the delay to be longer when the reward was present physically, supporting the interpretation that attention to the rewards in this situation increases frustration [D. T. Miller and R. Karniol, *J. Pers. Soc. Psychol.* **34**, 310 (1976)].
27. W. Mischel and B. Moore, *ibid.* **28**, 172 (1973).
28. B. Moore, W. Mischel, A. Zeiss, *ibid.* **34**, 419 (1976).
29. D. Berlyne, *Conflict, Arousal and Curiosity* (McGraw-Hill, New York, 1960).
30. W. Mischel and N. Baker, *J. Pers. Soc. Psychol.* **31**, 254 (1975).
31. B. S. Bloom, *Stability and Change in Human Characteristics* (Wiley, New York, 1964).
32. M. P. Honzik, J. W. Macfarlane, L. Allen, *J. Exp. Educ.* **17**, 309 (1948).
33. W. Mischel and C. J. Patterson, in *Minnesota Symposia on Child Psychology*, W. A. Collins, Ed. (Erlbaum, Hillsdale, NJ, 1978), vol. 11, pp. 199–230.
34. A. L. Brown and J. S. DeLoache, in *Children's Thinking: What Develops?* R. S. Siegler, Ed. (Erlbaum, Hillsdale, NJ, 1978), pp. 3–25; A. L. Brown, J. D. Bransford, R. A. Ferrara, J. C. Campione, in *Handbook of Child Psychology*, P. H. Mussen, Ed. (Wiley, New York, 1983), vol. 3, pp. 77–166.
35. D. H. Meichenbaum and J. Goodman, *J. Ab. Psychol.* 77, 115 (1971).
36. R. J. Sternberg and D. K. Detterman, Eds., *What Is Intelligence? Contemporary Viewpoints* (Ablex, Norwood, NJ, 1986).
37. N. Cantor and J. F. Kihlstrom, *Personality and Social Intelligence* (Prentice-Hall, Englewood Cliffs, NJ, 1987).
38. H. N. Mischel and W. Mischel, *Child Dev.* **54**, 603 (1983).
39. J. Piaget and B. Inhelder, *L'image Mentale Chez l'Enfant* (Presses Universitaires de France, Paris, 1966).
40. D. M. Ross and S. A. Ross, *Hyperactivity: Current Issues, Research and Theory* (Wiley, New York, 1982).
41. M. L. Rodriguez, W. Mischel, Y. Shoda, *J. Pers. Soc. Psychol.*, in press.
42. M. L. Rodriguez, Y. Shoda, W. Mischel, J. Wright, "Delay of gratification and children's social behavior in natural settings," paper presented at the Eastern Psychological Association, Boston, March 1989.
43. Although more reviewers than can be thanked here provided constructive criticism on earlier drafts, we are especially grateful to J. Hochberg and H. Zukier who were exceptionally generous with their time and commentary.

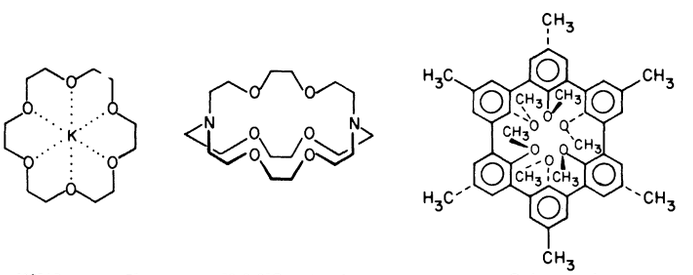
Molecular Recognition and Metal Ion Template Synthesis

THOMAS J. MCMURRY, KENNETH N. RAYMOND,* PAUL H. SMITH

Methods for the design and synthesis of ligands intended to be specific for a metal ion have been a recent chemical development. This article describes how this process can be inverted so that the specifics of the coordination environment around the metal ion can be used as a template in large-scale ligand synthesis. The synthesis of macrobicyclic ligands for ferric ion has been accomplished by using active esters of catechol ligands in which catecholate coordination to iron is a prelude to the organic chemical reactions that link the coordination subunits together into one ligand system surrounding a central metal ion coordination site. The lanthanide(III) ions, which are among the most labile metal ions known, have coordination numbers of 8 or higher, and thus their encapsulation into a macrobicyclic structure is a challenging problem. Lanthanide amine complexes have been used as metal templates in the synthesis of such macrobicyclic lanthanide complexes. There is evidence that such a complex is inert to exchange in aqueous solution.

MOLECULAR RECOGNITION IN BIOLOGICAL SYSTEMS OCcurs at a level of sophistication and beauty that is rarely matched in the laboratory. Efforts to understand these complex processes on a molecular level have led chemists to study synthetic receptors, that is, small (<2000 daltons) molecules designed to complex a particular substrate, be it organic or inorganic (*1*). The synthetic analogs are held together by covalent bonds such that a cavity is formed, with appropriate electron donor (or acceptor) groups directed toward the proposed substrate binding site. In contrast, a protein or polynucleotide utilizes noncovalent interactions to enforce the tertiary structure necessary for substrate binding. The limited number of receptor-substrate interactions present in a synthetic model system, combined with the relatively small receptor size, simplifies the study of molecular recognition. In addition, systematic variation of fundamental receptor properties, for example, cavity size, can be achieved through synthesis.

Perhaps the most familiar and illustrative examples of such studies emanate from the pioneering work of Pedersen (*2*), Cram (*3*), and Lehn (*4*), who studied the effect of cavity size, shape, and rigidity on the binding of alkali metals with oxygen donor hosts, such as those shown in Scheme 1. The macrocyclic crown ethers incorporate



K^+[18-crown-6] [2,2,2]Cryptand Sphereand

Scheme 1

etherial oxygen donor groups within a macrocyclic ring. The macrobicyclic cryptands are cage molecules that form an ellipsoidal cavity of well-defined shape. The sphereands incorporate phenolic ether oxygen donors into rigid macrocyclic rings that are preorganized for metal binding. Thermodynamic evaluation of the binding of alkali metals to these receptors shows a dramatic correlation of cavity dimension with preferred ion size (*5*).

Cram has emphasized the importance of host preorganization in

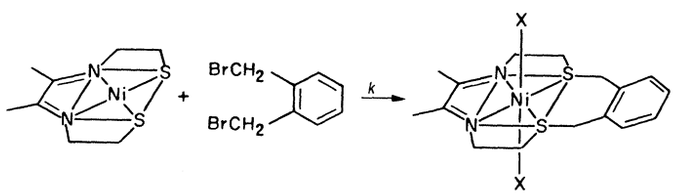
T. J. McMurry is at the Radiation Oncology Branch, National Cancer Institute, Bethesda, MD 20892. K. N. Raymond is in the Department of Chemistry, University of California, Berkeley, CA 94720. P. H. Smith is at INC-4, Mail Stop C-345, Los Alamos National Laboratory, Los Alamos, NM 87545.

*To whom correspondence should be addressed.

molecular recognition (*3*). For purposes of discussing the synthesis of metal ion receptors, we will emphasize an alternative perspective, namely, that the substrate can play a role in defining the cavity of a host. In other words, the selectivity mentioned above may be harnessed by assembling the receptor framework around the metal. If the reactants are preorganized within the coordination sphere, the metal can act as a template to direct the course of the reaction, thus minimizing the formation of undesired products, for example, oligomers. The enhanced yields resulting from this so-called template effect can be considered an expression of molecular recognition.

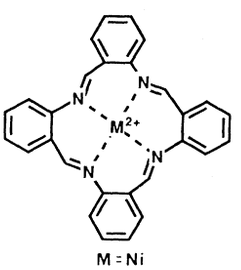
The template effect has both kinetic and thermodynamic origins (*6*). The kinetic coordination template effect results from the geometric arrangement of the reactants within the coordination sphere of the metal, which increases the likelihood that reaction will occur (the entropy of activation for the reaction is decreased). For competing reversible reactions, a thermodynamic coordination template effect allows the stability of the complex to determine the product. Chemists have become increasingly adept at using metal ion receptors in toxic metal decorporation (*7, 8*), radiopharmaceuticals (*9*), and magnetic resonance imaging (*10*). The template synthesis is one approach that can simplify the synthesis of such increasingly complicated ligand systems.

Busch and co-workers demonstrated in 1964 that coordinated ligands could react in a manner consistent with the kinetic coordination template effect (*11*). By reacting the square planar Ni(II) complex **1** with α,α′-dibromo-*o*-xylene, they obtained a quantitative yield of the macrocyclic thioether complex **2** (Scheme 2). The lack of



1 2

Scheme 2

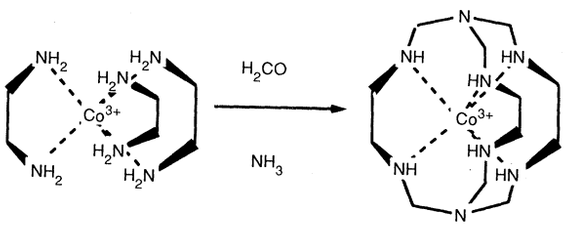


M = Ni

observed intermediates indicated that the rate of the second alkylation was enhanced by at least a factor of 10 over that of the first, thus conclusively demonstrating the existence of a kinetic template effect.

The first synthetic study that demonstrated that a metal template could stabilize macrocyclic products formed by reversible reactions was reported earlier; in 1954 Eichorn and Latif described remarkably stable structures resulting from the self-condensation of *o*-aminobenzaldehyde in the presence of copper(II) and nickel(II) (*12*). However, misled by inaccurate analytical data, these investigators did not appreciate the true macrocyclic structure and proposed instead a noncyclic trimer. A reinvestigation of this work by Melson and Busch (*13*) conclusively showed the products to be the tetradentate macrocyclic tetramer. In this case, the hydrolytic lability of the imine carbon-nitrogen double bonds is reduced by incorporation in a metal chelate ring, thus allowing the thermodynamically stable product macrocycle to accumulate.

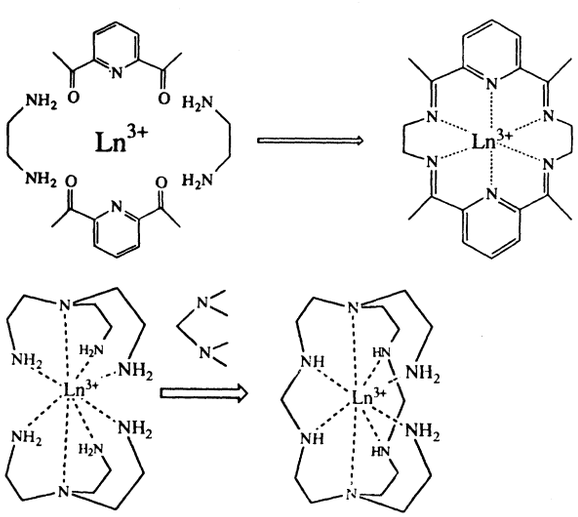
The elegant syntheses by Sargeson and co-workers of cobalt cage complexes, "sepulchrates," from $[Co(en)_3]Cl_3$, formaldehyde, and ammonia further illustrate the principles of the thermodynamic coordination template effect (*14*). The reaction involves the capping of three cobalt-bound ethylenediamines (en) with formaldehyde and ammonia as illustrated in Scheme 3. The kinetically inert cobalt(III)



Scheme 3

tris(ethylenediamine) complex has a rigid geometry that is spatially well suited to the formation of the two amine caps. An equally important factor in the extraordinarily high efficiency of this reaction (>90% yield) is the reversible nature of reactions that form carbon-nitrogen bonds. The coupling reaction is analogous to Schiff base condensations in the sense that one carbon-oxygen double bond is converted to two carbon-nitrogen single bonds. Schiff base condensations are typically reversible in nature. This reversibility allows the thermodynamically stable product to accumulate, because reactions to form higher energy products can be reversed.

An example of a template reaction that involves a reversible ligand-ligand interaction but lacks the metal-directing capabilities of cobalt has been reported by Hart (*15*), Fenton (*16*), and Vallarino (*17*) and their co-workers, as shown at the top in Scheme 4. In this



Scheme 4

case, lanthanides are used to bring together two equivalents each of ethylenediamine and 2,6-diacetylpyridine or pyridinedialdehyde to form a macrocycle in high yields (70 to 80%). Although the reactions leading to the formation of the carbon-nitrogen bonds of the macrocycle parallel those illustrated above for transition metal templates, the use of lanthanide ions as templates provides a more flexible coordination environment. Lanthanides resemble the alkali and alkaline-earth metals in showing little directional character in metal-ligand bonds. In contrast, the maximum coordination number, which is determined by the ion size and the ligands, is a real constraint.

A combination of the approaches used to prepare the cobalt

sepulchrate and the lanthanide Schiff base macrocycles has been used in the lanthanide template synthesis of a series of cage complexes from TREN [(tris-2-aminoethyl)amine] and a formaldehyde derivative, as shown at the bottom in Scheme 4 (*18, 19*). The interligand N–N distances in the simple bis(TREN) neodymium complex structure would suggest the use of propyl chains as bridging groups (*20*). However, the flexibility of the ligand structure also suggested the possibility of utilizing shorter bridging groups, including methylene, as in the Sargeson sepulchrate synthesis. The hydrolytic instability of lanthanide amine complexes required that water be excluded from the reaction. This instability precluded the use of formaldehyde, because the reaction produces water; but the formaldehyde equivalent, bis(dimethylamino)methane, reacts to give methylene bridges similar to those in the Schiff base reaction. This coupling reaction is presumably reversible and gives yields of approximately 70 to 80%.

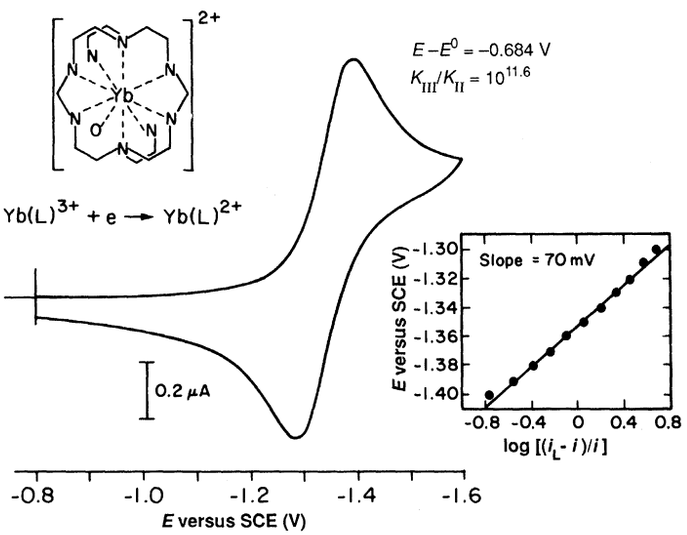
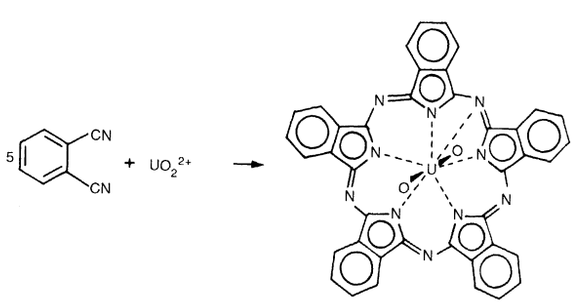


Fig. 1. Cyclic voltammogram of 3 m*M* Yb(L) $(trif)_3$ (trif, trifluoromethyl sulfonate) in propylene carbonate solution with 0.1*M* tetraethylammonium perchlorate (scan rate, 200 mV/s). Inset: Plot of potential (*E*) versus log[(i_L − *i*)/*i*] (*i* is current) for Yb(L)$(trif)_3$ obtained from the trace of current versus potential for a normal pulse polarogram performed at a scan rate of 5 mV/s and a pulse amplitude of 50 mV. The reaction is quasi-reversible, with a formal potential of −0.684 V.

Despite the reversible nature of these carbon-nitrogen bond-forming reactions, there is an unusual stabilization of the ligand when complexed to the metal ion. For example, the cobalt sepulchrate complex is demetallated only under conditions that destroy the ligand once the metal is released (*14*). A similar situation exists for the Schiff base macrocycles, which are stable to strong base when complexed to lanthanide ions but are readily hydrolyzed in the absence of the metal ion (*17*). The tribridged ytterbium species analogous to the dibridged lanthanum complex shown in Scheme 4 appears to be stable to hydrolysis (*19*). For the dibridged ytterbium complex shown in Fig. 1, a comparison of the reduction potential of −0.68 V (versus the standard calomel electrode, SCE) in propylene carbonate with the standard $Yb^{3+/2+}$ potential in this solvent (*21*) shows that the stability constant for the Yb^{3+} complex is $10^{11.6}$ times that for the Yb^{2+} complex (*19*).

The unique coordination requirements of the uranyl ion, $(O=U=O)^{2+}$, have been exploited in the preparation of macrocyclic nitrogen-donor complexes. The five-nitrogen version of a phthalocyanine, or superphthalocyanine, has been cyclized around the so-called "belly band" of the uranyl ion, as illustrated in Scheme 5 (*22*). The uranyl complex of the ligand at the top in Scheme 4 has also been prepared by using the uranyl ion as a template (*23*).



Scheme 5

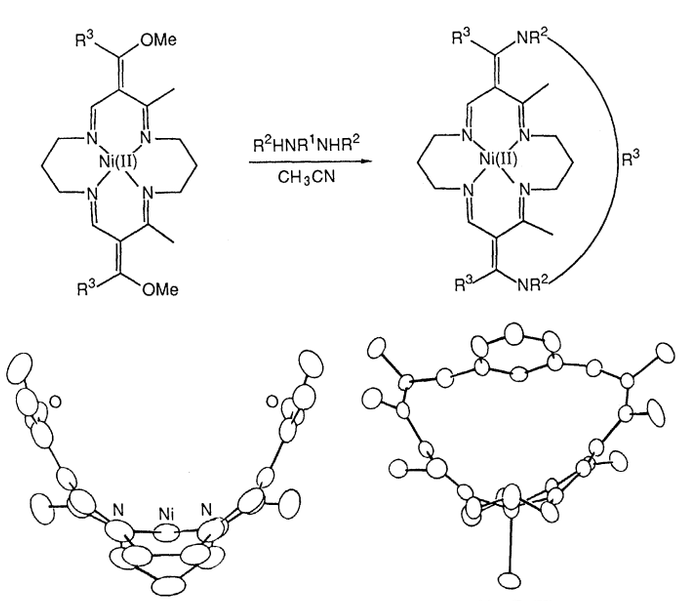
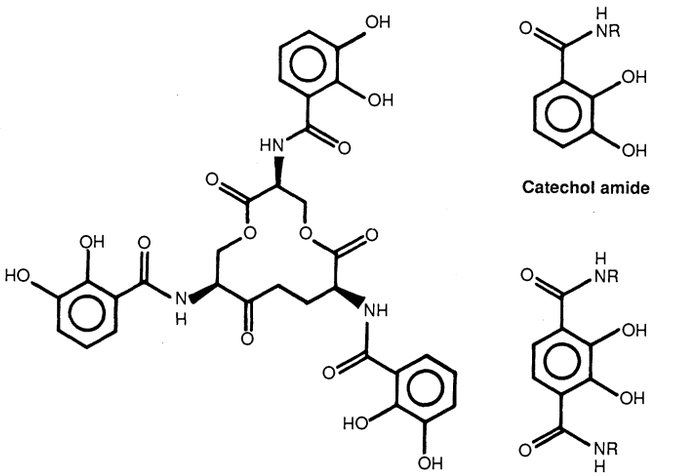


Fig. 2. Preparation of "cyclidene" complexes (*24*). The synthesis of the nickel complex is shown at the top (Me, methyl). Metal complexation forces a deep saddle geometry (lower left), which positions the reactive methoxy groups for an efficient cyclization reaction to give the product shown at the lower right.

If the free ligand is desired or if other metals are to be substituted for the metal ion template, a ligand-ligand bond that is irreversibly formed in the template syntheses is required. In this case, appropriate preorganization of the reactants by coordination to the metal center is of paramount importance. An example of such preorganization of reactants in a metal complex is the synthesis of "cyclidene" ligands by Busch and Cairns (*24*) (Fig. 2). These complexes incorporate a metal binding site as well as a cavity for substrate binding. The cavity is formed by the addition of a diamine $H_2NR^1NH^2$ to the cyclidene precursor. One can easily vary the structure of the bridging group R^1 by changing the nature of the diamine added to the precursor. Examination of the x-ray structure of the nickel complex of the precursor reveals the elegance of the synthesis: as a consequence of metal coordination, the ligand has a deep saddle structure formed with the reactive OCH_3 groups poised in a position to close the bridging ring (*25, 26*). The efficiency of the cyclization reaction can be attributed to the kinetic coordination template effect. A series of these ligands has yielded insights into oxygen binding and has resulted in the development of a synthetic O_2 binder that is functional under ambient conditions (*27*).

One of nature's difficult coordination chemistry problems is a consequence of the insolubility of Fe(III) at neutral *p*H (*28*). Microorganisms secrete siderophores, small molecules designed to

encapsulate specifically, and to transport, ferric ion under biological conditions (*29*). Enteric bacteria, such as *Escherichia coli*, produce enterobactin, which forms the most stable Fe(III) complex known (formation constant $K_f = 10^{52}$) (*29*), coordinating the iron through deprotonated catecholamide binding subunits (*30*) (Scheme 6).



Scheme 6

Efforts to understand this remarkable stability have included the synthesis of analogs (*30–32*). The ligand 2,3-dihydroxyterephthalate is much more effective than either catechol or 2,3-dihydroxybenzamide as a ligand for Fe(III) (*33*). The synthesis of a series of macrobicyclic tris-catecholamide ligands that incorporate this binding subunit (*34–36*) includes bicapped TRENCAM, which was synthesized by the use of a ferric ion template (*35*). In the reaction (Fig. 3), three equivalents of disuccinimido-2,3-dihydroxyterephthalate combine with $FeCl_3$ and Et_3N in DMF to form the tris-catecholate complex. If we assume approximately octahedral metal coordination (*37*), three *N*-hydroxysuccinimide active esters would be positioned at the opposing trigonal faces of the ferric complex. The proximity of the active esters in space provides an ideal orientation for the reaction with the tripodal tetraamine TREN to form three amide bonds at each face.

This reaction proceeds to form an unusual macrocyclic intermediate, which retains both a primary amine and an active ester moiety. Ring closure of the last amide bond to form the macrobicyclic cage structure (in 50% overall yield) was accomplished with heating in the presence of dimethylaminopyridine. X-ray structural analysis (*34*) of Na_3 [Fe(bicapped TRENCAM)]·17.5 H_2O revealed a trigonal prismatic structure, previously unknown for Fe(III) (Fig. 4). The entire catechoylamide group is planar, the result of a trans amide bond conformation and a strong hydrogen bond between the amide proton and the coordinated catechol oxygen. The trigonal prismatic structure, which can be visualized as the achiral (Bailar twist) (*38*) intermediate between the interconversion of the left-handed (Λ) and right-handed (Δ) stereoisomers of a tris(bidentate) "octahedral" complex, is a consequence of the small cage size and the stability of the six intramolecular hydrogen bonds. The structure suggests that the macrocycle intermediate (Fig. 3) accumulates during the reaction as a result of the energy barrier represented by the geometry change from octahedral to trigonal prismatic coordination.

The high thermodynamic stability of the ferric complex of bicapped TRENCAM is reflected in the formal reduction potential (at *p*H 12) of −0.97 V versus the normal hydrogen electrode (NHE) (*34*), corresponding to a ratio of the formation constants for Fe(III)L/Fe(II)L (where L is bicapped TRENCAM) of $10^{29.5}$. The stability constant of the ferric complex is 10^{43} (*36*), somewhat less than that determined ($10^{43.6}$) for the nonmacrobicyclic analog, TRENCAM (*32*). The apparent lack of a macrocyclic effect has also been noted for some macrocyclic ferric (2,3-dihydroxyterephthalamide) complexes (*39, 40*). In marked contrast to the macrocyclic ether complexation of alkali metal cations described earlier, these results show the dominance of enthalpy rather than entropy in the

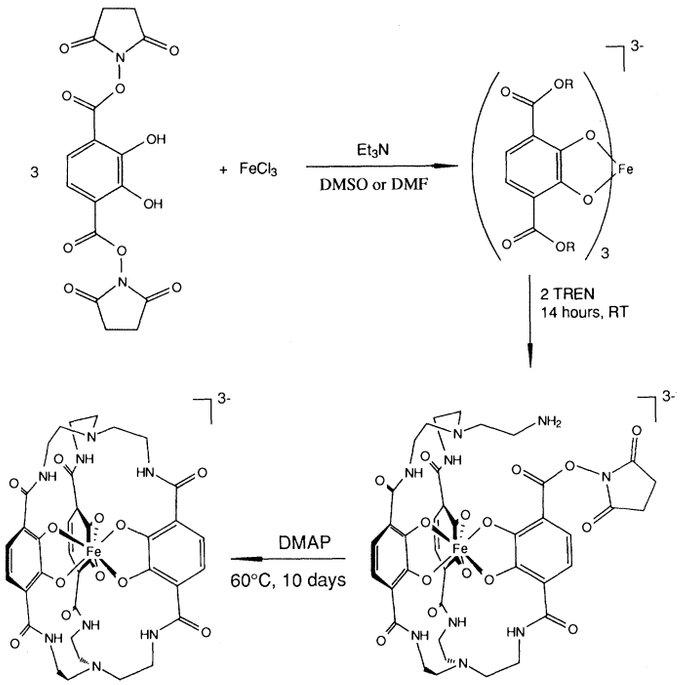


Fig. 3. The template synthesis of ferric (bicapped TRENCAM). Complexation of iron by the active ester catechol derivative in dimethylsulfoxide (DMSO) or dimethylformamide (DMF) with triethylamine (Et_3N) used as a base, gives the intermediate template complex; RT, room temperature. Reaction with tris(2-aminoethyl)amine gives the intermediate in which five of six possible amide bonds have been formed. Further reaction at high temperature with the catalyst 4-(dimethylamino)pyridine (DMAP) gives the macrocyclic complex product in overall 50% yield.

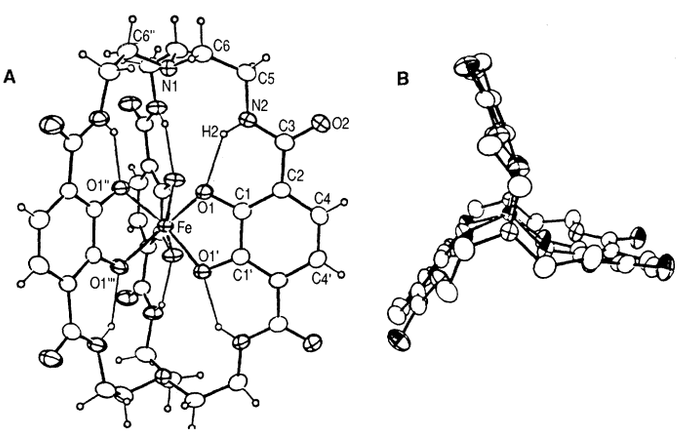
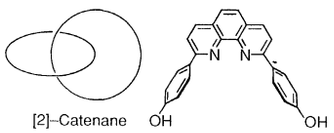


Fig. 4. Perspective views of the iron complex product of a template synthesis. The ellipsoids are scaled to represent the 50% probability surface. (**A**) Side view of Fe(bicapped TRENCAM). Note the amide N–H···O catechol hydrogen bonding, which holds each catechol ring in a rigidly planar array with its amide substituents. (**B**) Top view of Fe(bicapped TRENCAM). Oxygen atoms are marked by ellipsoids with one cross-hatched quadrant. Note the trigonal prismatic arrangement of the metal ion geometry with the iron atom lying out of the plane formed by the catechol ring.

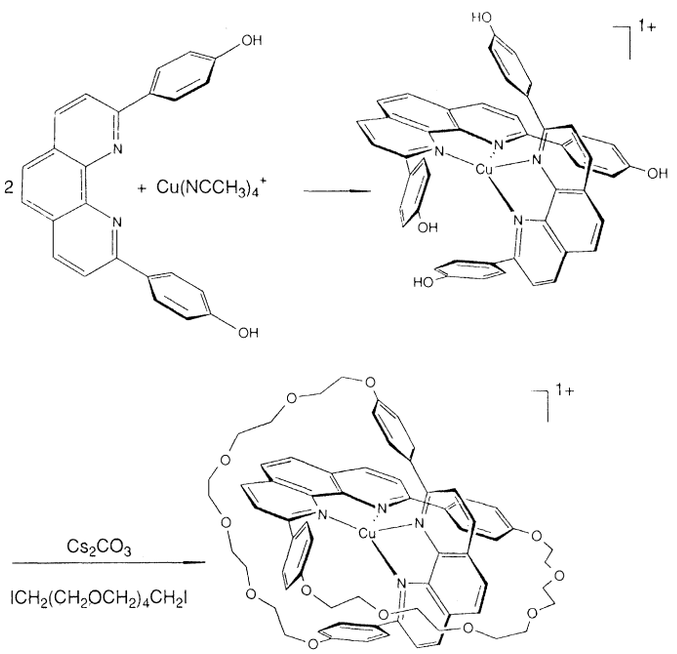
ferric-catecholate complexation reaction and represent an important factor to be considered in the design of complexing agents specific for highly charged metal ions.

Some of the most intriguing structures assembled to date with template methodology are catenanes, molecules composed of interlocking rings. Despite ingenious syntheses, it had only been possible to make minute quantities of molecules with this topology (*41*). Recently, however, excellent yields of catenanes containing the functionalized 1,10-phenanthroline ligand have been prepared by a template method (*42*) (Scheme 7).



Scheme 7

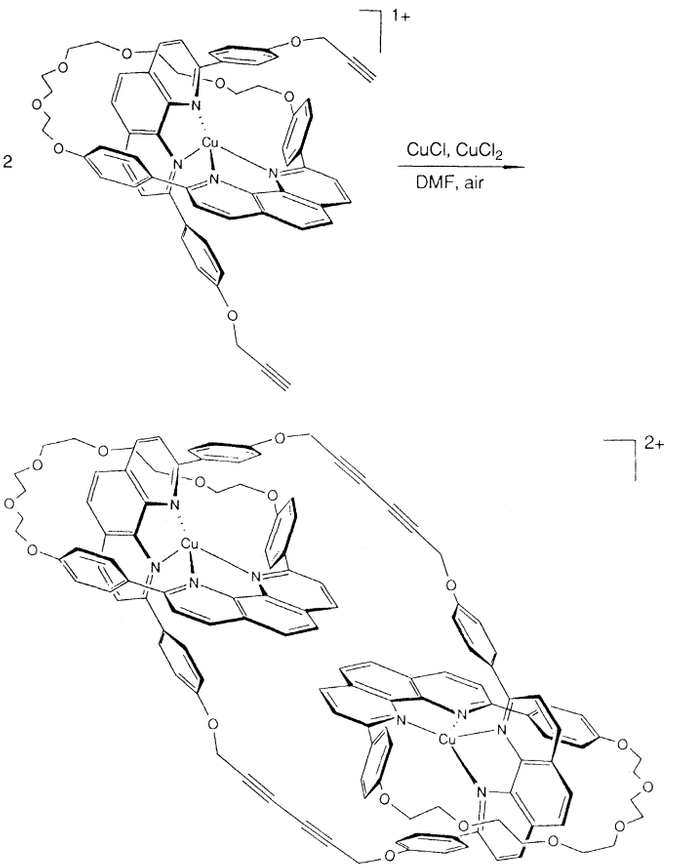
Coordination of two rigid phenanthroline derivatives (Scheme 7) to Cu(I) forms a complex with the nitrogen donors coordinated in a tetrahedral fashion (Scheme 8). Reaction of this complex with two



Scheme 8

equivalents of a diiodo pentaethylene glycol gave the Cu(I) catenand in 27% yield. This convenient, one-pot synthesis can be accomplished on a gram scale. Demetallation of the copper complex with CN^- provides the free ligand (the catenane), which can then be complexed with other metal cations (Zn^{2+}, Cd^{2+}, Ag^{2+}, Ni^{2+}). Among the unusual properties of the metal catenands is the stabilization of low oxidation states: for example, the Cu(I) catenand can be reduced at −1.67 V versus SCE in DMF to a dark blue, formally Cu(0) complex, whereas the Cu(I) complex of the open-chain ligand analog is demetallated under the same conditions. The stabilization of low-valent metals and the reported kinetic inertness (*43*) of these compounds are the direct result of the topological properties of the interlocked ring system (Scheme 9).

Recent advances indicate a [3]-catenate can be prepared in a 58% yield by oxidatively coupling terminal diynes (*44*). This reaction corresponds to a cyclodimerization of four reacting centers and is



Scheme 9

significantly more efficient than a synthesis involving an eight-center ether synthesis (*45*). The assembly of such a remarkable structure provides an ultimate demonstration of the synthetic utility of the metal template and suggests that chemists may become increasingly imaginative in using it to their advantage.

REFERENCES AND NOTES

1. For a pertinent introduction to synthetic receptors, see J.-M. Lehn, *Science* **227**, 849 (1985); T. J. Meade and D. H. Busch, *Progr. Inorg. Chem.* **33**, 59 (1985).
2. C. J. Pedersen, *J. Am. Chem. Soc.* **89**, 2495 (1967); *ibid.*, p. 7017.
3. D. J. Cram, *Angew. Chem. Int. Ed. Engl.* **25**, 1039 (1986).
4. J.-M. Lehn, *ibid.* **27**, 89 (1988); *Acc. Chem. Res.* **11**, 49 (1978).
5. For an exhaustive compilation of thermodynamic data, see R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb, J. J. Christensen, *Chem. Rev.* **85**, 271 (1985).
6. M. C. Thompson and D. H. Busch, *J. Am. Chem. Soc.* **86**, 213 (1964); *ibid.*, p. 3651.
7. R. A. Bulman, *Struct. Bonding (Berlin)* **67**, 91 (1987).
8. K. N. Raymond and T. M. Garett, *Pure Appl. Chem.* **60**, 1807 (1988).
9. A. E. Martell, Ed., *Inorganic Chemistry in Biology and Medicine*, (ACS Symposium Series 140, American Chemical Society, Washington, DC, 1980).
10. R. B. Lauffer, *Chem. Rev.* **87**, 901 (1987).
11. Fully reported in E. L. Blinn and D. H. Busch, *Inorg. Chem.* **7**, 820 (1968).
12. G. L. Eichorn and R. A. Latif, *J. Am. Chem. Soc.* **76**, 5180 (1954).
13. G. A. Melson and D. H. Busch, *ibid.* **86**, 4834 (1964); *Proc. Chem. Soc. London* **1963**, 223 (1963).
14. I. I. Creaser *et al.*, *J. Am. Chem. Soc.* **104**, 6016 (1982).
15. J. D. Backer-Dirks, C. J. Gray, F. A. Hart, M. B. Hursthouse, B. C. Schoop, *J. Chem. Soc. Chem. Commun.* **1979**, 744 (1979).
16. D. E. Fenton, U. Casellato, P. A. Vigato, M. Vidali, *Inorg. Chim. Acts.* **95**, 187 (1984).
17. L. De Cola, D. L. Smailes, L. M. Vallarino, *Inorg. Chem.* **25**, 1729 (1986).
18. P. H. Smith and K. N. Raymond, *ibid.* **24**, 3469 (1985).
19. P. H. Smith, Z. E. Reyes, C.-W. Lee, K. N. Raymond, *ibid.* **27**, 4154 (1988).
20. C. W. Eigenbrot, Jr., and K. N. Raymond, *ibid.* **21**, 2867 (1982); *ibid.* **22**, 1972 (1983).
21. J.-C. G. Bunzli, in *Handbook on the Physics and Chemistry of Rare Earths*, K. A. Gschneider, Jr., and L. Eyring, Eds. (Elsevier Scientific, Amsterdam, 1987), vol. 9, table 24.

22. This compound was first prepared by R. Gradl and F. Lux. Reference to a synthesis can be found in the structure report: V. W. Day, T. J. Marks, W. A. Wachter, *J. Am. Chem. Soc.* **97**, 4519 (1975).
23. L. De Cola, D. L. Smailes, L. M. Vallarino, *Inorg. Chim. Acta* **110**, L1 (1985).
24. D. H. Busch and C. Cairns, in *Synthesis of Macrocycles: Progress in Macrocyclic Chemistry*, R. M. Izatt and J. J. Christensen, Eds. (Wiley, New York, 1987), vol. 3, pp. 1–51.
25. D. H. Busch *et al.*, *J. Am. Chem. Soc.* **103**, 1472 (1981).
26. N. Herron *et al.*, *ibid.* **105**, 6585 (1983).
27. N. Herron, J. H. Cameron, G. L. Neer, D. H. Busch, *ibid.*, p. 298.
28. P. Saltman and J. Hegenauer, Eds., *The Biochemistry and Physiology of Iron* (Elsevier Biomedical, Amsterdam, 1981).
29. B. F. Matzanke, G. Müller-Matzanke, K. N. Raymond, in *Physical and Bioinorganic Chemistry*, T. M. Loehr, H. B. Gray, A. B. P. Gray, Eds. (VCH, Deerfield Beach, FL, 1989), pp. 1–121; K. N. Raymond, G. Müller, B. F. Matzanke, *Top. Curr. Chem.* **123**, 50 (1984); J. B. Nielands, *Annu. Rev. Biochem.* **36**, 285 (1982).
30. M. E. Cass, T. M. Garrett, K. N. Raymond, *J. Am. Chem. Soc.* **111**, 1677 (1989).
31. F. L. Weitl and K. N. Raymond, *ibid.* **101**, 2728 (1979); M. C. Venuti, W. H. Rastetter, J. B. Nielands, *J. Med. Chem.* **22**, 123 (1979); F. L. Weitl, W. R. Harris, K. N. Raymond, *ibid.*, p. 1281.
32. S. J. Rodgers *et al.*, *Inorg. Chem.* **26**, 1622 (1987).
33. T. M. Garrett, P. W. Miller, K. N. Raymond, *ibid.* **28**, 128 (1989).
34. T. J. McMurry *et al.*, *J. Am. Chem. Soc.* **109**, 7196 (1987).
35. T. J. McMurry, S. J. Rodgers, K. N. Raymond, *ibid.*, p. 3451.
36. T. M. Garrett *et al.*, in preparation.
37. Crystal structures of the unsubstituted tris(catechol) ferric complexes show approximately octahedral coordination: K. N. Raymond, S. S. Isied, L. D. Brown, F. R. Fronczek, J. H. Nibert, *J. Am. Chem. Soc.* **98**, 1767 (1976); B. F. Andersen, D. A. Buckingham, G. B. Robertson, J. Webb, *Nature* **262**, 722 (1976).
38. F. Basolo and R. G. Pearson, *Mechanisms of Inorganic Reactions* (Wiley, New York, 1967).
39. Y. Sun, A. E. Martell, R. J. Motekaitis, *Inorg. Chem.* **25**, 4780 (1986).
40. C. J. Rodgers, C-Y. Ng, K. N. Raymond, *J. Am. Chem. Soc.* **107**, 4094 (1985).
41. C. O. Dietrich-Buchecker and J.-P. Sauvage, *Chem. Rev.* **87**, 795 (1987).
42. ———, J. M. Kern, *J. Am. Chem. Soc.* **106**, 3043 (1984). The first template catenane synthesis used a slightly less efficient stepwise route reported earlier by Sauvage *et al.* C. O. Dietrich-Buchecker and J.-P. Sauvage, *Tetrahedron* **24**, 5091 (1983) and references therein.
43. A.-M. Albrecht-Gary, C. O. Dietrich-Buchecker, Z. Staad, J.-P. Sauvage, J. Weiss, *Chem. Commun.* **1986**, 1325 (1986).
44. C. O. Dietrich-Buchecker, A. Khemiss, J.-P. Sauvage, *ibid.*, p. 1376.
45. J.-P. Sauvage and J. Weiss, *J. Am. Chem. Soc.* **107**, 6108 (1985).
46. We thank our past and present co-workers for their contribution to the work from this laboratory, which is referenced herein.

Developmental Biology of T Cell Receptors

JACK L. STROMINGER

T cell receptors are the antigen-recognizing elements found on the effector cells of the immune system. Two isotypes have been discovered, TCR-γδ and TCR-αβ, which appear in that order during ontogeny. The maturation of prothymocytes that colonize the thymic rudiment at defined gestational stages occurs principally within the thymus, although some evidence for extrathymic maturation also exists. The maturation process includes the rearrangement and expression of the T cell receptor genes. Determination of these mechanisms, the lineages of the cells, and the subsequent thymic selection that results in self-tolerance is the central problem in developmental immunology and is important for the understanding of autoimmune diseases.

THE CURRENT ERA OF STUDIES OF IMMUNE RECOGNITION began with the discoveries that both transplantation rejection and immune responsiveness were controlled by polymorphic cell surface molecules. A single genetic region of all vertebrate species examined, the major histocompatibility complex (MHC) (located on chromosome 6 in man and on chromosome 17 in the mouse), encodes two classes of cell surface molecules. The primary role of these molecules, the class I and class II MHC antigens, is the presentation of foreign peptides derived from foreign antigens to the effector cells of the immune system—that is, to the T lymphocytes. Thus, rejection of transplanted organs is a by-product of the essential role that the polymorphism of these molecules plays in immune recognition, ensuring that a large number of foreign peptides will be recognized by the species and ensuring sufficient population diversity that the species as a whole will escape potentially catastrophic variations in environmental agents—for example, viruses. In the past several decades, an enormous amount has been learned about the structure and the function of these two classes of molecules and about the genes that encode them (*1*). Moreover, it was shown that T lymphocytes recognize foreign antigens in an MHC-restricted fashion—that is, the effector T lymphocytes from one individual recognize a foreign antigen presented by cells of another individual only if the two individuals share at least one allelic MHC antigen (*2*). A long debate ensued as to whether the effector cell contained two receptors, one for foreign antigen and one for the MHC restricting element, or only a single receptor that recognized both. Little doubt remains now that a single receptor recognizes the complex of foreign peptide with MHC antigen (*3*).

For several years the nature of this receptor, called the T cell receptor (TCR), was elusive. The search for this molecule was based on the idea that the diversity needed to recognize a very large number of foreign antigens in association with many different MHC molecules would be generated by mechanisms analogous to those used in the generation of diversity of immunoglobulins. About 5 years ago such a molecule was identified, first as a heterodimeric protein on the surfaces of murine and human T cells identified by clone-specific monoclonal antibodies, and then as the α and β genes that encode the two chains of the protein. As had been predicted, these genes are encoded as V, J, and C segments of the α gene on chromosome 14 in both man and mouse, and as V, D, J, and C segments of the β gene on chromosome 7 in man and on chromosome 6 in the mouse. The diversity of the α and β genes is generated by the selection of different segments for joining and by

The author is a professor in the Department of Biochemistry and Molecular Biology, Harvard University, Cambridge, MA 02138, and at the Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115.