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MOLECULAR ORGANIZATION, PORTAL TO SUPRAMOLECULAR CHEMISTRY. STRUCTURAL ANALYSIS OF THE FACTORS ASSOCIATED WITH MOLECULAR ORGANIZATION IN COORDINATION AND INCLUSION CHEMISTRY, INCLUDING THE COORDINATION TEMPLATE EFFECT

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CONTENTS

A. INTRODUCTION

Current intense activity in research areas related to molecular recognition and inclusion chemistry has directed our attention to the extent to which certain molecular species or molecular systems are organized prior to the occurrence of specific processes that are taken to be of immediate interest. It is the purpose of this paper to show the commonality of features of a range of chemical phenomena that all constitute manifestations of molecular organization.

As used here, molecular organization means any combination of characteristics that lends some element of order to a particular chemical process or property, given that in a more primitive system, that element of order would not exist. Depending on the process or relationship under examina-

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tion, various structural features may exhibit behaviors that fall within this general definition of molecular organization. A number of such phenomena have been recognized, defined and studied, including the chelate effect, the macrocyclic effect, the cryptate effect, the catenand effect, a tethering effect (not previously named), multiple juxtapositional fixedness, the template effect, the agostic effect, neighboring group or anchiomeric effects, and preorganization of organic host molecules prior to host–guest complex formation. The first six and the last named of these effects are all manifested by enhanced binding between metal ion and ligand and/or guest and host. The remaining three effects and other phenomena also imply molecular organization, e.g. bifunctional (or multifunctional) catalysis, regiospecific and chiral processes. Further, molecular organization is the rule rather than the exception in much of in vivo chemistry. To recognize organization in biochemical systems is to note the obvious. However, simpler chemical systems must be capable of manifesting the same organizational principles, and gaining the same extreme and subtle control in the laboratory as occurs in vivo depends on understanding and exploiting those principles.

Recent applications of molecular design to coordination and inclusion chemistry have produced many exciting new species, and the special effects of macrocyclic structures, rigid host structures, the template effect, and ligand and host systems having multiple chambers, among others, have been invoked along the way. It would seem appropriate to generate a retrospective overview of some of these relationships, since, at this point in time, some unification in concept might facilitate further progress. The most general feature of these many developments is organization at the molecular level.

B. FACTORS COMMON TO MOLECULAR ORGANIZATION

It is suggested that, in coordination and inclusion chemistry, varying manifestations of molecular organization constitute a recurrent theme that has been recognized in different structural relationships and chemical processes, giving rise to several "effects" and that these effects derive from a commonality of structural factors. The factors are elementary in the ultimate sense and five in number. They are, respectively, a topological (or linking) factor, a metric (or relative size) factor, a shape (or geometric) factor, a rigidity factor, and complementarity between interacting species. Complementarity involves compatibility between the partners in complex formation.

In the discussion that follows it will be suggested that the chelate effect and the macrocyclic effect are largely reflections of topologic and metric factors. Cram's preorganization [1] and Busch's multiple juxtapositional

fixedness [2] derive from the addition of rigidity and shape factors to the more rudimentary topological and metric contributions. In its simpler examples, the kinetic coordination template effect derives from the same metric and topological factors as the chelate effect. Complementarity, which has been defined similarly by Cram [3] and by Lehn [4] for guest–host complexation, requires a matching of shape factors and metric relationships for host and guest. However, Lehn has defined an additional energetic or electronic complementarity. For example, a cation of ideal shape and size would not be attracted by a cavity having a large positive charge. More subtly, the electronic structures of different metal ions favor different geometries for their bonds. In general and for an ideal partner, topology and rigidity determine the enhancement in binding due to ligand structure. Simultaneously, the shape and metric factors determine the fit to the partner, or the complementarity *.

C. COORDINATION OF LIGANDS TO METAL IONS AS MOLECULAR ORGANIZATION

As pointed out in the early papers that first defined and exploited the coordination template effect [2,5–8], the geometric relationship between ligand molecules that accompanies their entrance into the coordination sphere ** of a metal ion (octahedral, tetrahedral, square planar etc.) constitutes molecular organization. The randomly moving free ligands in solution represent a related more primitive system where such organization does not exist.

Both chemical and physical processes may respond to the order associated with the binding of the ligands to a metal ion and the examples are so familiar to the coordination chemist and the organometallic chemist that the order is taken for granted. Chemical examples are common in the intramolecular processes of homogeneous catalysis (e.g. insertion, reductive elimination, olefin isomerization and olefin metathesis) while the role of symmetry in molecular spectroscopy illustrates the physical consequences of this most elementary molecular organization.

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* This is equivalent to Cram's statement that the strength of binding is determined by preorganization while selectivity or molecular recognition is dependent on complementary [3].

** The phrase "coordination sphere" is meant to be more general than "coordination polyhedron." It implies the main region of binding to the metal ion, i.e. a first coordination sphere as opposed to a second coordination sphere. Further it is not restricted to labile or inert species and it does not distinguish between those central ions of fixed coordination number and geometry and those having little electronic basis for fixed coordination number or geometry.

D. THE CHELATE EFFECT AS MOLECULAR ORGANIZATION

The following discussion focuses on the intramolecular structural relationships associated with the chelate effect. The important role of solvation is not treated. In the most general case the successive binding of identical monodentate ligands to a metal ion of fixed coordination number is associated with progressively decreasing binding constants. Further, when alkyl groups are added to ammonia, the affinity of the nitrogen atom for various Lewis acids [9–16], including the proton [17], increases in gas phase measurements where the stoichiometry of reaction is one-to-one. In contrast, secondary and tertiary amines in monodentate and polydentate ligands often show decreased affinities for metal ions in structures exhibiting coordination numbers of four and higher. The role of steric repulsion in this situation is unquestioned, although other considerations may also be important.

(i) The topological factor in the chelate effect

The chelate effect summarizes the peculiar fact that the linking together of two functional groups, for example, two primary amine donors, with a two or three carbon chain, leads to remarkably enhanced binding constants [17]. According to recent investigators [18] the ammonia and ethylenediamine complexes of nickel(II) and copper(II) provide the best examples for examining the chelate effect. The free energy change associated with displacement of two water molecules from the hydrated nickel(II) ion by two ammonia molecules is -6.93 kcal mol^{-1} (eqn. (1))

$$Ni(H_2O)_6^{2+} + 2NH_3 \rightleftarrows Ni(NH_3)_2(H_2O)_4^{2+} + 2H_2O \quad (1)$$

while that for replacing two water molecules from the hydrated nickel(II) ion by one molecule of ethylenediamine is -10.03 kcal mol^{-1} (eqn. (2)) [17]:

$$Ni(H_2O)_6^{2+} + en \rightleftarrows Ni(en)(H_2O)_4^{2+} + 2H_2O \quad (2)$$

The respective values for replacing a total of four water molecules by the amines are -11.08 and -18.47 kcal mol^{-1}. On the basis of the greater basicity of the primary amine groups over ammonia, one might have expected [19] an enhancement of ΔG by a factor of 1.15; the observed enhancements are by factors of 1.44 and 1.67. The extra enhancement in the relative stability of the chelated derivative illustrates the chelate effect.

Long ago, Schwarzenbach [20,21] addressed the structural aspects of the chelate effect in terms of the average proximity of the still-unattached donor

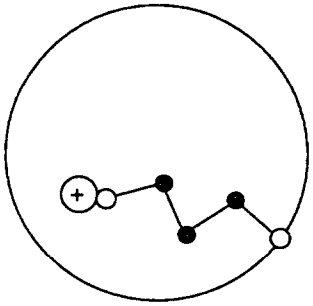


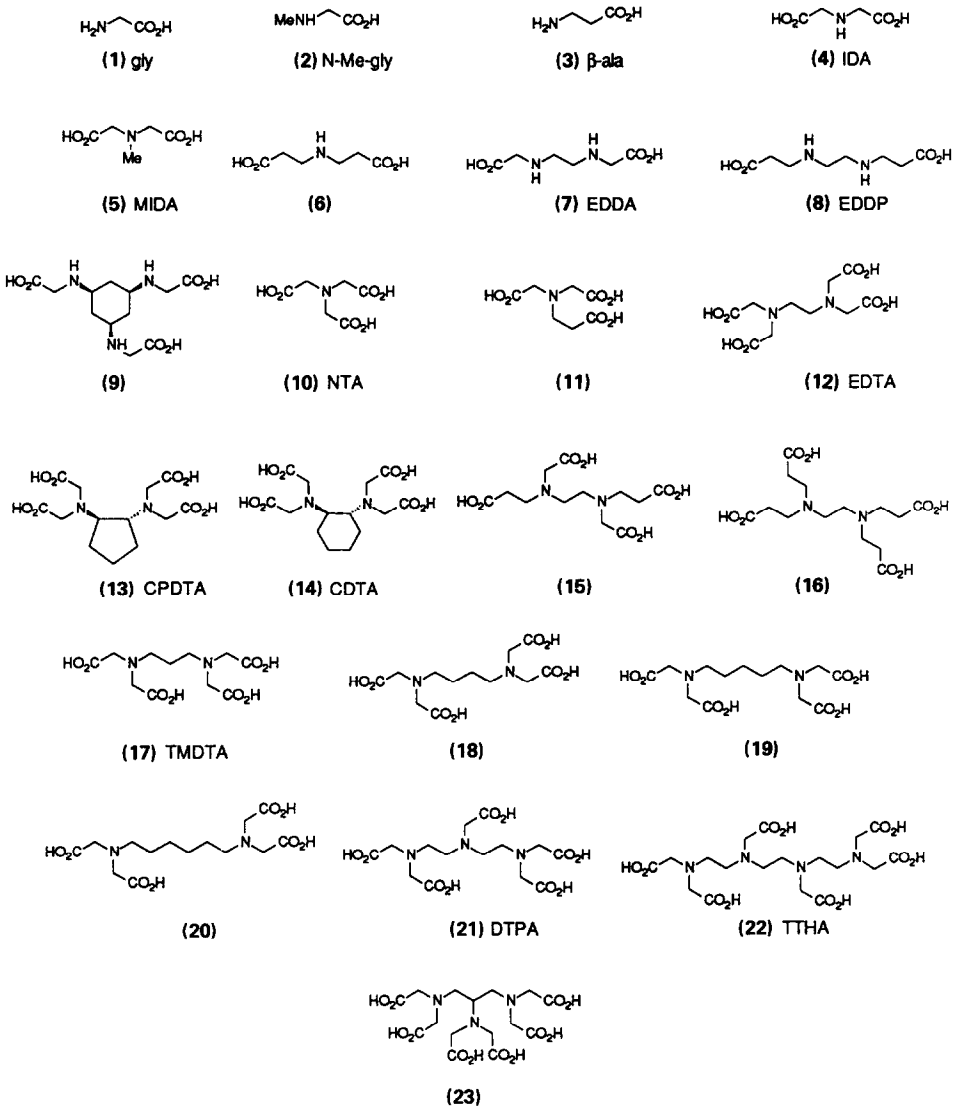
Fig. 1. Schwarzenbach's image of the effect of proximity in the binding of a chelating ligand to a metal ion.

atom after the first donor atom had become bound to the metal atom (Fig. 1). More specifically, his model concerned the volume accessible to the free donor group of a monodentate-coordinated bidentate ligand as compared with that for a free monodentate ligand. That accessible volume corresponds to some hypothetical high concentration of a similar monodentate ligand that would, on average, place that species in the same proximity from the metal ion.

The presence of the two donor atoms, as parts of a single molecule, both of which are capable of binding to a single metal ion, constitutes molecular organization vis-a-vis a system composed of strictly monodentate ligands. This is the essential result of a topological factor, i.e. the simple linking of the two donors by a connecting chain is central to the occurrence of a chelate effect. It is germane to this view that the most general treatment of the entropy change associated with the chelate effect is dependent on the number of chelate rings alone and not on their size or composition [17,19,21,22].

In a polydentate ligand, the propitious location of a set of donor atoms, all accessible by the same metal ion, lends order to their successive binding as the complicated ligand wraps about the metal ion. The cumulative advantage of the increasing organization as additional donors are built into the ligand is reflected in enhanced chelate effects, i.e. increased difference in the comparable binding constants (structures **1**–**23**, Table 1, and structures **24**–**39**, Table 2).

The phenomenon reflects, among other effects, the facilitating of the next step after a given donor has bound. However, at least equally important, the chaining together of the donor atoms profoundly affects the ligand dissociation process. When a given donor separates from the metal, the possibility of the process being reversed by rebinding of that donor is enhanced by its linkage to the rest of the molecule that is still bound to the metal ion (Table



3). As pointed out by Margerum et al. [23], trien (**35**) dissociates from $[Ni(trien)(H_2O)_2]^{2+}$ with a calculated dissociation rate of 1.4×10^{-9} s^{-1} whereas the rate of dissociation of NH_3 [24] is 5.7 s^{-1} and the exchange rate for coordinated water [25–27] in $[Ni(H_2O)_6]^{2+}$ is 3×10^4 s^{-1}.

In the absence of acid, the dissociation rates for chelating ligands are not measurable, for although individual steps are not slow, successive equilibria leading to ligand dissociation are highly unfavorable. For this reason, studies

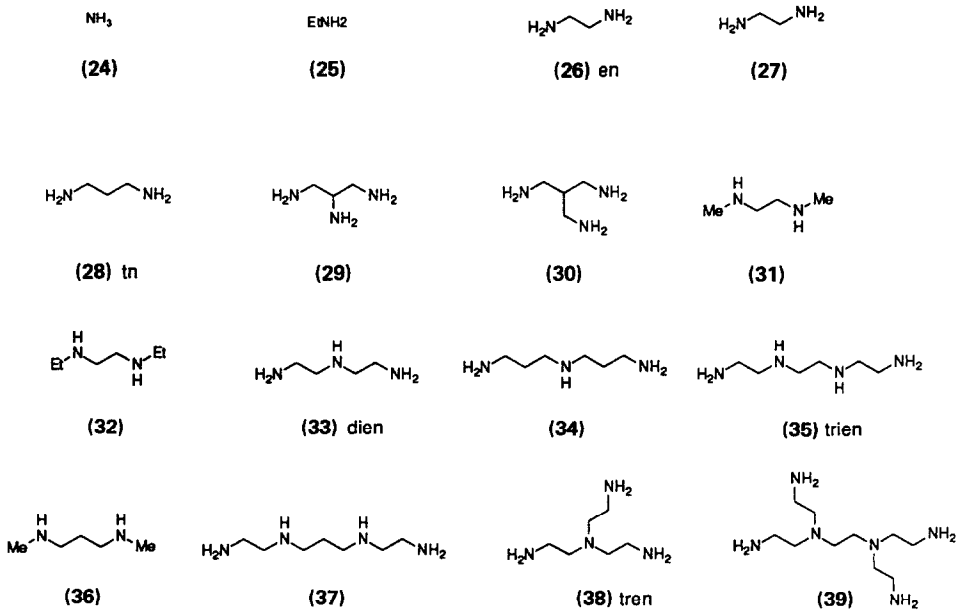
TABLE 1

Stability constants for aminocarboxylate ligand binding to M^{2+} ions [17]. Values reported are log K_n where K_n refers to the equilibrium: $M + nL \rightleftarrows ML_n$

Ligand [a]	n	Co	Ni	Cu	Zn	Conditions [b]
1	1	4.64	5.78	8.15		25, 0.1
	2	8.46	10.58	15.03		
	3	10.81	14.00			
2	1		5.24	7.84	4.31	25, 0.5
	2		9.54	14.34	8.3	
3	1	3.58 [c]	4.46	7.04	3.9	25, 0.5
	2	6.14 [c]	7.84	12.54	7.20	
			9.55		10.04	
4	1	6.94	8.13	10.57	7.24	25, 0.1
	2	12.23	14.1	16.54	12.52	
5	1	7.6	8.67	11.04	7.63	25, 0.1
	2	13.84	15.85	17.76	14.01	
6	1	4.92	6.14	9.36	4.95	30, 0.1
	2	8.18	9.91	13.04		
7	1	11.25	13.65	16.2	11.22	25, 0.1
8	1	7.3	9.3	15.1	7.6	30, 0.1
9	1	13.81	16.56	17.13	13.41	25, 0.1
10	1	10.38	11.50	12.94	10.66	25, 0.1
	2	14.33	16.32	17.42	14.24	
11	1	10.0	11.4	12.6	10.0	25, 0.1
12	1	16.26	18.52	18.70	16.44	25, 0.1
13	1	12.07				20, 0.1
14	1	19.58	20.2	21.92	19.35	25, 0.1
15	1	14.9	15.5	16.3	14.5	30, 0.1
16	1	7.6	9.7	15.4	7.8	30, 0.1
17	1	15.52	18.07	18.82	15.23	25, 0.1
18	1	15.64	17.27	17.25	14.99	25, 0.1
19	1	13.34	13.8	16.10	12.64	25, 0.1
20	1	12.99	13.71		12.63	25, 0.1
21	1	19.15	20.17	21.38	18.29	25, 0.1
22	1	18.4	19.4	20.5	18.0	25, 0.1
23	1	13.8	18.0	18.37	15.80	25, 0.1

[a] These are structure numbers. [b] Conditions refer to temperature (°C) and ionic strength. [c] 25, 0.2.

have been performed under acidic conditions so that the amine groups are trapped in a protonated form as they dissociate from the metal ion. This also allows the observation of successive steps in the dissociation of a polydentate ligand (Table 3). Thus for $[Ni(trien)]^{2+}$ in 0.5 M acid, Melson and Wilkins [28] observed rate constants of 15 s^{-1}, 4 s^{-1} and 2 s^{-1} corresponding to single Ni–N cleavage steps for $[Ni(trien)]^{2+}$, $[Ni(Htrien)]^{3+}$ and



$[Ni(H_2trien)]^{4+}$ respectively. It is significant that the rates of dissociation of individual amine groups are of the same general magnitude as the dissociation rate for ammonia. This emphasizes the fact that it is the combined effect of the linked donors that produces the net kinetic inertness.

To this point, the chaining together of the donor atoms into chelate ligands has been the focus of discussion (structures **1**–**39**). No consideration has been given to the nature of the linkage between the donors. Consequently, this discussion has been limited to the topological aspect of the chelate effect, i.e. the mere fact that the donor groups in a chelating ligand are chained together.

(ii) The metric factor in the chelate effect

Now let us assume that the ligands in question are highly flexible species. For these ligands, the magnitude of the chelate effect is strongly influenced by a metric factor, in addition to the topological factor. As all coordination chemists know, the size of the chelate ring is very important. For most metal ions and in the case of saturated structures, five-membered chelate rings are better than those of six members. For example, the stability constants for ethylenediamine **26** and its *N*,*N*′-dimethyl derivative **31** are greater than those of the corresponding trimethylene derivatives **28** and **36** (see Table 2). Chelate rings of greater size or lesser size, although well known, are

TABLE 2

Stability constants for amine binding to M^{2+} ions [17]. Values reported are log K_n where K_n refers to the equilibrium: $M + nL \rightleftarrows ML_n$

Ligand [a]	n	Co	Ni	Cu	Zn	Conditions [b]
24	1	2.10 [c]	2.81	4.24 [c]	2.38	25, 2.0
	2	3.67 [c]	5.08	7.83	4.88	
	3	4.78 [c]	6.85	10.80	7.43	
	4	5.53 [c]	8.12	13.00	9.65	
	5	5.75 [c]	8.93	12.43		
	6	5.14 [c]	9.08			
25	1				2.3	25, 0.5
	2				4.33	
	3				6.0	
	4			11.5		
26	1	5.6	7.35	10.54	5.7	25, 0.1
	2	10.5	13.54	19.6	10.62	
	3	13.8	17.71		13.23 [d]	
27	1		6.75	10.19		25, 0.65
	2		12.08	18.57		
	3		14.1			
28	1		6.31	9.75		25, 0.1
	2		10.6	16.9		
	3		12.3 [d]			
29	1	6.80	9.30	11.1	6.75	20, 0.1
30	1	6.25	9.90	10.85		20, 0.1
	2	7.89				
31	1		6.89	10.02	5.51 [f]	25, 0.1
	2		10.83	17.05	9.73 [f]	
	3		13.3 [e]			
32	1		5.58	8.85	5.47 [f]	25, 0.1
	2		8.02		9.0 [f]	
33	1	8.0	10.5	15.9	8.8	25, 0.1
	2	13.9	18.6	20.9	14.3	
34	1	6.92	9.19	14.20	7.92	25, 0.1
			12.74			
35	1	10.95	13.8	20.1	12.03	25, 0.1
			18.6 [g]			
36	1		5.1	8.38		25, 0.5
37	1		16.4	23.9	12.8	
	2		20.1			25, 0.5
38	1	12.7	14.6	18.5	14.5	25, 0.1
39	1	15.6	19.1	22.1	16.06	25, 0.1

[a] These are structure numbers. [b] Conditions refer to temperature (°C) and ionic strength. [c] 30, 0.2. [d] 25, 0.15. [e] 25, 0.65. [f] 25, 0.46. [g] 25, 0.5.

TABLE 3

Nickel(II) amine dissociation rate constants in acid at 25 °C

Ligand	k_1 (s^{-1})	k_2 (s^{-1})	k_3 (s^{-1})	pH
27	0.32			0.5
29	63	0.34		0.5
33	14	2.8		0.2
34	11	1.7		0.2
35	15	4.0	2.1	0.5
38	66	0.22		0.5
39	70	49	3	0.5

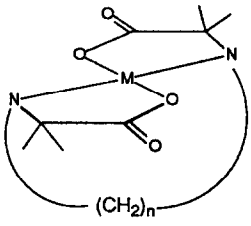
relatively unfavorable and no chelate effect is expected for rings of eight and more members.

The metrics associated with chelate rings are dependent on the conformations of those rings. Remarkably, the reason the six-membered chelate ring is less stable than the five-membered ring for most metal ions is that the larger-membered ring prefers smaller metal ions than does the five-membered ring [18,29]. The least-strained ethylenediamine chelate ring would occur with a relatively large metal ion (M–N = 2.5 Å) while the larger 1,3-propanediamine ligand maximizes at M–N = 1.6 Å. A moment's reflection will reveal the obvious nature of this fact. After all, cyclohexane exists in a relatively low energy chair conformation that is copied in six-membered chelate rings. Six-membered rings made up of such light atoms as carbon, nitrogen and oxygen fit carbon better than they fit most metal ions. The former is much less strained than the latter.

From the rate data presented above for the stepwise removal of trien from $Ni(trien)^{2+}$ in acidic aqueous solution, the breaking of the first Ni^{2+}–N bond is more rapid than either of the successive bond breaking steps, even though successive protonation of the dissociated amine functions should produce increasing coulombic repulsions. This has been attributed to relief of strain in the first dissociation step. That, in turn, derives from the metric relationships in the tetradentate ligand trien. The metrically derived strain is removed by inserting an additional methylene unit in the central dimethylene group of ligand **35** (trien), forming ligand **37** (see Table 2).

A more dramatic illustration of the effect of metrics is found when long distances are to be traversed. For example, if one wishes to string a donor atom from the periphery of a porphyrin ring and reach the metal ion within the ring, then a much longer chain is required [30]. Further, if, in the design of a ligand, one chooses very long flexible chains, then the bifunctional ligand may span *trans* positions within the coordination sphere rather than chelating in the usual fashion in adjacent coordination sites. Such a structure was first reported by Schlesinger (structure **40**) many years ago [31,32] and it

has been exploited more recently in the lacunization of tetradentate Schiff base chelates (structure **41**) [33,34]. Thus the overlaying of the metric factor on the topological one, for even simple cases, can have great structural consequences.



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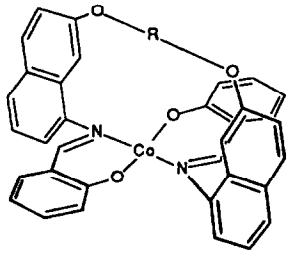


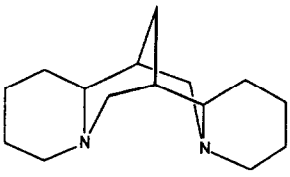
(41)

It should be possible to select the geometries of the coordination spheres of metal ions with such linear tetradentate chelating ligands as **40** and **41** with substantial variations in the lengths of the central bridging unit. The shorter chains (two and three methylene groups) should favor the formation of the planar nickel(II) and cobalt(II) complexes while longer chains that are still too short for *trans* spanning might favor tetrahedral structures. It is certainly true that the electronic structures of the metal ions may limit the coordination geometries that are available so that ligand control of structure in this way may be restricted by the requirements of the metal ion.

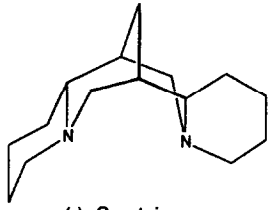
E. PREORGANIZATION, MULTIPLE JUXTAPOSITIONAL FIXEDNESS AND THE RIGIDITY AND SHAPE FACTORS

If the flexibility is removed from the chelating ligand, effects are observed that are due to the resulting increase in molecular organization. This phenomenon was generalized in 1970 with the half-serious label "multiple juxtapositional fixedness" [35,36]. The phrasing was intended to call attention to the consequences of having multiple ligating atoms arrayed in a fixed geometry suitable for binding to some given metal center.

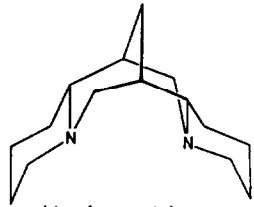
The bidentate ligand sparteine (structures **42**, **43** and **44**) produces remarkably inert complexes even with the highly labile copper(II) ion [37,38].



(+)-β-Isosparteine
(42)



(-)- Sparteine
(43)



(-)-α-Isosparteine
(44)

TABLE 4

Hydrolysis data for sparteine complexes at 25.0 °C

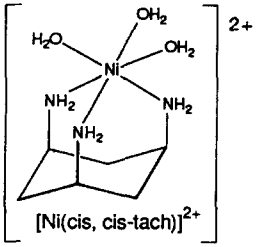
Complex	Ligand	10^3k (s^{-1})	$t_{1/2}$ (min)
(+)-β-Isosparteine·$CuCl_2$	**42**	3.85	180
(−)-Sparteine·$CuCl_2$	**43**	2.62	264
(−)-α-Isosparteine·$CuCl_2$	**44**	2.35	295

This may be attributed, at least in part, to the fixed geometry and substantial spatial requirements of the bidentate ligand. It is relatively difficult to visualize a pathway by which one end of the ligand could be removed from the metal ion with retention of coordination by the donor at the opposite end of the ligand. Since virtually all substitution pathways for transition metal centers proceed in stepwise fashion, this interferes with the main mechanisms for substitution and the consequences are both kinetic and thermodynamic. From a comparison of the isomers of sparteine, it has been suggested [37] that blocking sites where ligands could attack the metal ion are responsible for differences in rates of aquation (Table 4) among these closely related complexes. Thus the isomer producing the greatest substitution inertness interferes with both dissociative and associative substitution pathways. Similar effects have been observed on the rates of displacement of 2,9-disubstituted-1,10-phenanthrolines from pseudotetrahedral copper(I) by cyanide [39].

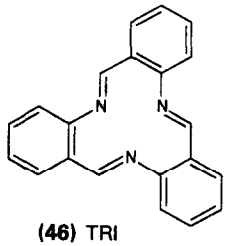
Similarly, the tridentate ligand, 1,3,5-triaminocyclohexane, *cis,cis*-tach, produces an octahedral nickel(II) complex of extraordinary substitution inertness (structure **45**) [40]. The half-life of the reaction given in eqn. (3)

$$[\mathrm{Ni}(cis,cis\text{-tach})]^{2+} + 3\mathrm{H}^+ \rightarrow \mathrm{Ni}^{2+}cis,cis\text{-tachH}_3^{3+} \quad (3)$$

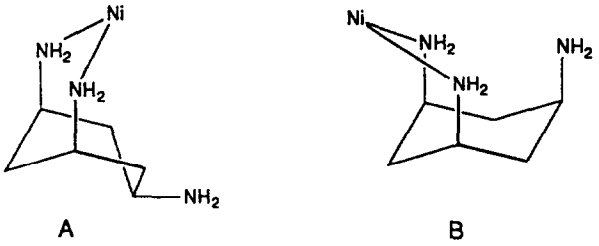
is 7 min at 25 °C in 5 M nitric acid whereas the dissociation rates of linear tridentate ligands under comparable conditions are small fractions of seconds [28]. The fixed orientation of the three donor atoms is difficult to alter



(45)



(46) TRI

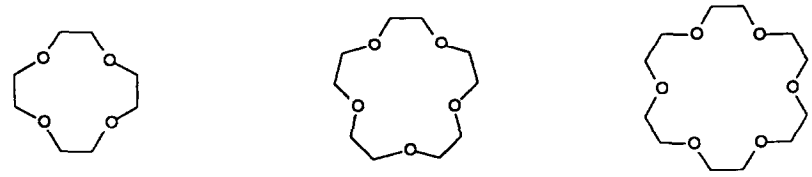


A B

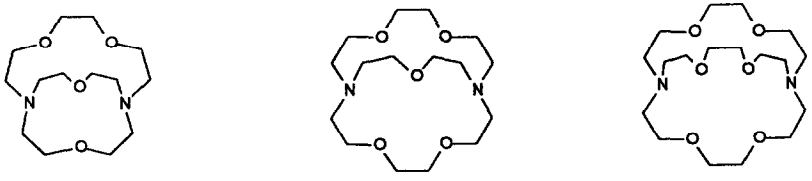
Fig. 2. Possible intermediates in the dissociation of a donor atom from [Ni(*cis*,*cis*-tach)$(H_2O)_3]^{2+}$.

in order to dissociate a single donor atom, unless the conformation of the cyclohexane framework is altered. As pointed out by Childers and Wentworth [40], the dissociation of one of the amino groups should produce either conformation A or B (Fig. 2) and both of these conformers are destabilized by substantial strain energy contributions [40]. From cyclohexane, the first (A) represents an addition to the barrier of about 10 kcal mol^{-1}.

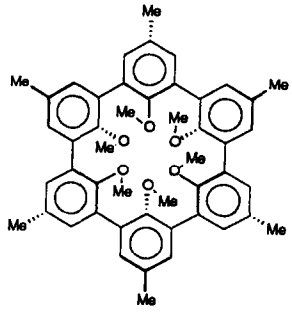
Such rigid macrocycles as the trimeric condensation product of *o*-aminobenzaldehyde (TRI, structure **46**) exhibit extreme unreactivity for the same basic reason [41]. The complex ion Ni(TRI)$(H_2O)_3^{2+}$ has been resolved into optical isomers which show no evidence of racemization over a period of 3 months at room temperature in neutral or acidic solutions. At higher pH the ligand appears to undergo hydrolysis, providing a pathway to racemization. In the absence of the hydrolytic pathway, no low energy mechanism exists



(47) (48) (49)



(50) (51) (52)



(53)

for the stepwise dissociation of the TRI ligand from the nickel complex. The coupling of an energetically costly conformational change to the loss of a ligand from the coordination sphere of a metal ion epitomizes the rigidity factor that has been expressed by the labels "preorganization" and "multiple juxtapositional fixedness."

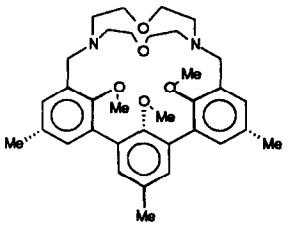
Although it may represent a digression from the logical process of proceeding from the simple to the more complex, it is convenient at this point to consider examples of preorganization provided by Cram [3]. Ligands such as the cyclic polyethers [42] and the cryptates [4] (structures **47–52**) undergo both conformational reorganization and desolvation in order to form complexes. In contrast, Cram's spherands (structure **53**) are completely preorganized [3,43]. Further, the hydrophobic environment of the donor groups militates against solvation of the free ligand. If a guest molecule, for example a metal ion, is complementary to the preorganized cavity, then there is no alternative to the formation of an octahedral complex [44].

It is illuminating to compare the stabilities of certain complexes of the spherands with those of similar open-chain ligands called podands [45]. The two ligands differ only in the replacement of one C–C bond in the spherand by two hydrogen atoms. The podand is not preorganized for guest binding; it exists as a mixture of conformers, each of which is characterized by some degree of solvation. The difference in negative $\Delta G°$ values for the binding of the lithium ion to these two ligands is greater than 17 kcal mol^{-1} and this represents a difference in equilibrium constants by a factor exceeding 10^{13}. Similar but smaller differences were found for Na^+. Cram and his associates have concluded that preorganization is a central determinant of binding power.

In the spherand case, the several aspects of molecular organization are all at work. The topology produces a set of chelating donor atoms favorable for binding to a single metal ion; the metrics favor small ions such as $Li^+ > Na^+$;

and the shape is fixed at octahedral, reflecting the fact that the rigidity factor is extreme in this example. If one chooses to discuss the overall binding effect in terms of the traditional list of effects, then the chelate effect, macrocycle effect, preorganization/multiple juxtapositional fixedness and complementarity must all be invoked. Clearly it is adequate to recognize that the five fundamental structural factors associated with molecular organization are all optimized for the complex of the spherand with Li^+.

A counter-example emphasizes the significance of complementarity [43]. The smaller cryptaspherand having structure **54** selects Na^+ over K^+ by a factor of 13 000. In contrast, the larger cryptaspherand (structure **55**) selects



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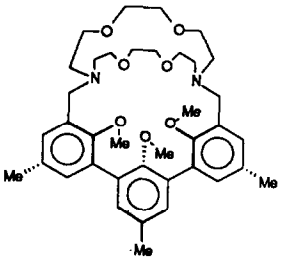


(55)

in the opposite direction by a factor of 11 000. Further, the crystal structure of the sodium ion complex with the larger ligand shows that the sodium is too small to bind to all the donor atoms of the enclosing cryptaspherand—a direct observation of non-complementarity.

F. THE MACROCYCLIC EFFECT AS MOLECULAR ORGANIZATION

The macrocyclic effect has generally been recognized as an enhancement in the thermodynamic stability of metal complexes with macrocyclic ligands as compared with complexes of other, usually linear, polydentate ligands. This is manifested in equilibrium constants and is accompanied by exceptional kinetic inertness. The property was first recognized among the first row transition metal complexes of tetraazamacrocycles, including species having varying degrees of unsaturation. Recognition of the great stability of the complexes accompanied the identification of the macrocyclic ligands in these complexes [46–49] and their exceptional kinetic inertness and stability became evident shortly thereafter. Stable diastereoisomers and even optical isomers were found whose isomeric character depended on the inertness of the macrocyclic complex [50–55].

In reporting the first quantitative study of the relative thermodynamic and kinetic stability of a macrocyclic ligand (specifically, tetraazamacro-

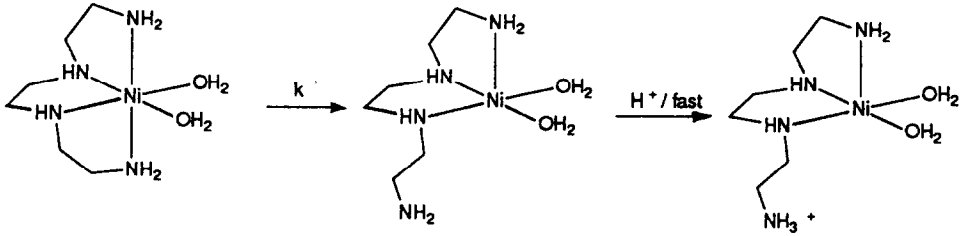


Fig. 3. First steps in the removal of a linear polyamine from nickel(II) in acidic media.

cycles) as compared with closely related linear tetradentate ligands, Cabbiness and Margerum [56] named the macrocyclic effect. Subsequent to further studies on the tetraazamacrocycles [57], the tetrathiamacrocycles were studied extensively [58] and much attention has been given to alkali metal complexes of crown ethers [59,60], and various metal ion derivatives of cryptates [4]. It is characteristic of the systems in question that the structures are relatively flexible so that the principal structural contributions to the macrocyclic effect are topological and metric in nature.

The topological factor associated with the macrocycle effect is most dramatic as it relates to the rates of dissociation of the ligands from the metal complex. As Fig. 3 indicates, the usual mechanism for displacement of a linear or branch chain polydentate ligand by solvent in acidic solution is stepwise. Further, the dominant pathway for many metal ions is dissociative in nature. For linear and related ligands, this process involves successive dissociation of donor atoms of the polydentate ligand, followed rapidly by protonation of the dissociated basic group. The process begins at one end of the ligand.

For the macrocycle, topology intervenes and prevents a ligand dissociation mechanism correspondingly as simple as that of linear ligands—a ring has no end. As Fig. 4 shows, some profound change in the conformation of the chelated macrocycle must accompany the dissociation of one of its ligands. In the obvious possibility that is illustrated there is folding of the ligand. Clearly this places a substantial barrier in the way of macrocycle dissociation. Significantly, quantitative studies have shown that the rates of dissociation of macrocyclic ligands are much more greatly retarded than the corresponding rates of complex formation. This is consistent with the topological relationships [23].

Martell and Hancock [18] have pointed out the fact that molecular organization is higher with macrocycles than with linear tetradentate ligands. They suggest that the increased molecular organization has already brought the ligand to a high energy state with respect to conformation, dipole–dipole repulsion and solvation. As Cram observes, the cost in energy for complex

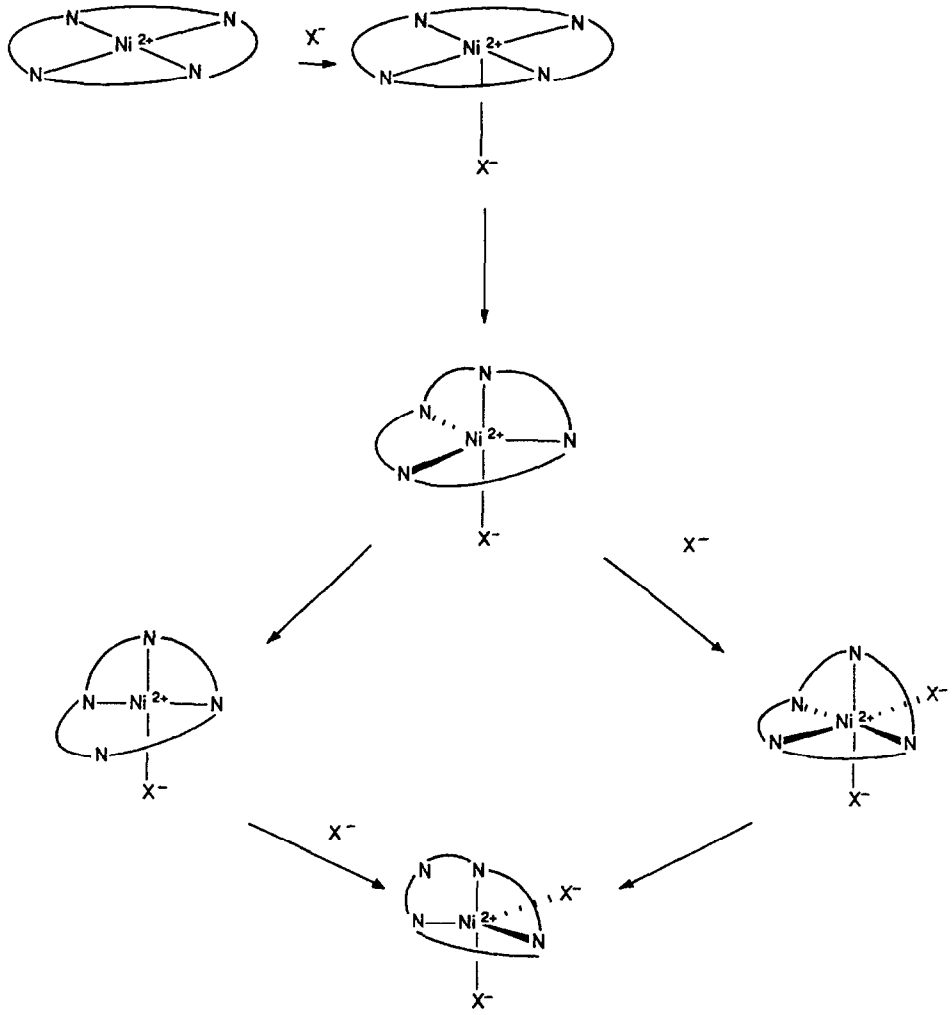


Fig. 4. Model for the removal of a macrocyclic polyamine from nickel(II).

formation can, in fair measure, be prepaid during the synthesis of pre-organized ligands or hosts [3]. The extent to which this is realized depends on the topology and rigidity of the ligand and on the complementarity with the metal ion of the shape and metric factors.

As reported in early studies on cryptates by Lehn and Sauvage [61], macrobicyclic ligands exhibit remarkably larger stabilization effects than do ordinary macrocycles *. In the terms used here, for corresponding rigidity

* "Those macrobicyclic complexes of this topology that were synthesized prior to Lehn's work were transition metal derivatives prepared by template reactions [62] and their thermodynamic properties were not readily evaluated."

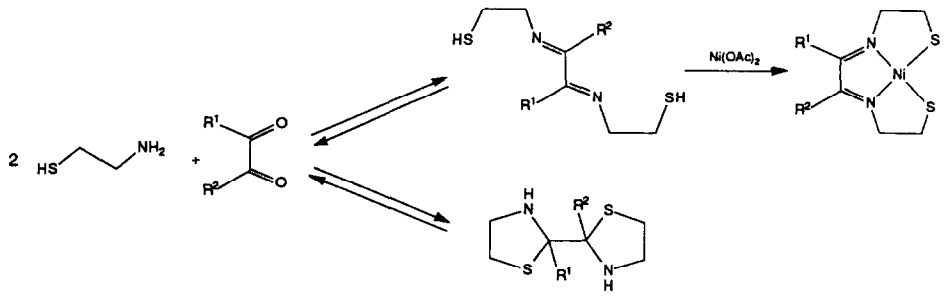
and complementarity, the topology of the macrobicyclic cryptates greatly enhances complex stability.

G. COORDINATION TEMPLATE EFFECT AS MOLECULAR ORGANIZATION

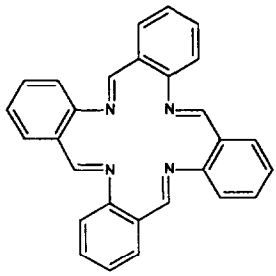
The same work that defined the coordination template effect illustrated it with reactions leading to the formation of new ligands, including the first intentionally synthesized new macrocyclic ligand [2,5–8]. Two distinct classes of coordination template effects were recognized and these were termed the kinetic and the thermodynamic template effects on the basis of their different origins. Those labels recognize the character of the phenomenon but they do not indicate the importance of the various structural factors to the two classes.

The thermodynamic or equilibrium coordination template effect is a sequestration phenomenon. In the absence of the metal ion, the desired ligand molecule is presumed to exist in equilibrium with one or more other molecular species and to have a much greater chelating ability than the competing products. The high chelating ability of the desired product allows a metal ion to sequester it and shift the equilibrium toward a high yield of the chelated product.

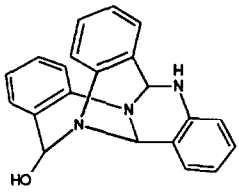
The first recognized example of the thermodynamic coordination template effect involved the formation of the nickel(II) complex of the Schiff base formed between β-mercaptoethylamine and an α-diketone (Scheme 1) [5,6]. In the purely organic system [63–65], thiazolines are formed in competition with Schiff bases of this kind. Also, in some systems, mercaptals are formed. Despite the fact that the Schiff base is not the main product in the organic system, the formation of the ligand in the presence of the metal ion leads to yields of the Schiff base complex in excess of 70%. Examples that appear to involve this class of coordination template effect are common, especially in the formation of macrocyclic ligands [2,5–8].



Scheme 1.



(56) TAAB



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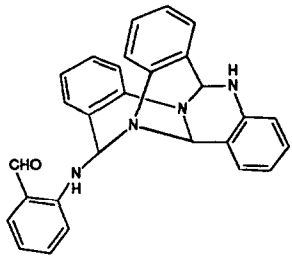

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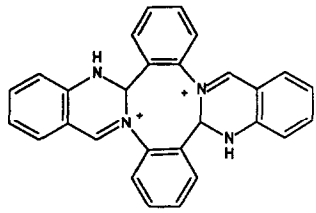
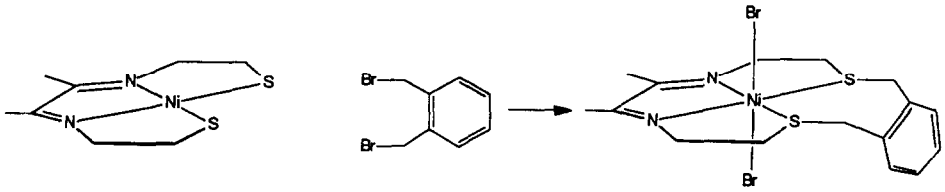


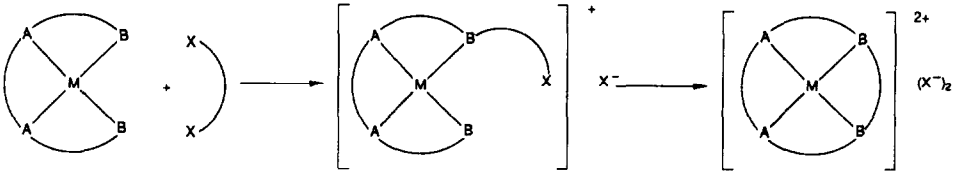
(59)

The first highly likely example of inadvertent use of this effect in synthesis, by Eichhorn and Latif [66] in 1954, preceded the recognition and deliberate use of the effect by almost a decade. Eichhorn and Latif investigated the self-condensation of *o*-aminobenzaldehyde in the presence of divalent transition metal ions. In view of the limited techniques available at that time, it is not surprising that they were unable to separate and identify the macrocyclic complexes in the mixture of tetrameric and trimeric complexes formed by their reaction. The *o*-aminobenzaldehyde case is of much interest because the macrocycles (structures **46** and **56**) [67,68] cannot be formed in the absence of metal ions; the polycyclic condensates formed in the absence of metal ions have rather different structures, **57**, **58** and **59** [69,70].

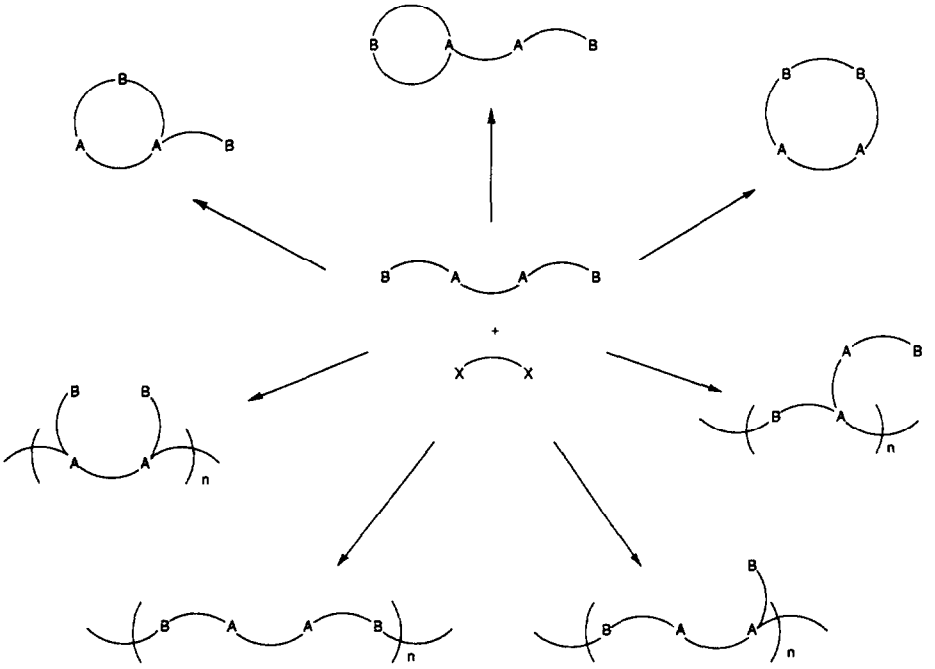
It is often difficult to provide unequivocal evidence for the thermodynamic coordination template effect, because of complications in the equilibrium systems. Also, most of the evidence for a template effect is often synthetic in nature, i.e. a high yield of an unusual product. The literature suggests that the macrocycles produced by condensation of ethylenediamine with acetone are formed by such a template reaction [55,71,72]; however, the data are not convincing. These macrocycles were first discovered [73] by



Scheme 2.



A



B

Scheme 3.

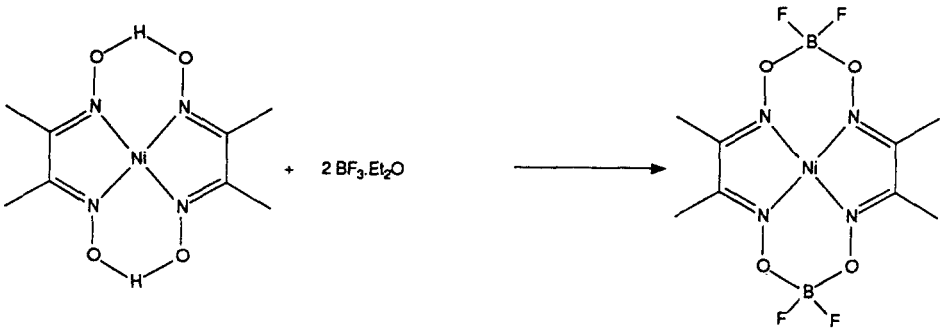
Curtis in 1960, who reported the correct structures in 1961 [46]. The reported yield of more than 80% obtained with the acetone/ethylenediamine reaction in the presence of nickel is closely approximated (ca. 75%) in the absence of the metal ion [74]. Further, the yield obtained in the absence of the metal ion must be considered even more remarkable since a pure isomer was obtained whereas the product of the nickel system contained position isomers [74]. If the second isomer had also crystallized in the nickel-free system, the yield might have exceeded that of the nickel-containing system.

Emphasis in the thermodynamic coordination template reaction process is on complementarity. If a ligand from an equilibrium mixture of organic materials is distinctly complementary to an available metal ion, then the phenomenon occurs—the metal ion selectively binds to the complementary ligand and shifts the position of the pure organic equilibrium.

The kinetic coordination template effect, as it was first illustrated (Scheme 2) [5–7], takes advantage of the molecular organization represented by the coordination of ligands to a metal ion. Its success is largely traceable to the same topological and metric factors that dominate the chelate effect. Scheme 3B presents a simplified image of the possible reactions between a linear tetradentate ligand and a difunctional electrophilic reagent that can combine with any of the ligand functional groups. If the metal ion is not present, the two reagents will combine to form a variety of polymeric and cyclic products. However, the presence of the templating metal ion profoundly alters the process. The metal ion is chosen because it will selectively bind to the linear ligand in a planar fashion (Scheme 3A); this rigidly fixes the two end functional groups into adjacent positions within the coordination sphere of the metal ion. Now if these terminal donor atoms are capable of acting as nucleophiles while bound to the metal ion, they are well positioned for reaction with the same molecule of the difunctional electrophile.

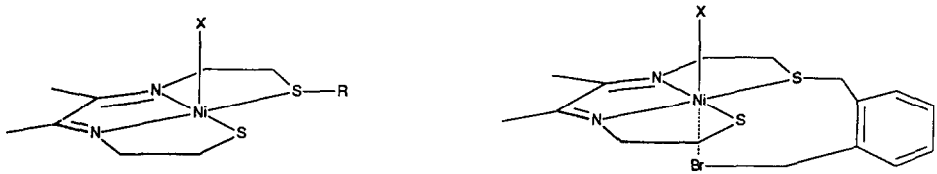
Scheme 3A shows the intermediate formed when one end of the electrophile has combined with a bound donor atom. This closely resembles the intermediate formed when one end of a chelating ligand attaches to a metal ion. Closely similar topological and metric advantages and constraints apply to the closure of this new chelate ring by a ligand reaction. In detail, the process is not the same as closing a chelate ring since the reaction occurs at a donor atom, not the metal center. In fact, such reactions have been carried out on atoms β to the metal center as shown in Scheme 4 [75,76]. This latter example shows how different the metrics can be; only a single atom is inserted between the two oxygen atoms of adjacent oxime functions.

Kinetic effects similar in kind to those associated with chelation have been displayed in demonstrating the kinetic coordination template effect. When the tetradentate reactant complex in Scheme 2 reacts with monofunctional alkyl halides, the reaction with the first mole of alkyl halide is much



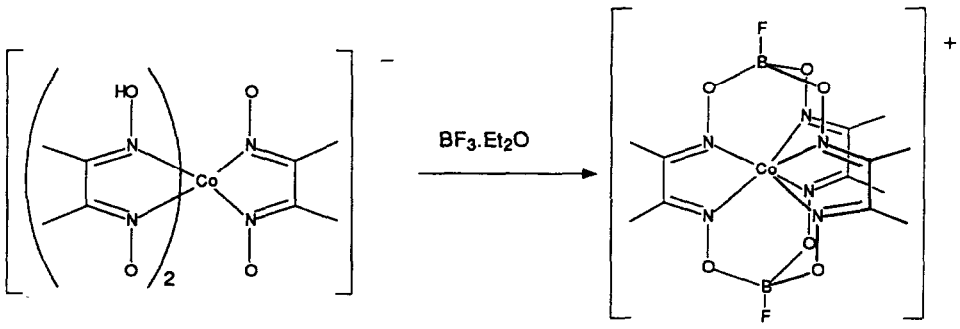
Scheme 4.

faster than with the second. Thus one observes the formation of the monoalkylated intermediate (structure **60a**) [77]. However, when the same starting complex reacts with an appropriate dihaloalkane, no such inter-



(60a) **(60b)**

mediate is observed (structure **60b**)—one sees only the starting material and the macrocycle formed by reaction at both reactive sites of the reagent. This requires the second step to proceed more rapidly than the first and the overall relative acceleration of the second (ring closing) step has been estimated to be a factor of at least 350. This is attributed to the kinetic coordination template effect and it derives from the topology of the inter-



Scheme 5.

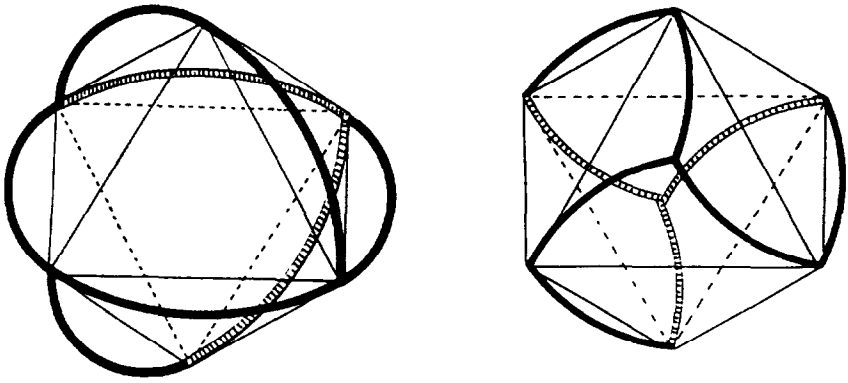
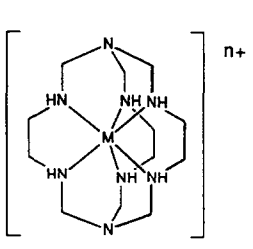


Fig. 5. Two possible topologies for encapsulation of metal ions.

mediate. It is of course necessary that the bridging group be chosen to fit the edge that is being spanned, i.e. the metrics must be right to produce a new ligand that is complementary to the templating metal ion.

In a template reaction, the metal ion usually organizes two or three reactive sites at an edge or face of its idealized coordination polyhedron. When an edge is involved, a new chelate ring forms and the usual product is a macrocyclic ligand. When a face is involved, the product may be a cage compound. The first example of the latter was due to Boston and Rose (Scheme 5) [62]. The tris(dimethylglyoximato)cobalt(III) complex has three oxime oxygen atoms protruding from each of two of its octahedral faces. A mole of BF_3 reacts at each face to form two tripodal FBO_3 bridges, producing an encapsulated metal ion. A number of novel encapsulation studies have used template reactions [62,78–84]. Sargeson's sepulchrates constitute the equivalent of tetraazamacrocycles among cage compounds



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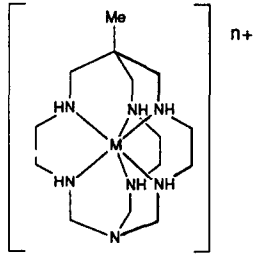
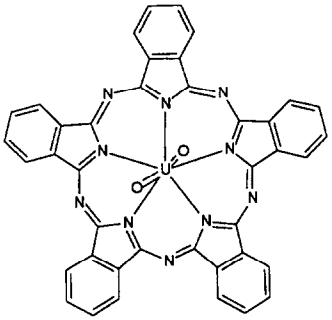


(62)

(structures **61** and **62**), i.e. no class of ligands is simpler to the coordination chemist than those saturated ligands containing only amine nitrogen donors. In these cases the topology associated with the template process is identical



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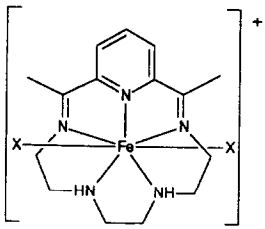
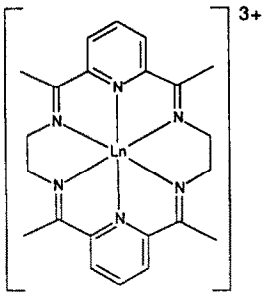


(64)

with that of the cryptates; the two best-known topologies for encapsulation of metal ions and other cubic or "spherical" species are shown in Fig. 5 [72].

The sepulchrates demonstrate the advantages of rigidity and complementarity in a kinetic coordination template reaction. The locations of the ethylenediamine nitrogen atoms in $[Co(en)_3]^{3+}$ are rigidly locked in position and this is a major cause for the very high yield of the reaction, which exceeds 90%. From the structures, the shape factors for the three amino groups at an octahedral face of $[Co(en)_3]^{3+}$ are nicely complementary with the tripodal $N(CH_2)_3$ and $RC(CH_2)_3$ bridges.

As the macrocycle and cage ligand examples show, the goals of template reactions may often be defined in terms of the topology that is being sought. Rigid templates are provided by metal ions that are substitution inert and whose coordination polyhedra exhibit stereochemical integrity. Thus cobalt(III) is a reliable octahedral template while nickel(II) has been used extensively as a square-planar template. Under some conditions, non-spherical transition metal ions, such as copper(II) and chromium(II), can provide reliable stereochemistries while still being highly labile. The tendency of Cu^{2+} to bind in a tetragonal fashion is reflected in the products of its template reaction with *o*-aminobenzaldehyde. Only the encircling tetradentate oligomer (TAAB, structure **56**) is formed with copper(II), whereas the octahedral nickel(II) template produces both that ligand and the tridentate oligomer (TRI, structure **46**); the latter occupies one octahedral face of the idealized coordination polyhedron. Fundamentally, they are anisotropic six-coordinate species. The uranyl ion $O{=}U{=}O^{2+}$ is an extreme example of an anisotropic template. The O–U–O axis is not available for further metal ion ligation so that ligands assemble in the plane orthogonal to that axis. The synthesis of pentadentate superphthalocyanine (structure **63**) proceeds by a template reaction using uranyl ion [83,84]. The consequences of rigid



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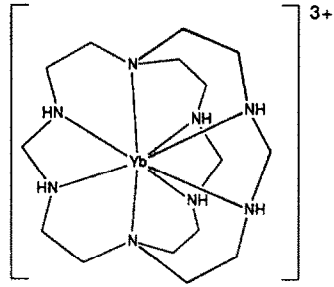
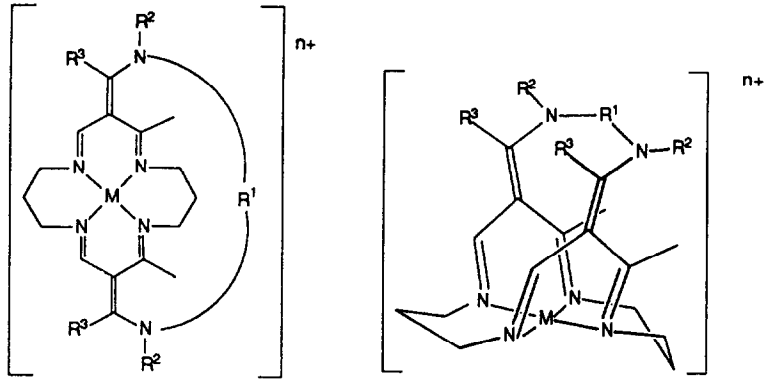


(66)

templates of known geometries have been well illustrated by the preceding examples.

In contrast, spherical ions and ions of low stereochemical integrity provide templates for the synthesis of molecules not so readily attainable using the rigid species. The formation of a planar pentadentate ligand in a complex having a pentagonal bipyramidal structure by the condensation of triethylenetetramine with 2,6-diacetylpyridine in the presence of an iron(III) salt (structure **64**) is attributable to the stereochemical flexibility of the high spin d^5 Fe^{3+} ion [85]. Similarly, recent studies using lanthanide ions have produced interesting new hexadentate macrocycles (structures **65** and **66**) [86–89]. Structure **66** is the product of a reaction closely similar to Sargeson's synthesis of the sepulchrates, although carried out under anhydrous conditions with reagents that do not produce water. In this reaction, bis(dimethylamino)methane was used in place of formaldehyde to give a high yield of the new macrobicycle.

Template reactions at sites substantially remote from the ligating atoms of a metal complex have been key steps in very important syntheses. The synthesis of families of lacunar [90,91] and vaulted [92] cyclidene complexes (structures **67** and **68**) has been accomplished by template closure of the second ring that creates the cavity (labeled a lacuna or vault, depending on size). Structure **69** shows the structure of the precursor. The conformation of the macrocyclic ligand in this precursor fixes the two reactive centers in close proximity, with a rather limited but useful flexibility that facilitates the use of a wide range of difunctional reagents to close the ring in high yield reactions. In a very real sense, the rigidity of the square-planar nickel(II) template is projected to the remote functional groups involved in the ring closing reaction. Scheme 6 traces the course of this synthesis. In this case, the binding of the highly flexible precursor ligand to the metal ion produces a rigid structure favorable to the desired ring closure process. Parentheti-



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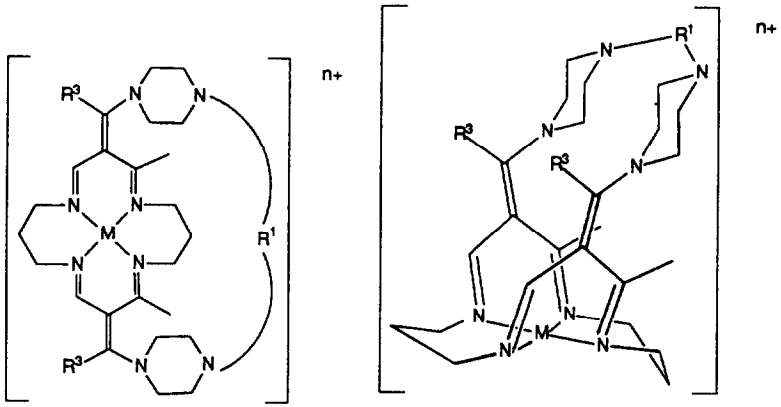
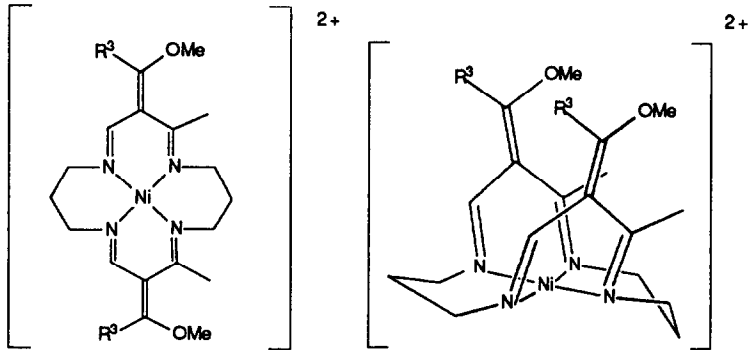
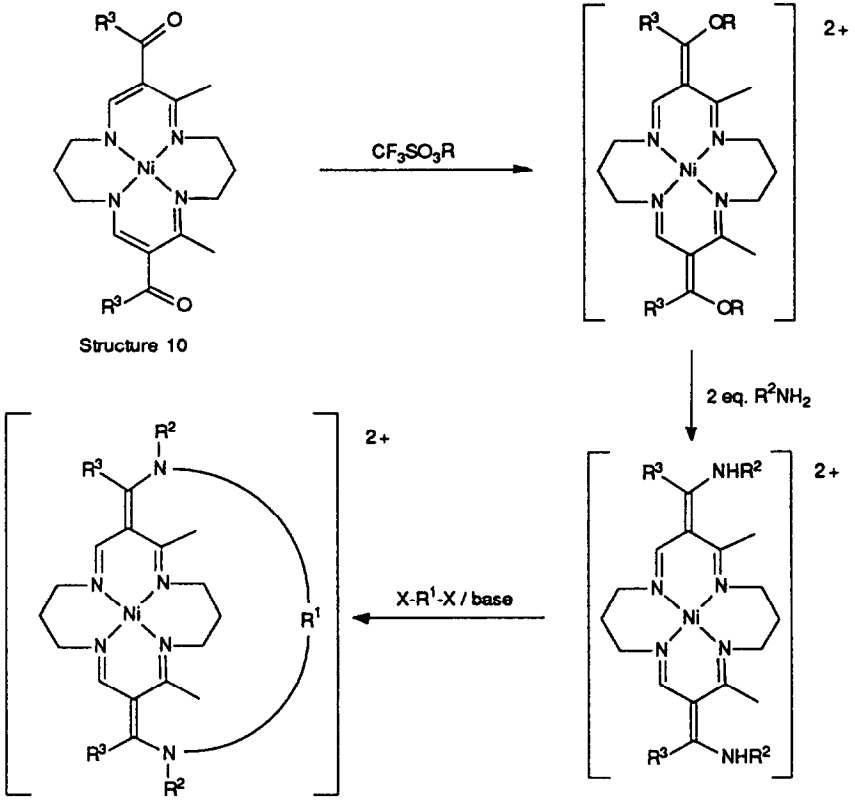


(68)

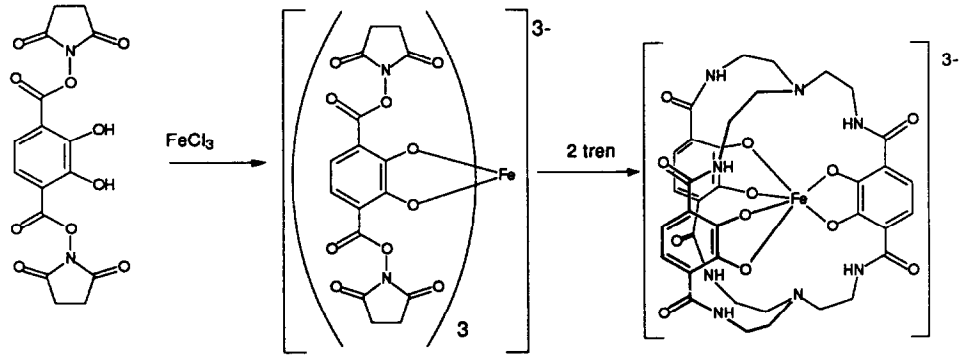


(69)

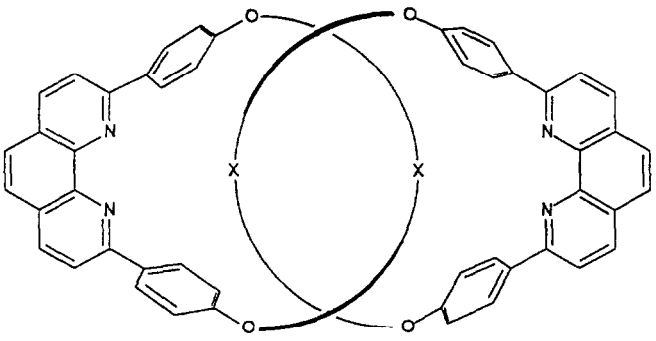


Scheme 6. Preparation of nickel(II) lacunar cyclidenes.

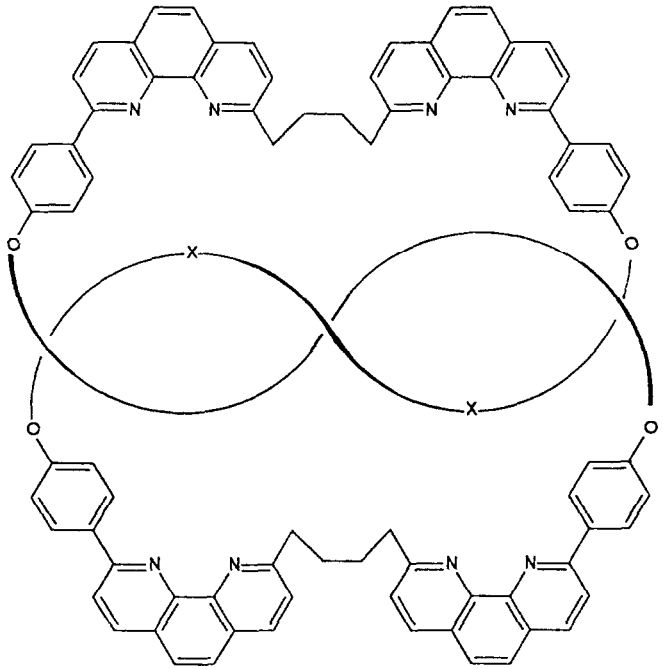
cally, it might be pointed out that in this and many other template reactions, the metal ion serves in other roles in addition to acting as the template. In the present case, the metal ion masks the donor atoms so that they cannot



Scheme 7.



(70) X = -$CH_2CH_2(OCH_2CH_2)_5$-

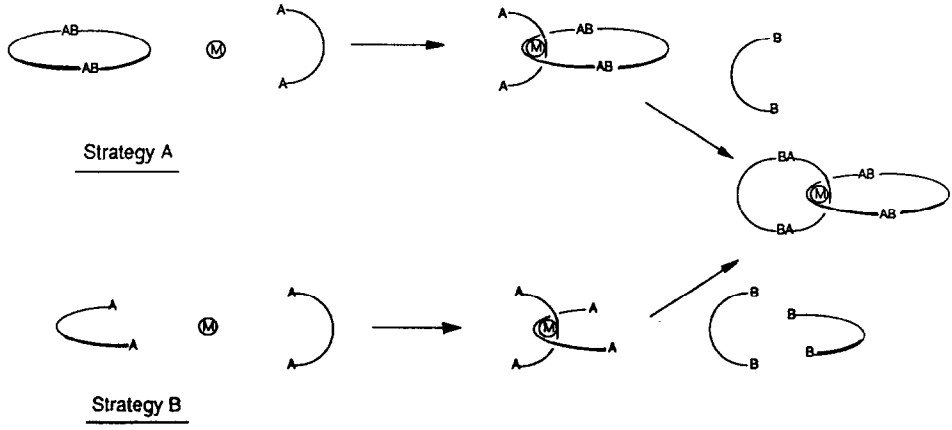


(71) X = -$CH_2CH_2(OCH_2CH_2)_5$-

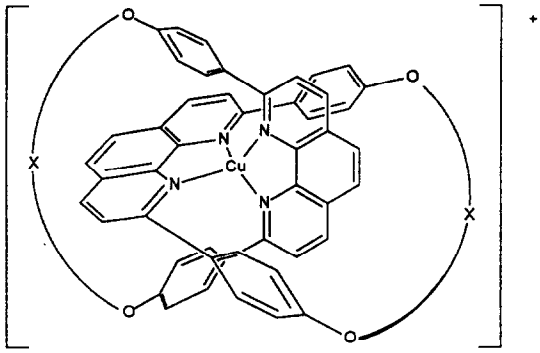
act as nucleophiles during the course of Scheme 6. Also, the chelation of the metal ion to the primary cyclidene macrocycle prevents reactions of the labile Schiff base linkages.

The ingeniously simple synthesis of an encapsulated siderophore model by Raymond and coworkers [93] also involves reactions at centers substantially remote from the metal center (Scheme 7). The starting ligand is a diester of 2,3-dihydroxyterephthalic acid and this species forms a three-to-one complex with iron(III). Tripodal caps are formed by the reactions of sets of three of the ester functions with β,β',β''-triaminotriethylamine (TREN). Thus the topology is the same as that for the other known encapsulation compounds of the transition metal ion, as mentioned above. However, the metrics are very different; the reactive planar carbon centers are four atoms removed from the iron atom and much of the displacement is lateral with respect to the coordination polyhedral face that is (remotely) capped. It is therefore not surprising that the successful tripodal bridge has C2 legs rather than the C1 legs of the sepulchrates.

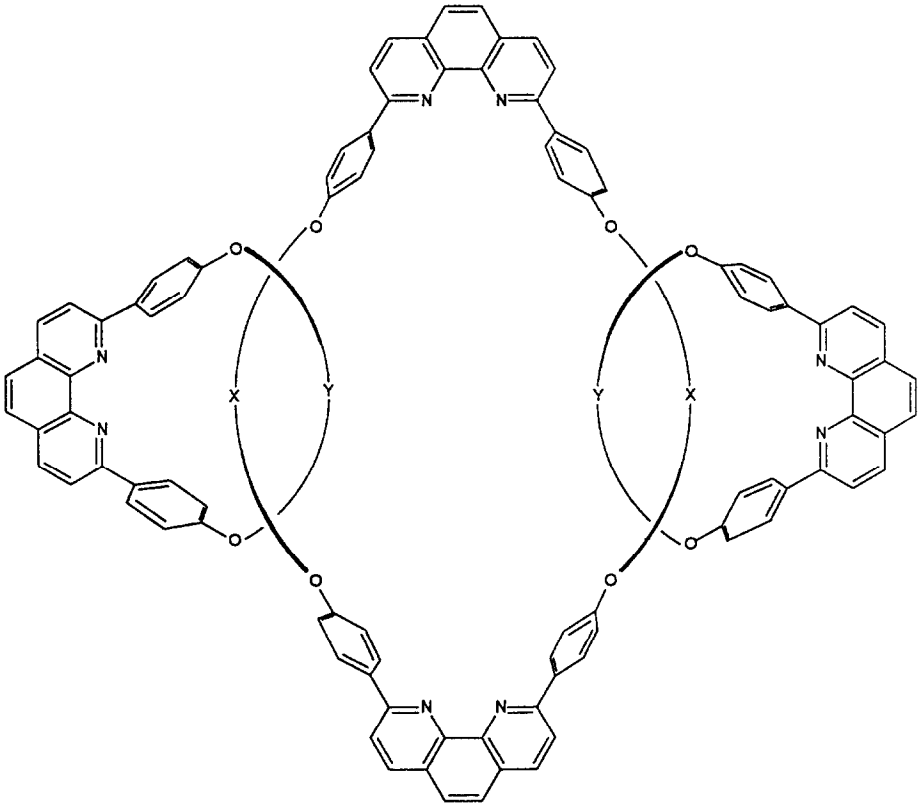
From the cases discussed above it is apparent that given topologies repeat in rather great abundance and that the hypothetical catalog of the available forms of matter is most greatly amplified and diversified when new topologies appear. The innovations of Sauvage are most striking in just this context. The template synthesis of catenanes (structure **70**) [94] and the trefoil knot (structure **71**) [95] have involved topologies that are the first of their kinds to be produced by coordination template reactions. These results are the most exciting in this area since the template synthesis of the first encapsulated metal ion, and they compete in importance with the first demonstration and understanding of the coordination template effect itself.



Scheme 8.



(72) X = -$CH_2CH_2(OCH_2CH_2)_4$-



(73) X = -$CH_2CC.CCCH_2$-

Y = -$CH_2CH_2(OCH_2CH_2)_4$-

In their catenand synthesis (Scheme 8), these investigators used a tetrahedral copper(I) ion to hold two reagent ligands in identical but orthogonal orientations. Then ring closures were carried out using each fragment with the template-determined result that two interlocking rings were formed (structure **72**). Two strategies were used. The more conservative involved use of one ligand as a pre-formed ring with the necessity to close only the one incomplete ring in the template process (strategy A in Scheme 8). Although simpler in appearance, that strategy is limited by the necessity to synthesize first a cyclic ligand and by statistical distribution of the two ligands in the metal complexes such that not all of the complexes contain one mole of each ligand. In fact, the simpler reaction, formation of both rings in a single reaction system, proved to be most desirable. The overall yield, tracing all the way back to 1,10-phenanthroline, was 20%. This group has subsequently generalized the template-controlled catenand-forming process to include formation of three linked rings (structure **73**) [96].

H. THE CATENAND AND TETHERING EFFECTS

Dietrich-Buchecker and Sauvage [98] have correctly identified the extreme stability and inertness of the metal complexes formed by their catenands with their novel topology; they have labeled this the catenand effect. In terms of their contributions to the relative inertness of compounds, the interlocking rings of the catenand are semiquantitatively comparable with a macrocyclic ligand or with the fused rings of a cryptate. The free catenand ligands (structure **70**) are even less well organized for tetradentate chelation than a flexible tetradentate macrocycle, and this suggests that the bidentate components of the two phenanthroline moieties may be optimally misoriented insofar as tetradentate, or is it bis(bidentate), chelation. Considering this possibility and the process of chelating the second phenanthroline group after the first is bound to the metal ion, the pathway is very specific from the conformational point of view. Assuming the worst initial orientation with the second ring remote from the first and the phenanthroline groups as far away as possible, the motion to bring it into the position for chelation is not simple. If ion-dipolar forces tend to orient that second ring, that ring will need to reorient constantly with respect to the cationic center as it slides along the first ring. Since the successful path is but one of many perambulations the second ring might make about the first, the system would seem to be rather more disorganized than other topologies. Perhaps an analogy between the catenand effect and the chelate effect is appropriate. In both cases, the advantages stem from the fact that when a coordinated moiety dissociates, it is confined by a link to a group that remains coordinated.

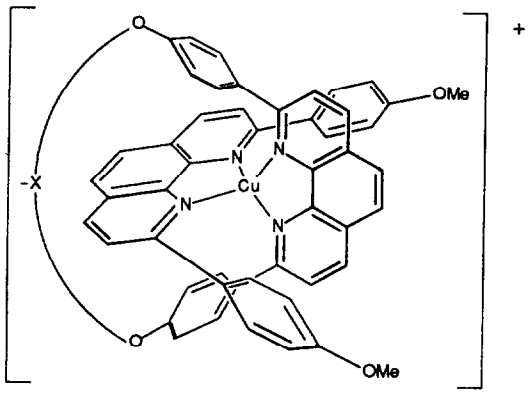
The data of Albrecht-Gary et al. [39] show that there are two effects to be

TABLE 5

Decomplexation of catenand and related copper(I) complexes by KCN [a]

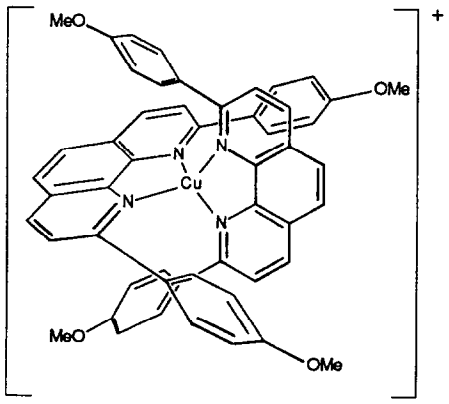
Complex	k_D (s^{-1}) [b]	k_{CN} (mol^{-1} L s^{-1})
72	$(1.8 \pm 0.9) \times 10^{-4}$	0.16 ± 0.01
74a	$< 4 \times 10^{-5}$	0.15 ± 0.02
74b	$(1.4 \pm 0.5) \times 10^{-3}$	1.7 ± 0.2
75	0.48 ± 0.01	6.5 ± 0.1

[a] In acetonitrile–water (9:1 by weight), ionic strength 0.1, temperature 25°C. [b] k_D refers to spontaneous dissociation of copper(I) and k_{CN} to a biomolecular CN^--promoted process.



(74a) X = $-CH_2CH_2(OCH_2CH_2)_3-$

(74b) X = $-CH_2CH_2(OCH_2CH_2)_4-$



(75)

considered in these systems. They studied the rates of displacement of the ligands from copper(I) by cyanide ion and they used three kinds of systems: (1) the complex of the catenand, i.e. two interlocking rings as ligands; (2) a complex containing one of the rings intact but only a 2,9-dimethoxy-1,10-phenanthroline as the second ligand, i.e. one acyclic ligand and one ring that encircles the other ligand; and (3) bis(2,9-dimethoxy-1,10-phenanthroline) copper(I) (structures **72**, **74** and **75**, Table 5).

From their work, the biggest effect is not due to the presence of the catenand but rather is due to the presence of a ring that entirely encircles the metal ion and the second chelating ligand. Remarkably, the compound **74**, which is intermediate in structure, shows the greatest change from its comparison compound, **75**, in the direct or first-order rate constant, a factor of about 300. This is a topological effect associated with including the dissociating ligand within the compass of the cyclic ligand. One might think of it as a tethering or inclusion phenomenon. As Table 5 shows, both rate constants have strong metric dependences and the smaller monocyclic ligand produces a retardation in the second-order rate constant of about 40 times. In contrast, the catenate shows no more than a factor of ten in its retardation effect when compared with the complexes having only one cyclic ligand. However, the combined effects are large.

I. CONCLUSIONS

The fields of coordination and inclusion chemistry have accumulated an astounding array of so-called effects that are associated with the strength and selectivity of various complexation phenomena, including the chelate effect, the macrocyclic effect, the cryptate effect, the catenand effect, a (not previously named) tethering effect, multiple juxtapositional fixedness, and preorganization. A common perspective can be found on these effects, if one recognizes that they are all manifestations of molecular organization. The universal structural factors underlying these manifestations of molecular organization involve topology, size, shape, rigidity and complementarity.

The occurrence of the unexpected tethering or inclusion phenomenon described in the preceding section of this paper suggests that all of the possible effects on the stabilities and inertness of complexes that are associated with molecular organization may not yet have been observed and labeled. It further suggests that it may be time to focus on the broad occurrence of molecular organization in complex formation of all kinds and on the universal factors that underlie the effects of that organization. A qualitative discussion has been presented of the relative importance of the different factors in each of the complexation effects, but it is hoped that

these factors may eventually find general quantitation that spans the various labeled effects.

As indicated in the introduction, similar consequences of molecular organization are apparent in a variety of reactions and interactions; template effects, anchimeric or neighboring-group effects, the agostic effect, multifunctional catalysis and biological systems were mentioned. The template effect was discussed as an example of the influence of molecular organization on chemical reactions. The introduction of new topologies invariably launches new surges of activity and excitement about template reactions. The subjects of biomimicry, catalysis and the concept area of molecular devices may see the greatest advantages of an analytical approach to the structural sources of molecular organization.

ACKNOWLEDGEMENT

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