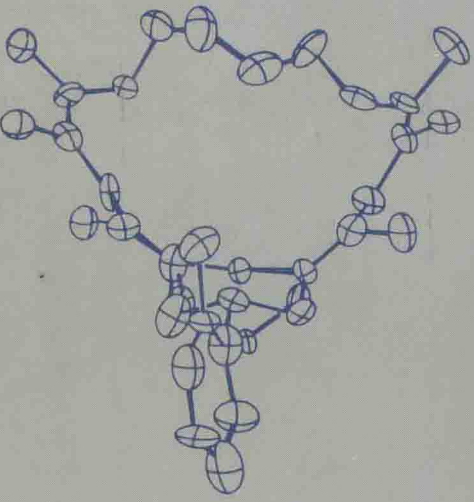
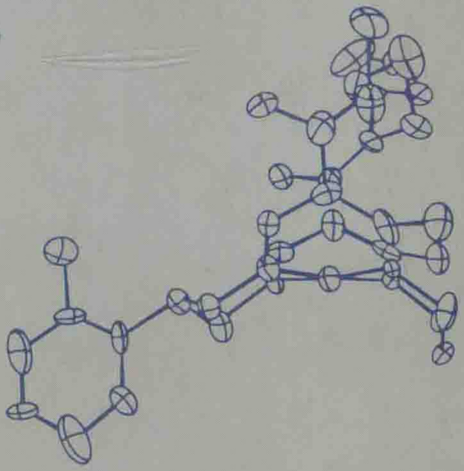
SYNTHESIS OF MACROCYCLES

The Design of Selective Complexing Agents

Progress in Macrocyclic Chemistry
Volume 3





Edited by Reed M. Izatt
and James J. Christensen

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Progress in
MACROCYCLIC CHEMISTRY
VOLUME 3

Dedicated to
Charles J. Pedersen
Whose early work on macrocyclic polyether ligands
provided a foundation for much of the work in this field
and who served as a catalyst for the work of many of us

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PREFACE

The Pimentel Report, *Opportunities in Chemistry* (National Academy Press, Washington, D.C., 1985), points out that chemistry is on the verge of a renaissance because of the emerging ability to fold experiment and theory together to design chemical structures with properties of choice. Nowhere is this assessment better exemplified than in the recent progress seen in macrocyclic chemistry. In this field, scientists with organic and inorganic backgrounds have produced novel compounds that show remarkably selective chemical behavior. This work has attracted attention in many fields where selectivity is of primary concern, including chemical catalysis, enzyme action, selective transport of ions and molecules in membrane systems, and chemical separations.

The creation of new molecules with predetermined properties is not a trivial process. Its successful accomplishment requires a combination of abilities, including recognition of a problem, a creative approach to its solution, ability to visualize the molecular requirements needed, and the ability to synthesize the required compound. Central to this process must be the thought processes and rationale that precede the actual synthetic work. This volume attempts to reduce these processes to writing by the involvement of individuals who have been particularly successful in creating new molecules. Using specific examples of their work, the authors bring out many of the thought processes that led them to the creation of particular molecules for specific uses. It is felt that the volume should be useful to others who desire, either in their own research or in their teaching, to evaluate the strategies and procedures involved in molecular design. Those who should find the book useful include workers in the main disciplines of chemistry as well as those in chemical separations, ion and neutral molecule detection, organometallic chemistry, bioinorganic chemistry, and medicinal chemistry. It is hoped that the book will be of particular value to those whose interest is in the design and synthesis of novel reagents for use in these related fields.

Macrocycles provide especially good bases for the development of reagents having selectivity for ions and molecules and for reagents that can modify the chemical properties of the complexed species. Excellent examples of the latter types of macrocycles are those whose creation is described in Chapters 1 and 4. In Chapter 1, the rationale is given for the development of superstructure macrocycles capable of altering the properties of coordinated iron and cobalt to permit the binding of dioxygen. In Chapter 4, the necessary and fundamental concepts that must precede the design of macrocycles capable of selective cation or anion complexation are presented and illustrated with pertinent examples. An aim of the work described in Chapter 2 is to develop a basis for the rational design of new cyclic reagents having predetermined properties enabling them to interact selectively with heavy metal cations. These interactions are characterized using kinetic, thermodynamic, structural, and theoretical methods. Chapter 3 deals with calixarenes. These macrocycles are of particular interst to the scientist involved in molecular design because they afford one with the opportunity to build "molecular baskets" capable of interacting with both ions and molecules in enzyme-like fashion. The logic of building these "baskets" is described together with projections of their possible uses as enzyme mimics in bioorganic studies. Chapter 5 presents a coordinated theoretical–synthetic approach to the design of artificial ionophores based on the use of nonactin, enniatin, and valinomycin as models. The principles involved in the interaction of these model macrocycles with cations are identified and used as a basis for the design of novel ionophores and the computer-aided description of the geometry and ion binding properties of these macrocycles. In Chapter 6, the development of synthetic strategies for the construction of manifold bridging leading to molecular holes, niches, and clefts is presented and discussed. Such cavities hold promise for the selective encapsulation of organic guest molecules. In Chapter 7, the principles involved in designing macrocycles capable of forming crystalline inclusion complexes with water and uncharged organic molecules are discussed.

R. M. IZATT
J. J. CHRISTENSEN

Provo, Utah
November 1986

CONTENTS

CHAPTER ONE

LIGANDS DESIGNED FOR INCLUSION COMPLEXES: FROM TEMPLATE REACTIONS FOR MACROCYCLIC LIGAND SYNTHESIS TO SUPERSTRUCTURED LIGANDS FOR DIOXYGEN AND SUBSTRATE BINDING

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1 INTRODUCTION

The various families of inclusion compounds are particularly exciting because of indications that they may generate many new areas of fundamental chemistry and many opportunities for applied chemistry. The cyclodextrins, crown ethers, ionophores, cryptands, and related structures are outstanding examples of monomolecular hosts that participate in inclusion chemistry. Broad families of solid state inclusion systems include the well-known clathrates, zeolites, and intercalated derivatives of graphite and of transition metal chalcogenides. Such systems offer promise in broad areas of catalysis of various classes of reactions, including redox and substitution chemistry; various aspects of transport phenomena, for example, phase transfer catalysis and facilitated transport; creation of specialized microenvironments for highly specific purposes such as hydrophobic binding, protection of water- or air-sensitive reaction centers, and delivery of highly polar sites in nonpolar media.

The relatively new concept of *ligand superstructure* joins with the *coordination template effect* to provide a general strategy for the synthesis of discrete metal complexes designed to form inclusion compounds. The principal conceptual and experimental developments that have established and exploited this strategy are summarized here. A brief review of the coordination template effect and subsequent developments is presented as an essential basis for the main subject. A broad family of ligands called cyclidenes, well suited for forming inclusion complexes, provides the main focus of this report. The discussion presents (1) the evolution of appropriate superstructure ligands, (2) selection of appropriate examples and their alteration in order to form transition metal dioxygen complexes, and (3) eventual refinements of the structures in order to form species that bind both dioxygen and organic molecules. The examples provide an interesting mix of deliberate planning, persistent pursuit of goals, and serendipitous opportunism.

2 COORDINATION TEMPLATE REACTIONS

In the early 1960s there was growing awareness of the multitude of roles that metal ions or metal compounds can and do play in the catalysis, promotion, and control of chemical reactions (1, 2). It was in this context that the coordination template hypothesis was stated and demonstrated by the synthesis of macrocyclic ligands (3, 4).

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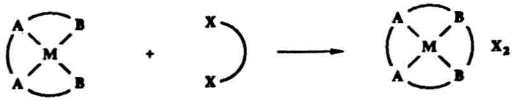
2.1 Kinetic Coordination Template Effect

According to the *kinetic coordination template hypothesis*, the geometric arrangement of ligands within the coordination sphere of a metal ion provides constraints that can be used to control the structure of a product formed by reactions of coordinated ligands. Specifically, the coordination sphere of the metal ion may serve as a template to hold reactive groups in proper position for sterically highly selective, multistep reactions.

A specific example chosen for early demonstration of the kinetic coordination template effect involved the formation of macrocyclic ligands which completely enclose a planar metal ion as shown in Eq. 1 (3, 4). Three requirements must be met in order to conduct template reactions of the kind shown in Eq. 1: (1) The original ligand must be tetradentate and chelate in a planar or other suitable fashion (*cis*-octahedral would fail but tetrahedral would be suitable). (2) The terminal groups (B) must undergo a characterized addition reaction with the ring-forming groups. (3) Suitable reagents must be available to provide the final ring-forming linkage. Equation 1 also suggests that the metal ion may stabilize macrocyclic organic molecules that are not otherwise stable (see discussion of thermodynamic coordination template effect, below).



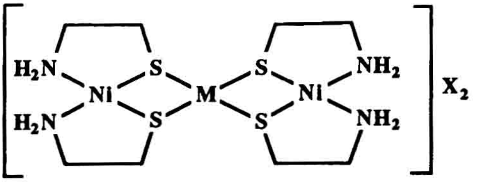
(1)

Realization that these requirements exist led to investigations into the basic questions raised by items 1 and 2, above. Specifically, it was necessary to identify functional groups, either monoatomic or polyatomic, that can undergo the necessary addition reactions while attached to the metal ion. In principle, such groups could be electrophilic or nucleophilic, or they might react by radical pathways. Practically, coordinated nucleophiles seemed most promising because ligating atoms are generally electron pair donors. Examination of the literature revealed precedents for such reactions for a few functional groups. Notably, both coordinated mercaptide ions and coordinated oxime groups had been shown to undergo reaction with alkyl halides, a reaction that seemed especially appropriate.

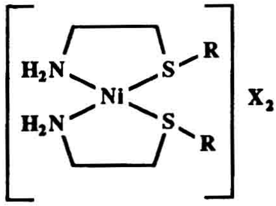
Ensuing investigations were directed toward synthesis of appropriate sulfur-containing ligands and verification that (1) suitable complexes could be synthesized and (2) the critical alkylation reactions do indeed occur while the sulfur atom remains bound to the metal ion. Of course, the ultimate test required the demonstration that the template reaction does indeed occur by successful synthesis of the predicted macrocyclic ligand within the coordination sphere of the metal ion.

Studies on the reactions of the sulfur atom of coordinated mercaptides with electrophiles made use of the earliest available soluble, molecularly discrete complexes having terminal sulfurs. Such species were rare at that time, largely because sulfur bridging was a persistent problem. Bis(2-aminoethanethiolato)nickel(II) was prepared for study but its solubility was too slight to permit useful conclusions to be drawn about the reactivity of its coordinated sulfur atoms.

Two moles of this compound combine with various ions including Ni^{2+} to form soluble salts of the cation having structure **I**, within which all the sulfur atoms form bridges between pairs of metal ions (5, 6). Nonetheless, the sulfur atoms do react with alkyl halides forming compound **II** (7). Further, the kinetics show a half-order dependence on the concentration of the nickel(II) ion, which suggests that a NiL_2 unit dissociates from the trinuclear species and that it is the unbridged terminal groups of the monomer that add the alkyl groups (8).

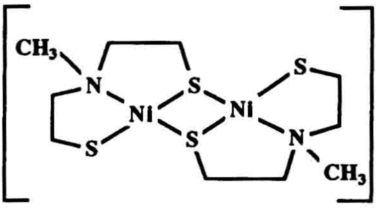


I



II

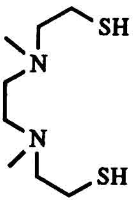
The nickel(II) and palladium(II) complexes of structure **III** were also available for early studies (9, 10). Reaction with alkyl halides, such as methyl iodide and benzyl bromide, revealed that the terminal mercaptides are much more reactive toward electrophiles than are the bridged groups.



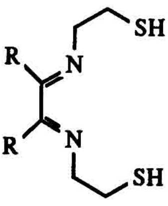
III

It became clear that mercaptoamines containing secondary and tertiary amino groups offered the advantage that soluble neutral monomeric complexes NiL_2 could be synthesized and studied (7, 8, 10, 11). The nickel(II) complexes of *N*,*N*-dialkylmercaptoethylamines were especially helpful (11, 12). In these cases the coordinated sulfur atoms reacted with alkyl halides cleanly in noncoordinating solvents by simple second-order reactions. The less hindered secondary amine derivatives displayed rate behaviors that indicated preequilibrium binding of the alkyl halide with the metal ion prior to the electrophilic displacement process (12). The weak interaction of the halide with the metal ion may enhance the electrophilicity of the carbon center, thereby promoting the reaction. These studies provided strong support for the contention that coordinated mercaptide groups do indeed add alkyl groups while remaining bound to the metal ion. Now it remained necessary to produce suitable complexes containing mercaptide groups in order to test the kinetic coordination template hypothesis.

The template reaction represented by Eq. 1 required the synthesis of appropriate tetradentate ligands and the preparation and characterization of their metal complexes. Nickel(II) soon became the preferred metal ion because (a) it was known to give square planar chelates with appropriate sets of donors (S_2N_2, if S is mercaptide) and (b) its chemistry was not complicated by easily accessible redox processes. In the studies directed toward this end, synthesis of two specific new tetradentate ligands having the requisite donor atom set were undertaken (structures **IV** and **V**). Ligand **IV** was prepared by a straightforward, if tedious and somewhat dangerous (13), route; however, the dominant complex has a trinuclear structure (8, 14) (structure **VI**) in which the reactivity of the sulfur atoms and the geometric control of the reaction were both impaired (15).

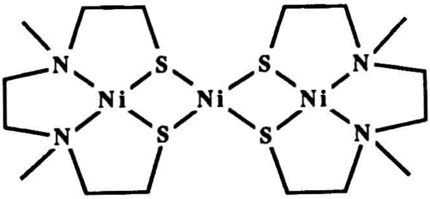


IV



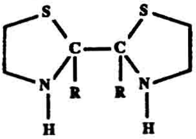
V

On the other hand, it soon became apparent that the reaction of mercaptoamines with carbonyl groups does not yield Schiff bases of structure **V** but, rather, the bis(thiazolines) of structure **VII**. This was not an ob-

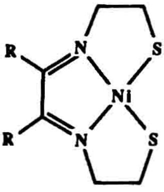


VI

stacle to the progress of the program since it was soon shown that the thiazolines rearrange to the desired Schiff base ligands upon reaction with, for example, nickel(II) ion, a reaction for which precedent had been provided among both thiazolines (16) and oxazolines (17). Thus, complexes of structure **VIII** were first made available for testing the kinetic coordination template hypothesis (3, 7).



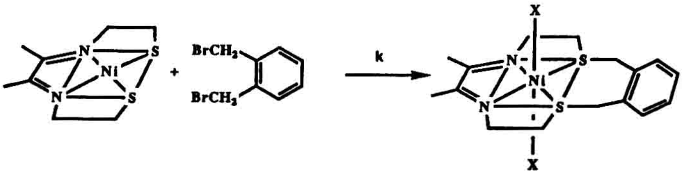
VII



VIII

All of the foregoing studies opened the way for the demonstration of the kinetic coordination template effect (3) by the reaction of Eq. 2. Note that the second reagent, α,α'-dibromo-*o*-xylene, was chosen because of the favorable orientation of the two replaceable bromides. The macrocyclic product was prepared in essentially quantitative yield with no evidence for the presence of either stable intermediates or oligomers. Subsequent studies showed the generality of the reaction (18).

Studies on the kinetics (19) of reaction 2, compared to the non-ring-forming reactions of Eqs. 3 and 4, were especially revealing. In the non-template case (Eqs. 3 and 4) the first step proceeded at a rate approximately 36 times that of the second step, so that the concentration of the intermediate built up in the solution during the course of the reaction. In contrast, the template synthesis of the macrocycle (Eq. 2) appeared to proceed in a single step; that is, no intermediate could be detected. Thus, the formation of the hypothetical intermediate of structure **IX**, in which the remaining thiolate and the bromide are oriented in position for the cyclization reaction, could not be detected. One can therefore conclude that the template effect produces a relative acceleration of the second



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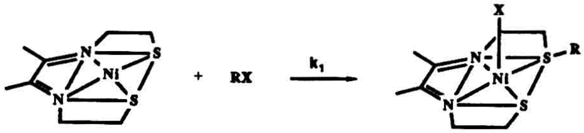
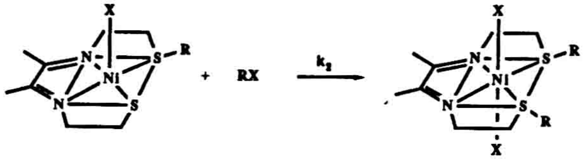
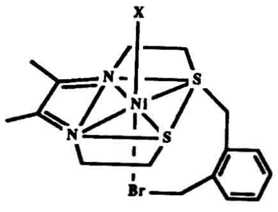


(3)



(4)

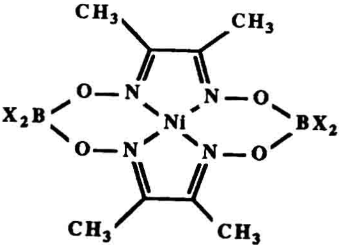
step, compared to the first, of at least 10. This indicates that the relative rates of the first and second consecutive steps change by a factor of at least 350 in going from the process involving benzyl bromide to that using α,α′-dibromo-*o*-xylene. Thus the hypothesis of a kinetic coordination template effect was conclusively demonstrated.



IX

During the research in these laboratories on this subject, a second major effort had been directed toward demonstration of the kinetic coordination template effect simultaneous with the work on coordinated mercaptide ions. This approach used functional groups having nucleophilic atoms α to the donor atom, for example, oximes and hydrazones.

Barker had shown (20) that the oxime oxygen atom of dimethylglyoxime (DMG) will add methyl iodide while the DMG is coordinated to nickel(II). That early work was confirmed and extended in this research group, but it was concluded that alkyl halides are not suitable for this reaction (a) because of the short distance to be spanned between the two oxygen atoms of adjacent oximes in bis(α-dioxime) complexes and (b) because of complications due to the halide ion and the change in charge (21). These studies were terminated because of two independent publications showing successful template ring closures with bis(dimethylglyoxime)nickel(II). In attempts to produce a Lewis acid–base adduct between $d_z{}^2$ electrons of nickel(II) and BF_3, Schrauzer discovered the macrocycle having structure **X** (22). Thierig and Umland (23) showed that a variety of species including $SiR_2{}^{2+}$ could be used to replace the proton in $Ni(DMG)_2$ after the fashion of structure **X**.

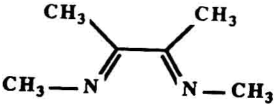


X

2.2 Thermodynamic (or Equilibrium) Coordination Template Effect

The contrasting thermodynamic coordination template effect acts, as the title states, not on the mechanism of the ligand forming process but, rather, in order to stabilize a ligand structure that might be otherwise disfavored in the pure organic chemical system at equilibrium. Prime examples exist both with macrocycles and with noncyclic ligand structures.

Early examples are the formation of such Schiff base ligands as biacetyl-bis(methylimine) (structure **XI**) and the tetradentate Schiff base of structures **V** and **VIII**. None of these ligands has been isolated as a separate pure compound.



XI

Perhaps the most important case of an equilibrium template process is the formation of the tetraazamacrocycles discovered by Neil Curtis (struc-

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