In particular, template reactions provide the basis of the synthesis of macroheterocyclic compounds, whose systematic preparation, wide research investigation, and applications are well-known. The features of the template synthesis of macrocyclic systems have been discussed in various aspects and to different extents in various monographs and reviews. However, the fast development of this fascinating area of synthetic chemistry has provided new results, which are related to the theory and practice of template synthesis itself and which need special consideration and generalisation.

This book describes template processes, their mechanisms, the 'centres' used for their realisation, and the basic classes of compounds synthesised by means of these reactions. Detailed consideration is given to ways of constructing macrocyclic systems. The main classes of substances examined are polyazamacrocyclic compounds, crown ethers and their hetero-analogues, and other products such as cryptands, sepulchrates, sarcophagines, catenanes, rotaxanes and knots. The conditions for carrying out such reactions, which are sometimes very specific in character, are also considered. Taking into account the recent achievements in the field of the template processes, the trends of research in this domain have been analysed.

It is a particular pleasure to acknowledge our colleagues, who have contributed in one way or another to this work. We wish particularly to thank Dr. V.N. Cebotari and V.G. Levitsky for technical assistance and S.A. Kostyuk for helping us to produce the text.

We should like to express our special gratitude to Professor K.B. Yatsimirskii and Dr. Ya.D. Lampeka from the Institute of Physical Chemistry of the Ukrainian Academy of Sciences for their advice and assistance during the period of writing. Special thanks go to many colleagues from different countries for kindly making available their recent research results. They are too numerous to name individually. We have tried to incorporate these works into our book. V.A. is greatly indebted to Professor M.T. Reetz of Max-Planck-Institut für Kohlenforschung who was an excellent host during the sabbatical in 1998, where the work on the manuscript was concluded and to the Alexander von Humboldt foundation for financial support. Where structural data have been presented, we wish to acknowledge the use of the EPSRC's Chemical Database Service at Daresbury.

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Chapter 1

Template processes

1.1 Introduction

The various aspects of template synthesis of macrocyclic compounds have been discussed in a series of monographs and reviews [1–21]. However, there is no strict definition of what can be called a template reaction. A synthetic chemist who takes advantage of the template effect in synthesis will have his own view of what constitutes a template process. It is therefore appropriate to commence here with a general definition, which is that the template effect is the enhancement of chemical reaction by complementary surfaces [22, 23]. One of the first examples was connected with the discovery of the double helix structure of DNA (Figure 1-1) by Watson and Crick in 1953 [24]. The template effect is operative in its replication. Each chain of the DNA double helix serves as template, or mould, for the formation of the second chain.

"A chemical template organises an assembly of atoms, with respect to one or more geometric loci, in order to achieve a particular linking of atoms." [16]. A mechanistically simple S_N2 alkylation of an amine (L1) by an alkyl halide (L2) in the presence of a template is shown in Scheme 1-1 [25]. In the first step of this templated synthesis the template binds simultaneously two substrates via hydrogen bonding, placing the reactive functionalities in close proximity to each other, so that their interaction becomes possible. This results in a new product appearing due to formation of a C–N bond. It remains temporarily bonded to the mould, and the dissociation of the complex gives the template-free product. The template can be then used again in later synthetic cycles. This is a general illustration of the template effect operating in a chemical reaction.

In this book we do not embrace the topic in a very broad sense. Rather, our aim is to try to show the exploitation of the template effect in a specific field – macrocyclic chemistry.

Macrocyclic compounds, various classes of which have been known for a long time, have attracted great attention in respect of the synthesis, physico-chemical and physical investigation of various new representatives of these substances. The search for applications has solved or made it possible to solve many significant

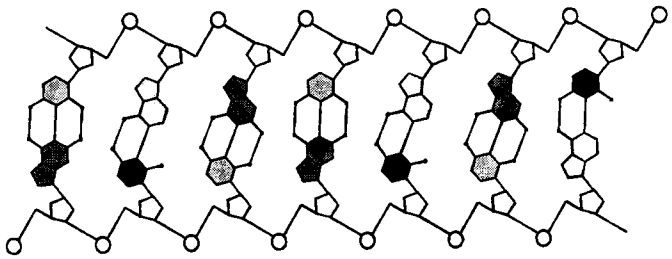


Figure 1-1. Schematic representation of the complementary strands in the double helix structure of DNA.

practical tasks in different fields of science and engineering (e.g. chemistry, electrochemistry, biophysics, metallurgy, catalysis, preparative organic synthesis, medicine, agriculture and ecology) [1, 4, 13].

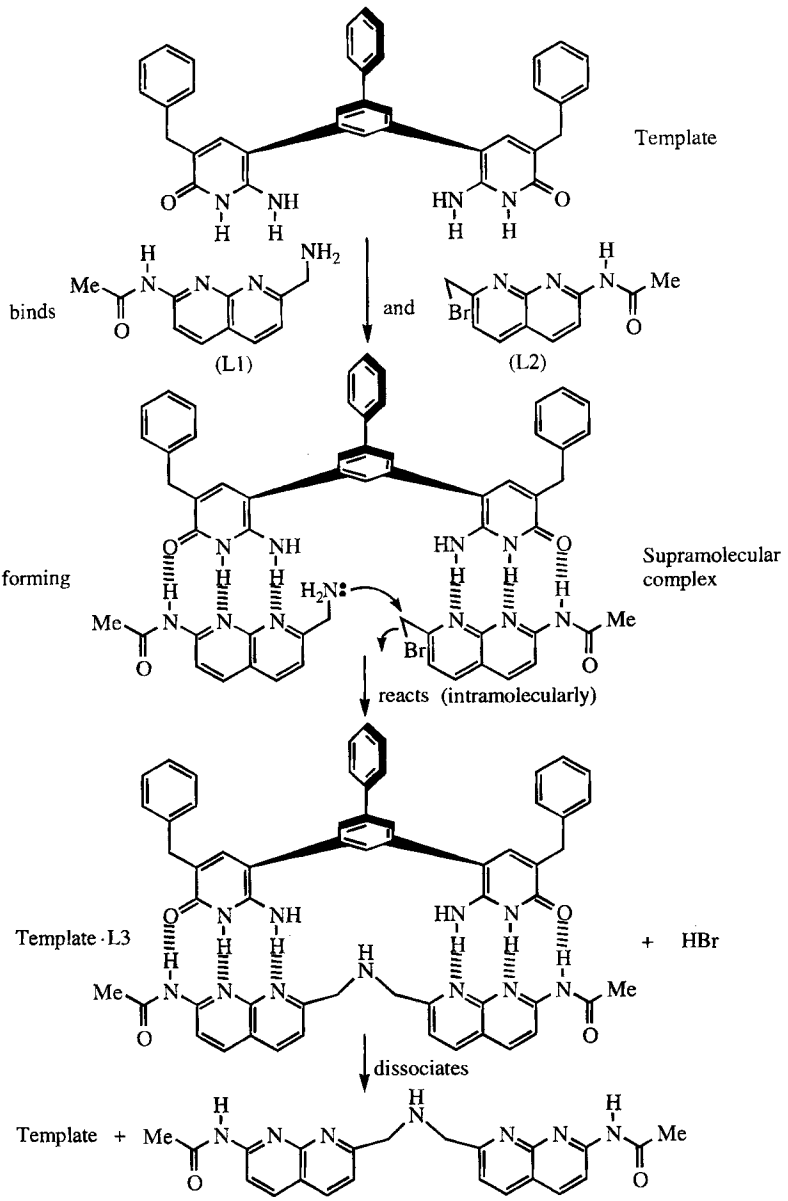
The use of template effects in the synthesis of new compounds was first demonstrated by the pioneering work of Busch, on metal template effect exploration in the synthesis of macrocyclic compounds in the 1960s. This then led to the renaissance of the chemistry of macrocyclic compounds in general. It is not an overstatement to say that the emergence of supramolecular chemistry, whose importance in life processes cannot be overestimated, was largely due to the exploration of template methodology. It is sufficient to remember that in the serendipitous discovery of Pedersen's crown polyethers, actively used in host–guest chemistry, the template effect of alkali metal ions played a paramount role. Moreover, self-assembly, as another conceptual category in supramolecular chemistry, can be considered as an extension of the template effect in both chemistry and biology.

As the discussion will focus mainly on metal template processes, the following definition of template processes seems to be appropriate:

Template processes are those in which the metal ion, or another centre that has a definite stereochemistry and electronic state, serves as a mould, pattern, form, or matrix for forming, from appropriate building blocks, reaction products whose synthesis is either difficult or totally impossible under other conditions [2, 11]. Put another way, template reactions may be called the transformations in which the interaction of initial ligands is either conditioned or considerably facilitated by their suitable spatial orientation as a result of coordination. This is dictated by the metal ion, or another centre, by its organising and sequestering role as well as by its effect on reactivity.

In addition, template synthesis has an advantage over other methods in that, in the majority of cases, it leads to the appearance of additional metallocycles and, in the process, to the tailoring of these metallocycles.

It is well known [26, 27] that coordination of one bidentate ligand to a metal ion is energetically more advantageous than the coordination of two monodentate ligands with analogous donor atoms, due to formation of a chelate or metallocyclic ring. This phenomenon is known as the **chelate effect** [28]. Moreover, in a series of related compounds, stability constants increase with an increase in the number of



Scheme 1-1. Template S_N2 alkylation of an amine by an alkyl halide.

chelate rings. In turn, the greater stability observed for the complexes of cyclic ligands, over those of open-chain analogues of similar structure, has been termed the **macrocyclic effect** [29]. Stability constants increase by several orders of magnitude on going from mono- to bidentate ligands, with further enhancement of the stability of cyclic ligand complexes over their linear counterparts [29–31]. The stability constants of metal complexes with crown ethers also appear to be several orders of magnitude higher in comparison with their corresponding open-chain analogues. As with the chelate effect, the macrocyclic effect manifests itself to a different degree, depending upon the nature of the metal as well as upon the nature, number and arrangement of donor atoms and other parameters of the macrocycle. The physico–chemical factors at the basis of the macrocyclic effect have been examined thoroughly in a series of sources [1, 32].

The use of template synthesis procedures makes it possible to carry out a wide range of reactions of either a stoichiometric or a catalytic nature. In all cases this pathway facilitates the preparation, from simple starting blocks, of more complex organic compounds, which are as a rule isolated as coordination compounds of the metal centre used as template. It should be emphasised that the use of template processes constitutes the basic strategy for the synthesis of macrocyclic compounds with nitrogen donor atoms, as well as of a number of crown ethers and of other cyclic systems containing various donor atoms. This is because, when building macrocyclic systems by non-template procedures, the entropy of the condensing fragments, related to the decrease of the number of rotational and vibrational degrees of freedom, decreases markedly. As a result the probability of formation of the cyclic products is reduced. In contrast, in the presence of the template, the starting ligands are coordinated. This results in a preliminary entropy lowering, which facilitates the following stages necessary for the final assembly of the macrocyclic product [4, 33, 34]. At present the reactions on matrices are so dominant in the synthesis of macrocyclic compounds, that in cases where the latter are obtained without using the template effect, the authors make special mention of this fact [5].

1.2 Fundamental terms and notions

The term "template" has been widely used since 1964 [35]. Daryle Busch introduced the template notion in coordination chemistry in 1963 [36]. Since 1968 the synonym of this term – matrix – has also been widely used [2, 10, 37]. The concept of a template or mould first appeared in 1953 in molecular biology, which, in turn, had borrowed the term from engineering (polygraphy, punching). It is worth noting that "template" in the *Oxford English Dictionary* is defined as "an instrument used as a guide in bringing any piece of work to the desired shape". Matrix, as a synonym of template, is also used in many other languages.

In the literature devoted to template synthesis several specific terms and expressions are used. Some have become generally accepted while others, though not as

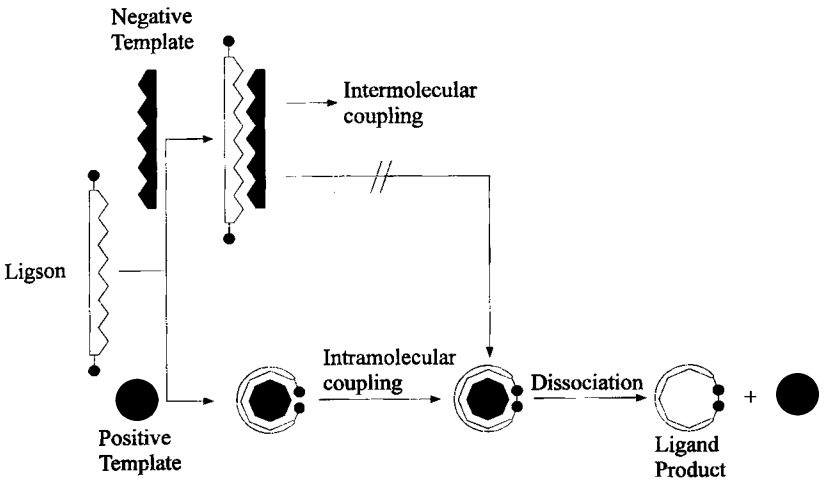


Figure 1-2. Schematic illustration of positive and negative template effects in directed synthesis of chemical species.

widely used, are necessary for the following discussion on the synthesis of macrocyclic systems, e.g. [1, 4, 38–42]:

- **Template centre** (template, matrix, mould, form, model, pattern) – the metal ion or another particle (molecule, anion) which can orientate and activate the ligands for their subsequent interaction.
- **Positive template** – a template which brings together the reactive end groups of a molecule (molecules) facilitating intramolecular coupling.
- **Negative template** – template which prevents the reactive end groups of a molecule (molecules) coming together suppressing intramolecular coupling and favouring intermolecular reactions. A schematic illustration of both kinds of templating is shown in Figure 1-2 [42].
- **Template bonds** – forces by means of which the corresponding template orients (and/or activates) the reacting ligands, organising their preparation for the reaction. Metal-ligand binding, hydrogen bonding, and π–π interactions can be successfully exploited with a high degree of control in syntheses of macrocycles.
- **Ligand synthon or ligson** – a polyfunctional, usually chelating, ligand that takes part in the assemblage reactions at the template centre (a building block for the template synthesis).
- **Chelant (chelator)** – the open-chain ligand which occupies several coordination places in the inner sphere (coordination shell) of the template centre.
- **Assemblage reaction** – the organic reaction at the template centre, by means of which coupling of ligands occurs.
- **Construction (chelatogene) bonds** – covalent bonds formed as a result of assemblage reactions and providing the skeleton of the appearing chelatocycles.

- **Ligand product** – the final organic product (ligand) which is formed as a result of ligsons interaction.
- **Template information** – the totality of coordinative-stereochemical characteristics of the template centre which stipulates a definite spatial arrangement of ligsons.
- **Template complementarity** – a matching between the template information of the matrix and the geometrical (conformational) and electron donor-acceptor parameters of the ligsons and of the ligand product.

As this book deals mainly with macrocyclic systems we include here the following definition:

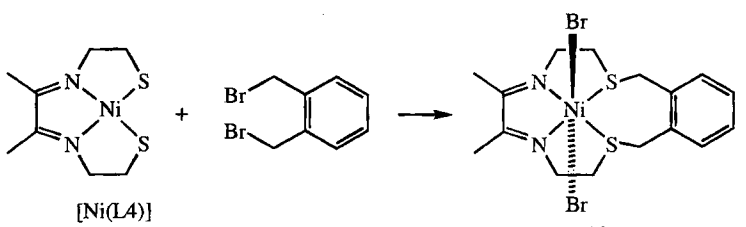
- **Macrocyclic compound** – a cyclic compound with nine or more atoms in the ring, of which not less than three are electron pair donors.

1.3 Mechanistic aspects of the template effect

The template centre plays the key role in matrix reactions. If the steric course of macrocyclisation, or other multistep reaction, is directed and facilitated by the ligsons' spatial structures, and their activation by coordination to the metal ion or another centre, then the process is controlled by the **kinetic coordination template effect**. If the metal ion (or another centre) sequesters one of the components from an equilibrium mixture (starting ligsons and other competing molecular species) and, as a consequence, shifts the position of the equilibrium towards the formation of the desired product in the form of its metal complex, then the **thermodynamic (or equilibrium) coordination template effect** is considered to be operative for the reaction.

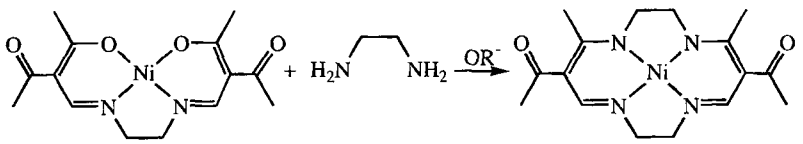
Two distinct classes of template effect have been distinguished since 1964 [39]. Both types of effect are, chemically, manifestations of molecular organisation by means of coordination to the template centre [14]. This is their common feature.

Reactions with a pronounced kinetic coordination template effect are found, in particular, in cases of preparation of macrocyclic compounds by ring-closure of chelate precursors. For example, when the complex [Ni(L4)] is electrophilically alkylated with 1,2-bis(bromomethyl)benzene, the macrocyclic product $[Ni(L5)Br_2]$ is isolated (Eq. 1.1).



[Ni(L4)] $[Ni(L5)Br_2]$ (1.1)

A kinetic study of this reaction showed [39] that the interaction of the starting chelate with the difunctional alkylating agent proceeds in two steps. The first, slow, step consists of 1,2-bis(bromomethyl)benzene attack at the coordinated mercaptide group, followed by the very fast step of macro-ring closure. Note that reaction of the initial complex [Ni(L4)] with benzyl bromide or methyl iodide, unlike the process just described, occurs in two slow consecutive steps. In this case the reaction with the first mole of alkyl halide is much faster than with the second. As a result, in the formation of the monoalkylated intermediate with 1,2-bis(bromomethyl)benzene, the potential reacting functions are, owing to their coordination to the nickel ion, held in close proximity to each other, poised for the reaction between them to occur. Thus the first step is rate-determining.

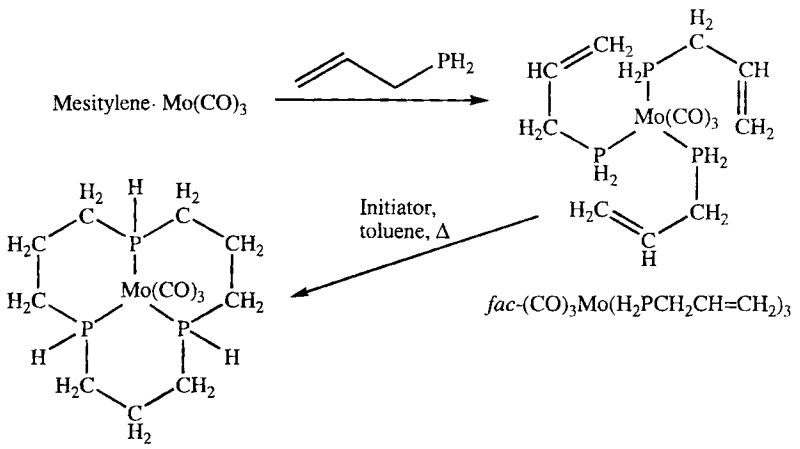


[Ni(L6)] [Ni(L7)] (1.2)

During template condensation of chelate [Ni(L6)] with 1,2-diaminoethane (en) in the presence of base, the kinetic coordination effect is also revealed (Eq. 1.2) [41]. In this case it resides in the spatial structure of the reacting components as well as in their considerable activation. Kinetic measurements confirm formation in the initial step of the six-coordinate adduct Ni(L6)·2en with the molecules of en axially arranged. The central ion thus polarises the amino-groups of coordinated en molecules and carbonyl groups of $(L6)^{2-}$. A proton dissociates from the polarised coordinated 1,2-diaminoethane $-NH_2$ group under the influence of hydroxide or ethoxide ion, and the highly reactive nucleophile $^{-}NH-(CH_2)_2-NH_2$ grouping is formed. Polarisation of the CO groups of the tetradentate ligand in turn increases the electrophilicity of these carbon atoms. This facilitates the condensation of a deprotonated amino-group of en with one of the coordinated CO groups. This sluggish step is followed by a rapid process of ring closure by the second $-NH_2$ group interacting with another coordinated CO-group of the tetradentate ligand. It should be noted that the topology of the intermediate is undoubtedly of major importance for the ring closure reaction to occur. It is obvious that steric factors must also contribute to the realisation of the reaction [14].

In the above examples of the kinetic coordination template effect, the metal ion serves to transfer information to interacting compounds, so the structure of the reaction product is predetermined. In such cases the strict geometry of the metal ion coordination sphere [2, 11] may be considered as an information source.

Mesitylene·$Mo(CO)_3$ reacts with allylphosphine in benzene to produce *fac*-$(CO)_3Mo(H_2PCH_2CH{=}CH_2)_3$, which under the action of a free-radical initiator {2,2′-azobis(isobutyronitrile)} in toluene is converted into the macrocyclic triphosphine complex *fac*-$(CO)_3Mo(L8)$ [43] (Eq. 1.3).



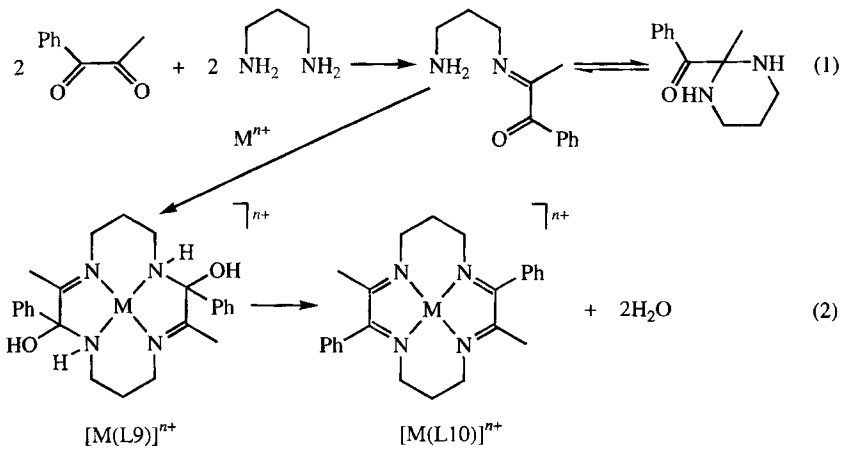
(1.3)

It should be noted that uncoordinated allylphosphine does not cyclise when treated with initiator. This gives evidence for the kinetic coordination template effect operating in this process. In conditions of kinetic control (enforced by spatial effects resulting from coordination to the metal), macrocyclic product formation by addition of P–H to the C=C double bond of a neighbouring coordinated allylphosphine proceeds contrary to Markovnikov's rule (phosphorus as a more electronegative element bonded to a less substituted carbon atom). This template process is notable for its exceptional regiospecific character in that the formation of Markovnikov addition products is not detected.

The following reactions provide examples of the thermodynamic coordination template effect.

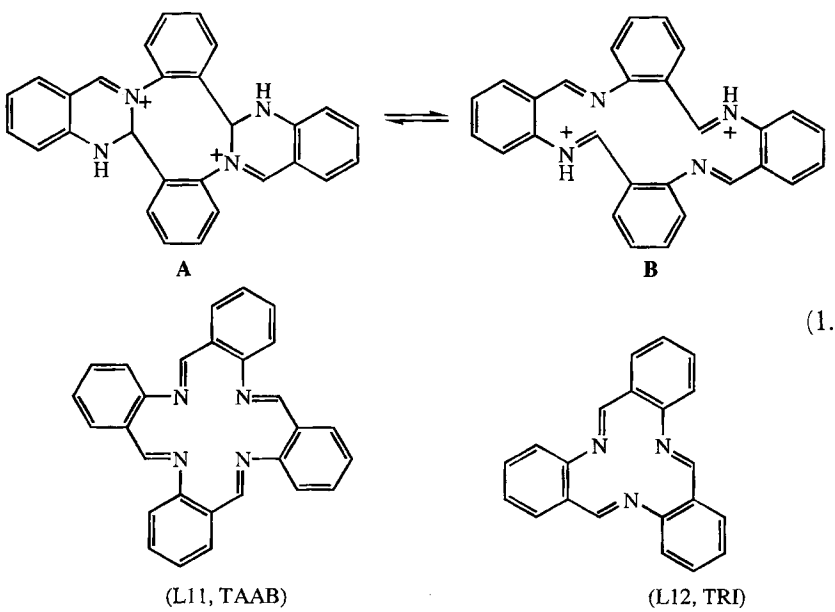
The template synthesis of macrocyclic complexes *trans*-$[M(L9)]^{n+}$ ($M^{n+} = Ni^{2+}$, Co^{3+}, Fe^{2+}) from 1-phenyl-1,2-propanedione and 1,3-diaminopropane occurs [44] according to Scheme 1-2. Reaction (1) represents the "organic" reaction prior to addition of a metal salt. When a methanolic solution of the latter is added to the reaction mixture, the metal-directed condensation is realised, producing the carbinolamine and final products. It is obvious that reaction (2) is a consequence of shifting the position of tautomeric equilibrium under the influence of a metal ion exclusively towards $[M(L9)]^{n+}$, the latter subsequently being transformed into $[M(L10)]^{n+}$. That the condensation reaction actually takes place within the metal coordination sphere has been demonstrated by the isolation of the corresponding cobalt(III) macrocyclic complexes with L9.

The self-condensation of *o*-aminobenzaldehyde may be taken as another example where the thermodynamic template effect is suggested to be operative [4, 45]. In the absence of metal salts it gives various products either of macrocyclic or non-cyclic nature. If there are strong mineral acids in the solution, a doubly protonated tetramer product A is formed, which is in equilibrium with its isomeric form B. In the presence of metal ions, *o*-aminobenzaldehyde gives (TAAB) or (TRI), bound in the corresponding complexes. Transition metal (3d) ions introduced into the equi-



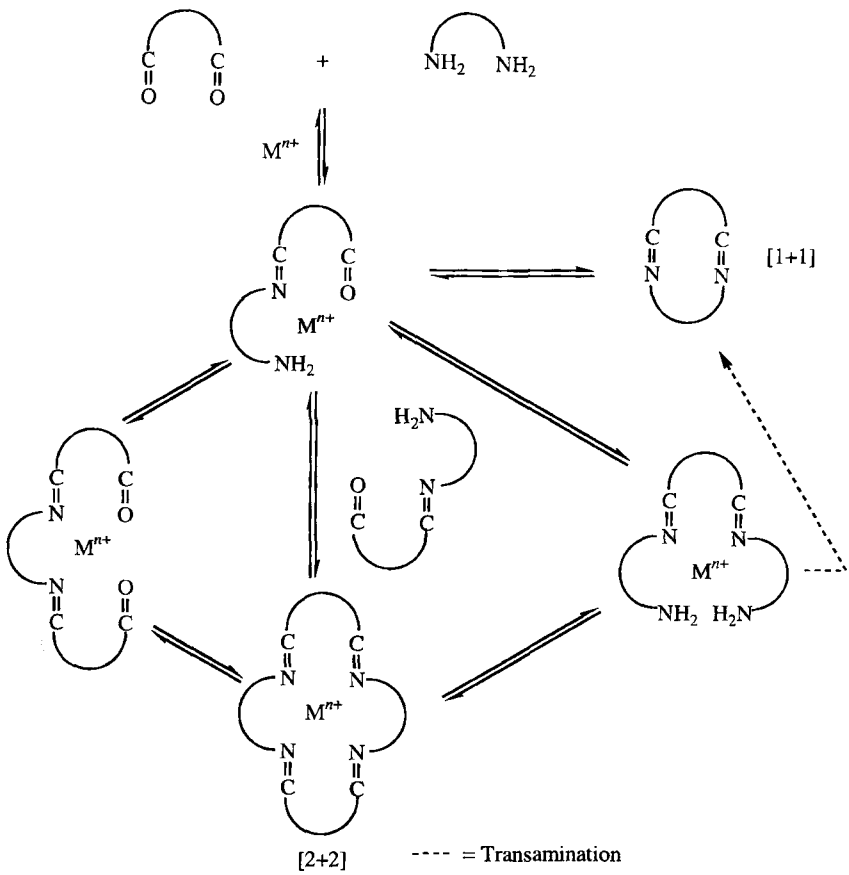
Scheme 1-2. Template synthesis of $[M(L10)]^{n+}$.

librated system A ⇌ B give only [M(L11)] (Eq. 1.4). Hence the kinetic coordination template effect, which could cause a transformation of L11 into L12, cannot manifest itself. These observations affirm the prevalence of the thermodynamic coordination template effect in the synthesis of L11.



(1.4)

In the above-mentioned cases attention is intentionally paid to two different ways of conducting reactions on matrices. In one case the topological factor is empha-



Scheme 1-3. Possible synthetic routes for template assembly of [2 + 2] macrocycles.

sised, and in the other the sequestration of the desired product by means of coordination to the metal ion is outlined.

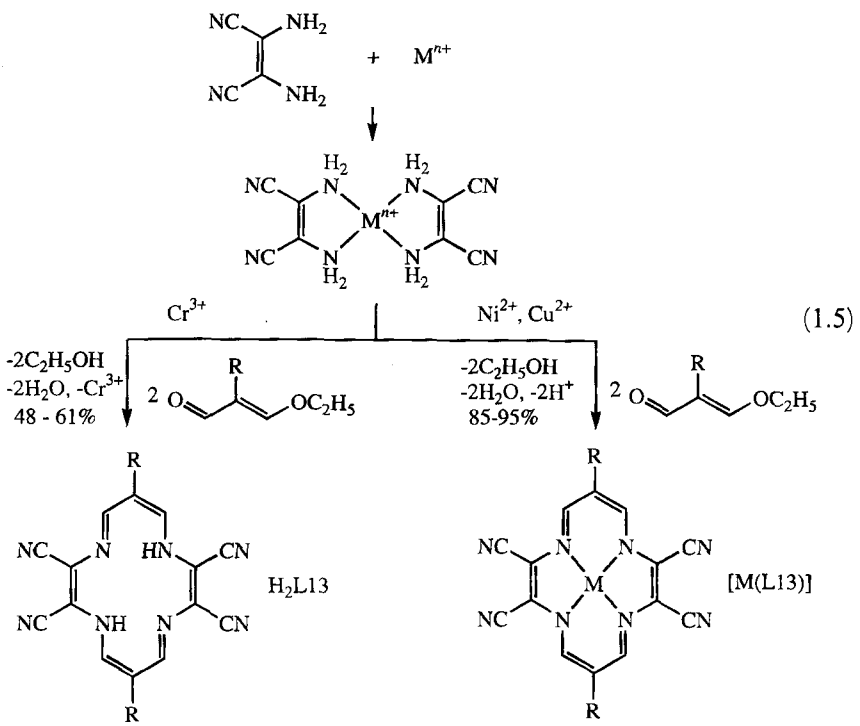
As a rule, template processes have a more complicated nature. They often involve several steps and alternative sequences may also occur. Scheme 1-3 represents the case of [2 + 2] building of macroheterocyclic compounds, described in detail in corresponding sections of this book. This diagram, adapted from [46], shows how a shift of the equilibrium in any direction implies participation of one of the two initial ligsons. Formation of systems of [1 + 1] type is possible if one of the building blocks contains at least one extra donor atom suitable for chelation. It should be noted that appearance of the [2 + 2] template condensation product by synchronous interaction between four corresponding ligsons is scarcely probable, and has therefore been omitted from Scheme 1-3. The substances that result from template transformations depend, among other factors, on the kinetic lability and thermodynamic stability of every species participating in the equilibria. In particular, at

any reaction step either kinetic or thermodynamic factors play the key role but, for the overall process, only one of them may be of prevailing significance.

Thus, when we say that, for instance, a kinetic coordination template effect is responsible for the production of some product, it does not mean that a possible contribution from the thermodynamic coordination template effect is ruled out. The role of the matrix does not depend on one or other of the two coordination template effects prevailing. It consists not only in the strict suppression of side effects, but also in directing the process to its most favourable pathway [2, 4].

1.4 Generation of metal-free macrocycles

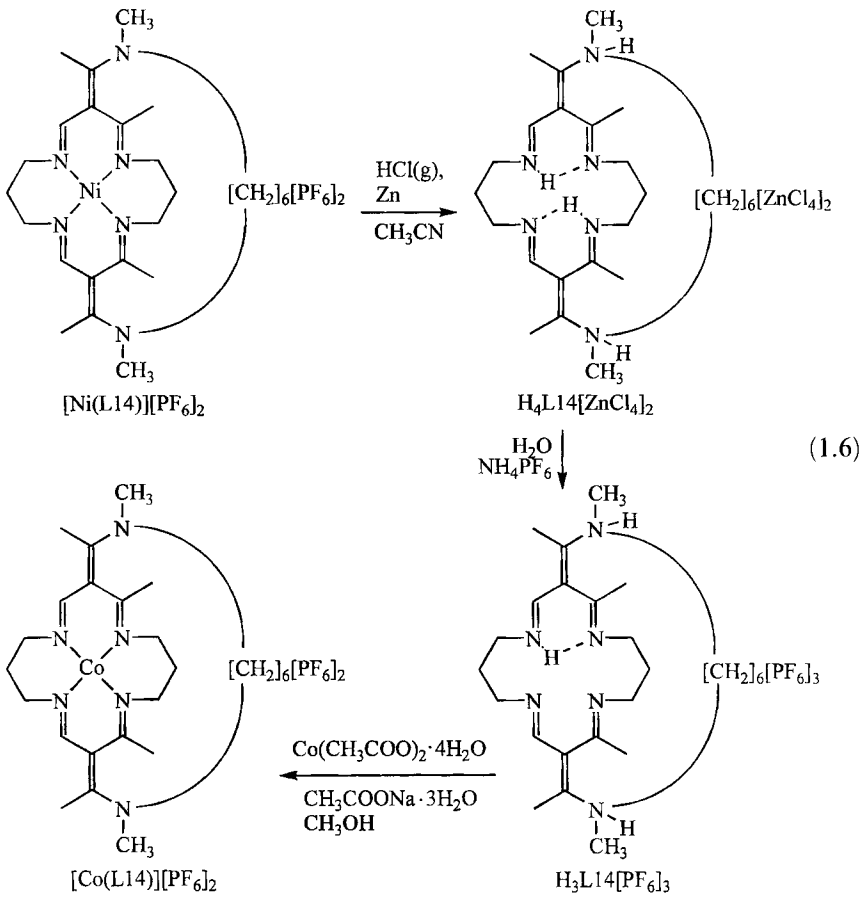
In the examples described so far, where a metal ion is used as template, macrocyclic organic compounds are isolated as complexes. There are also many template processes in which the organic product formed is isolated in the metal-free state. Frequently different templates allow the building up of the same product from the same ligsons, which may then be isolable as a coordination compound or in the metal-free state, depending on the nature of the metal ion. This is illustrated by the assembly of the macrocyclic system H_2L10 from diaminomaleodinitrile and 3-ethoxyacroleins in the presence of nickel(II), copper(II), or chromium(III) (Eq. 1.5) [47–49].



(1.5)

It should be noted that a metal complex is most commonly the final product when synthesising polyazamacrocyclic compounds. However, as a rule, crown ethers synthesised by template procedures are isolated in the metal-free state.

In some cases the macrocyclic metal complexes may be demetallated through the action of appropriate reagents, such as HCl, HBr, cyanides, H_2S, OH^- or ethylenediaminetetraacetate ion, leaving the metal-free macrocycle in solution. Thus on passing dry hydrogen chloride through an acetonitrile solution of $[Ni(L14)][PF_6]_2$, with the subsequent addition of the solution obtained from the reaction of metallic zinc with dry HCl in CH_3CN, $H_4L14[ZnCl_4]_2$ is isolated (Eq. 1.6).



(1.6)

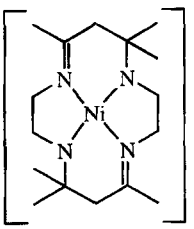
After dissolving this salt in water and adding NH_4PF_6, the metal-free compound $H_3L14[PF_6]_3$ can be isolated. This readily forms complexes with other metals [50].

The possibility of demetallating complexes is of special importance in cases where only one or a limited number of centres may be used for the synthesis of the macrocycle in the form of a complex. The isolation of free ligands enables coordination

compounds to be obtained with metal ions which are normally reluctant to act as matrices.

1.5 Transmetallation

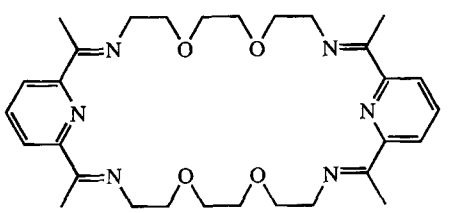
Situations are known when demetallation results in the formation of a macroheterocyclic organic compound which is unstable in the metal-free state. This is the case, for instance, when $[Ni(L15)](ClO_4)_2$ interacts with aqueous NaCN [51] (Eq. 1.7).



$[Ni(L15)](ClO_4)_2$

$$(ClO_4)_2 + 4NaCN + 4H_2O \longrightarrow Na_2[Ni(CN)_4] + 2NaClO_4 + 2 \text{ (acetone)} + 2\ H_2N(CH_2)_2NH_2 \quad (1.7)$$

This restricts possibilities of obtaining complexes of the corresponding ligand with metals unable to act as templates. One solution is transmetallation, namely, the treatment of a kinetically labile complex with a metal ion to form inert complexes. Thus it is possible to synthesise complexes of nickel(II), copper(II), iron(II), cobalt(II) and cobalt(III) with the unstable ligand L16 from the corresponding $[Pb(L16)]X_2$ or [Ag(L16)]X, themselves assembled with the use of lead(II) or silver(I) as templates [46] (Eq. 1.8).



L16 (1.8)

There are also many situations where demetallation of coordination compounds obtained by template pathways is impossible. The reason for this is the high thermodynamic and kinetic stability of these metal complexes according to the **principle of maximal correspondence between the cavity and the metal ion** (PMCCMI). This principle requires a number of conditions [32] to be fulfilled:

- matching of the macrocycle cavity size to the corresponding metal ion, i.e. the average cavity diameter must be equal to the diameter of the central metal ion;

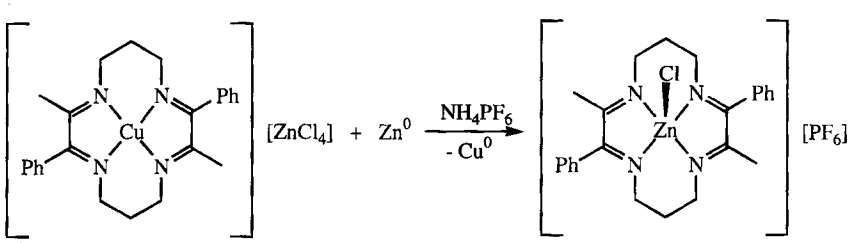
- certain electron donor characteristics of the atoms of the cavity, interacting with the central transition metal ion to form a donor-acceptor bond, i.e. the presence of electron pairs in orbitals of high energy (usually HOMO) overlapping the acceptor orbitals of the central ion;
- for central ions with partly filled d-orbitals, the LUMO of the ligand, capable of π-acceptor interaction, should have the lowest possible energy;
- the electrostatic characteristics of hard donor atoms and groups (effective charges, dipole moments, polarisability) should ensure the maximal value of the energy of interaction with alkali and alkaline earth metal ions, lanthanides and actinides;
- the correspondence of the number of donor atoms within the cavity to the optimal coordination number of the metal ion;
- the spatial arrangement of ligand binding sites within the cavity which should match the optimal coordination polyhedron for the given cation;
- macrocycle conformation flexibility (or rigidity) allowing the donor atoms to satisfy the metal ion stereochemical demands with a minimum strain energy.

Among complexes of the first row transition metals most often used as templates, copper(II) macrocyclic complexes demetallate least readily as the energy of vacant d-orbitals decreases along the d^5, d^6, d^7, d^8, d^9 ion series [4, 44]. In this case, reductive transmetallation may be used [4, 44]. Thus, by treatment of the copper(II) complexes with metallic zinc or zinc amalgam, it is possible to replace Cu by Zn [52] (Scheme 1.4).

On going from copper to zinc, PMCCMI requirements are perturbed significantly because the preferred stereochemistry (tetrahedral) and electron configuration (d^{10}) of zinc(II) differ from those of copper(II) (square-planar, d^9). As a result, it becomes possible to transmetallate zinc complexes with ions of other metals.

1.6 Template particle types for obtaining different ligand products

In all the examples described above, except for the synthesis of L8, metal ions are used as template centres. Most commonly they play the role of matrices, condi-



[Cu(L17)][$ZnCl_4$] [Zn(L17)Cl][PF_6]

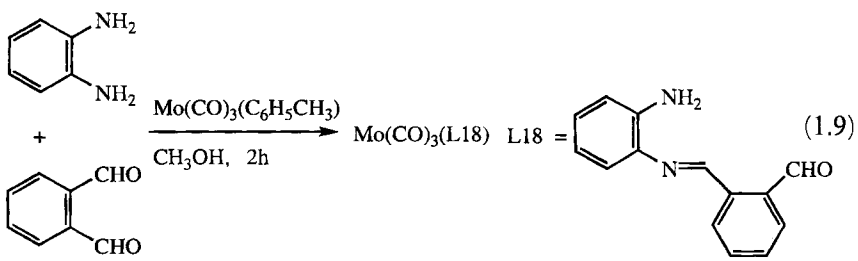
Scheme 1-4. Transmetallation.

tioned by one of the main criteria for template processes realisation – the ability to orient and activate interacting ligsons by means of coordination. No less important is the fact that ligand products generated are often isolated as metal complexes. In addition, depending on the nature of metal and ligand precursors, the template bonds formed may be of various kinds – donor–acceptor [38], hydrogen bonding [25], single- or multi-centre π-bonds [53], covalent [54], ion-dipole [3], π–π^*-interactions [19], or metal–carbon σ-bonds [55].

Metal ions with closed electron shells, such as s^2p^6, d^{10} or $d^{10}s^2$, serve mainly to obtain crown ethers – with the exception of small ions of comparatively high charge, such as Be^{2+}, Mg^{2+}, Zn^{2+}, Cd^{2+}, Al^{3+} and Sc^{3+}. To assemble poly-azamacrocyclic systems, 3d cations with either filled or incomplete electron shells are suitable.

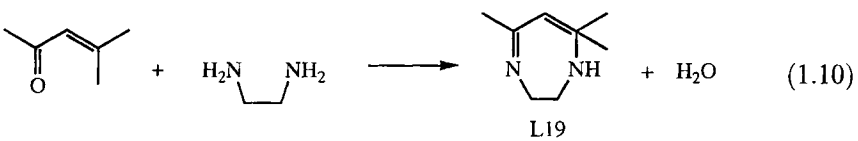
The ions of cobalt(III), rhodium(III) and iridium(III) are the best templates for assembling octahedral complexes with ligands of the sepulchrate type. To obtain macrocyclic polylactones and polylactams, templates with covalent character bonds, such as Sn, Si, Sb, or B, are used. Copper(I) is the most convenient centre for the synthesis of catenanes.

Metals in the zero oxidation state may also act as matrices. This is illustrated by the above-mentioned example [39] of assembling L8, where Mo(0) was used as a pattern, and by the $Mo(CO)_3(C_6H_5CH_3)$ reaction with *o*-phenylenediamine and *o*-phthalic aldehyde (in the ratio 1:1:1) in dry methanol [56] to form L18 (Eq. 1.9). This last reaction stops at the intermediate stage in the macrocyclisation process.



(1.9)

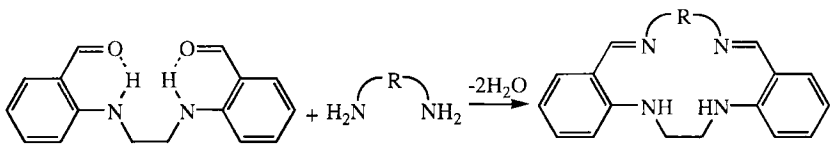
The proton is often used as an effective template centre for obtaining metal-free macrocyclic systems. Its role is not always obvious, so reactions with its participation are sometimes classified as "non-template" [57]. Thus, interaction of 1,2-diaminoethane monohydroperchlorate with acetone yields H_2(*trans*[14]diene)$(ClO_4)_2$ [51, 58]. The template role of H^+ here follows from evidence given in ref. [59], where it was shown that the reaction of dry unprotonated 1,2-diaminoethane with mesityl oxide gives the substituted dihydrodiazepin L19 (Eq. 1-10).



L19

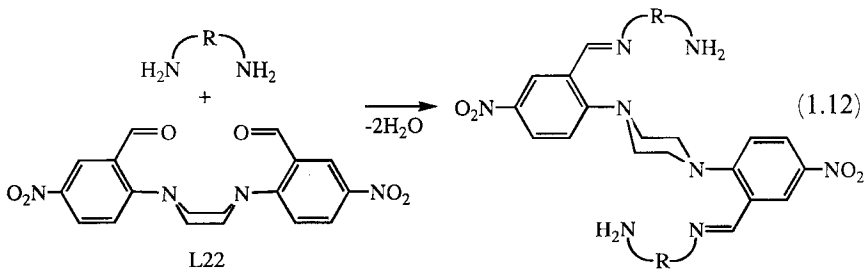
(1.10)

In the case of ligsons having elements capable of self-organisation through intramolecular hydrogen-bonding, new chelate bonds are formed at the expense of their own protons and without extra protonation from outside [57], as in the formation of H_2L21 (Eq. 1.11).



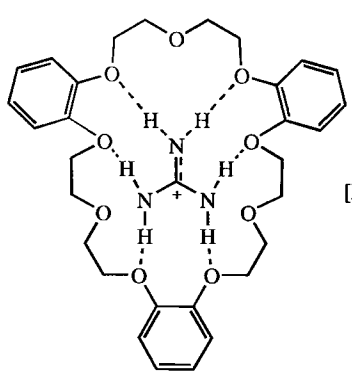
H_2L20 $\quad$ $R = (CH_2)_n$, $n = 2\text{-}4$ $\quad$ H_2L21 (1.11)

If there are no hydrogen atoms of secondary amino-groups in the starting material, as with L22, then macrocyclisation is impossible (Eq. 1.12) [57]. It is also clear that the conformation of the diazahexane ring in L22 may influence the course of reaction.



L22 $\quad$ L23 (1.12)

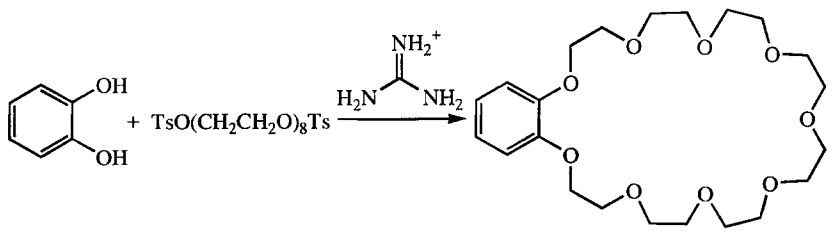
Processes using the proton as matrix are described as H-template. Ammonium ion, quaternary cations, or related species may be used as template centres in H-template reactions [11, 35]. Thus, tribenzo-27-crown-9 is obtained in the presence of guanidinium ion (Eq. 1.13) [60].



$[L24\{C(NH_2)_3\}]^+$ (1.13)

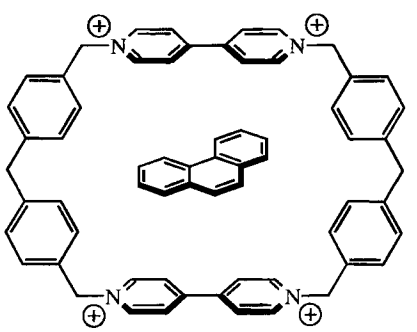
The guanidinium ion plays an important topological role in the last example. Owing to its shape, which is derived from its primary covalent structure, it favourably arranges protons for participating in hydrogen bonding. In this case a kind of tandem template is involved, where one of the partners predetermines the spatial arrangement of the another. The latter in its turn organises the corresponding ligsons for their subsequent interaction by virtue of the corresponding hydrogen bonds.

The guanidinium ion acts analogously in the process of synthesis of L25 (Eq. 1.14) [59]. Steric and functional complementarity between the guanidinium ion, ligsons and ligand product predetermine the success of the synthesis of 27-membered macrocycles L24 and L25.



L25 (1.14)

As previously mentioned, π–π^* aromatic forces can also be exploited for carrying out template macrocyclisation reactions. Thus the formation of L26 proceeds more effectively in the presence of π-donor species like phenanthrene (Eq. 1.15) [61]. The π-donor–π-acceptor interaction between the template and bipyridinium ions leads to a favourable arrangement of the latter for their subsequent reaction with the second molecule of the dibromoderivative.



$(L26)^{4+}$·Template (1.15)

Stoddart and co-workers also made use of aromatic electron donor-acceptor (EDA) interactions for highly effective synthesis of catenanes and rotaxanes (Figure 1-3) [62]. In this case, however, one of the ligsons acts as template, which is subsequently incorporated in the covalent structure of the ligand product (catenane or rotaxane).

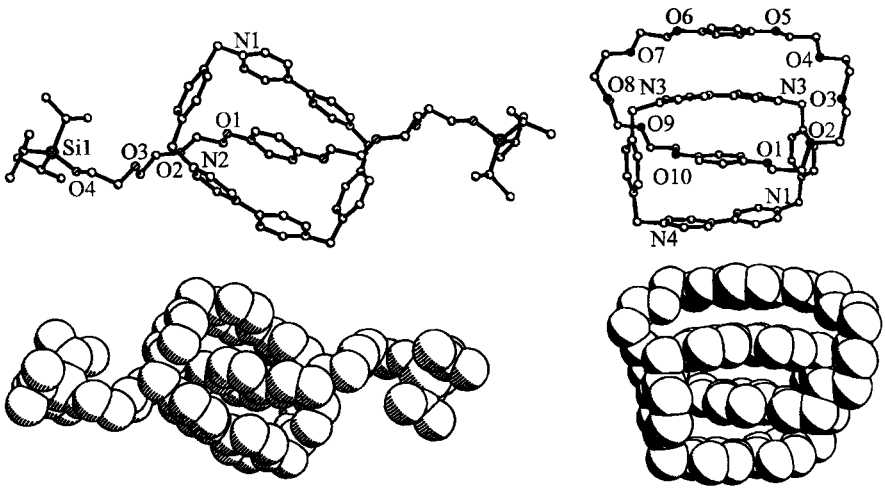
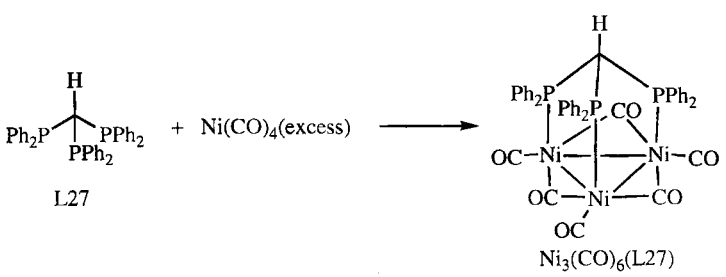


Figure 1-3. The molecular structures of a rotaxane (left) and catenane (right), the syntheses of which were promoted by aromatic π–π^* interactions between complementary hydroquinone and bipyridinium dication units of the corresponding ligsons [62].

The application of EDA aromatic interactions in the directed syntheses of various catenanes and rotaxanes is considered in more detail in Chapter 4.

A number of other organic compounds have been shown to play a template role in some reactions. Thus, the tripodal ligand $HC(PPh_2)_3$, L27, when used as matrix [63, 64] promotes simultaneous binding of three nickel atoms in a triangular disposition when treated with excess of $Ni(CO)_4$. As a result, a trinuclear nickel(0) compound is formed (Eq. 1.16).



(1.16)

Although a metal ion usually serves as a matrix for the synthesis of organic products, in this case there is a kind of functional work exchange between partners, with L27 assembling the trinuclear metal carbonyl cluster from mononuclear $Ni(CO)_4$. The cluster is isolated as a nickel complex incorporating the L27 template.