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STEREO- AND REGIO-SPECIFICITY IN ORGANIC SYNTHESIS PROMOTED BY METAL IONS

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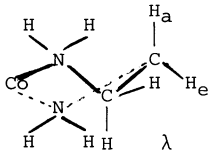
Abstract — This paper examines regio-and stereo-specificity for reactions of coordinated organic substrates. The reactions involve addition of coordinated nucleophiles where the specificity arises from non-bonded interactions, substituent effects on the metal, orbital steering directed by the chelates and electronic effects imparted by the geometry required for chelation. The reactions examined include hydration of olefins, addition of nucleophiles at coordinated imines, oxidation and alkylation of coordinated mercaptide ions, stereospecific deuteration for chelated *N*-benzyl glycine and amine synthesis organised by the metal.

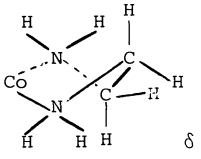
INTRODUCTION

Conformational characteristics of metal chelates were recognised (1,2) at least in the 1930's but it was not until a paper by Corey and Bailar (3) in 1959 revived these features that they captured the attention of inorganic chemists. In the last eighteen years there have been numerous publications on chelate conformational effects (4) mostly in connection with equilibria. Along with this has gone the development of quantitative conformational analysis (4) and our understanding of the reasons for isomer stability differences and the magnitude of the effects.

The metal ion introduces different aspects into the ring systems compared with the more traditional heterocyclic chemistry and some of the effects are quite substantial. For example, chelated ethylenediamine in cobalt(III) octahedral complexes shows pronounced conformational characteristics, such that the protons on the C atoms are almost strictly



λ



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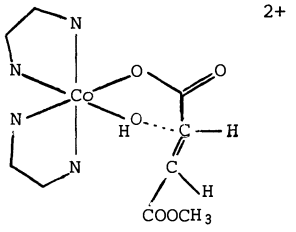
axial and equatorial although the N proton positions are less well defined in this sense. The difference between the chelate and cyclopentane stereochemistry arises largely from the 86° angle subtended at the metal ion. The chelate also has a chiral conformation λ or δ and the conformational change leads to a switch in axial equatorial position. It is also possible to stabilise one conformer or the other with suitable substituents (4). These effects and many others lead to steric properties of chelates and complexes which can be useful in directing stereospecific syntheses in such systems.

In more recent times our understanding of intramolecular organic reactions promoted by metal ions and the use of coordinated nucleophiles has also improved. We have seen, for example, that tying OH^- to a metal can provide a high concentration of the reagent at neutral pH even though it is somewhat modified by attachment to the metal. The ability of the metal ion to activate and protect organic molecules has also been seen to be substantial. It seemed apposite then that the structural and conformational properties of the complexes might be put together with the reactivity aspects to design some stereo-specific syntheses which are described in the following text. Most of the chemistry has been done with Co(III) complexes largely because the ligands do not exchange rapidly with the metal ion. In the examples given, the organic syntheses are conducted without metal ligand bond rupture. In this way the efficacy of the reactions can be assessed without complication from equilibria between metal and ligand. It is also significant that the complexes on the whole are cheap to make and the methods for manufacture are fairly routine and well-defined.

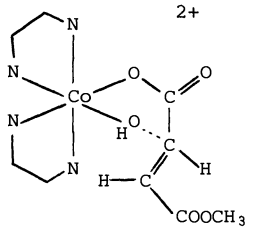
Stereospecific hydration of an olefin

The efficacy of coordinated nucleophiles has been established for the intramolecular hydrolysis of numberous substrates; for example, coordinated amino acid esters (5), amino nitriles (6,7) and 2-bromoethylamine (8). The same prospect for cyclisation exists with coordinated olefins (9,10) and two systems have been constructed to examine it as follows:



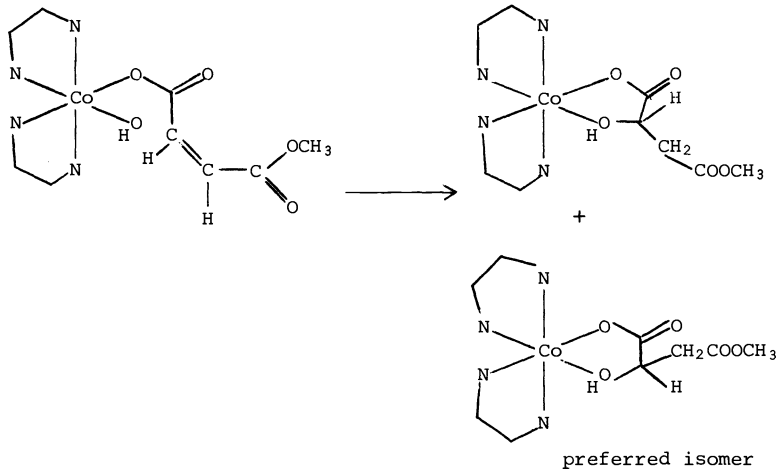
methyl maleate

and



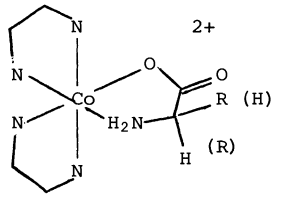
methyl fumarate

The addition of OH at the olefinic centre creates a chiral centre at carbon in conjunction with the chiral centre at cobalt. Two diastereoisomers are thereby produced. Addition of the bound OH is very rapid for the maleato system and essentially pH independent between pH 8 – 10. In this range the diastereoisomer ratio is ∿2:1 as shown below. However, at higher pH values the rate becomes first order in OH^- and in 0.1 M NaOH at 25° the half life for the production of malate is ∿3 sec (at least 10^6-fold faster than the uncoordinated hydration). Under these conditions the reaction becomes much more stereospecific with a 9:1 ratio of diastereoisomers. While it is clear that in the pH independent region H^+ addition at the β carbon atom is the rate-determining step, it looks as if in the high base region deprotonation of the CoOH entity and addition of $Co-O^-$ could be rate-determining.

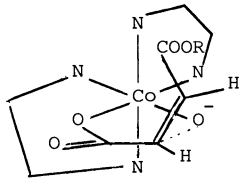


preferred isomer

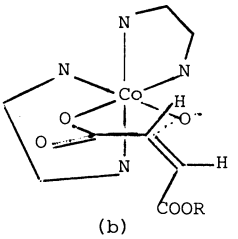
The same pattern was observed for the fumarate complex but the rates were about 1000-fold slower. The increase in specificity is the interesting and surprising feature. For analogous amino acid systems,



the ratio of the diastereoisomers (11) at equilibrium is about 2:1 or less with the same structural relationships as the analogous malate products. It appears therefore that the product ratio of the pH independent path resembles the equilibrium situation whereas the path dependent on base is far from that condition. An explanation for the increase could arise if $Co-O^-$ addition was rate-determining. In the transition states for the generation of the two isomers (see next page) configuration (a) will be more compressed than that of (b) by virtue of the non-bonded interactions between the substituents on the olefin and the adjacent Co(en) chelate. This steric compression will be much more evident in the transition states than in the product malates.



(a)



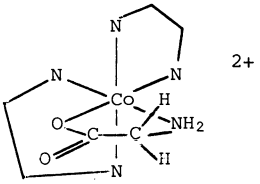
(b)

The other specificity feature which is interesting in this reaction is the exclusive formation of the five-membered chelate relative to the possible six-membered chelate. Clearly the ester group *exo* to the chelate is governing the addition and the carboxyl bound to the metal ion has no influence. The stereochemistry for the addition of $Co-O^-$ or $Co-OH$ requires the olefin and bound carboxyl π orbitals to be essentially orthogonal and it follows therefore that there is a minimal interaction between the two. The same restriction does not hold for the ester group *exo* to the chelate and the olefin is thereby sensitised. This is an interesting restriction placed on the reaction where the metal ion organises the stereo chemistry of the reactants and there will be other examples of such constraints where the metals are involved.

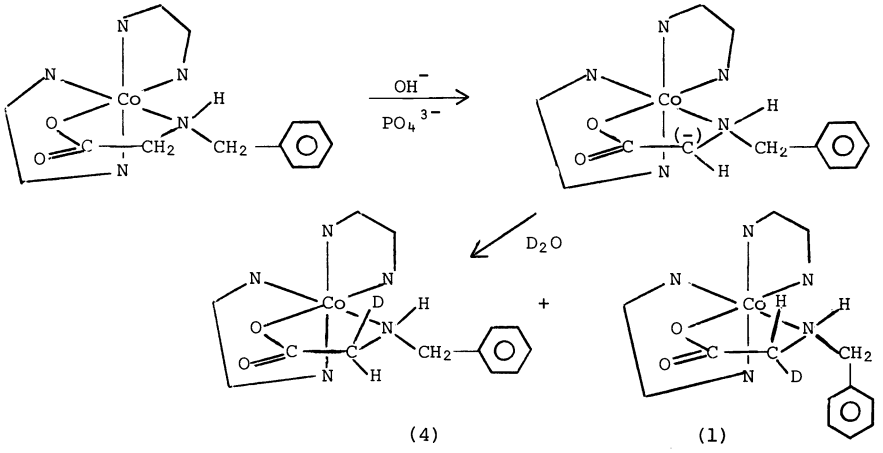
Synthesis of chiral glycine $NH_2C(H)(D)COOH$

One feature of chelated amino acids is the ability of the metal to labilise the protons of the α carbon atoms. In basic D_2O solution these protons can be exchanged for D^+ and the prospect of a synthesis of chiral $NH_2-C(H)(D)-COOH$ arises from this chemistry.

Molecules of this type are required to probe the stereochemistry of enzymic reactions such as serine synthetase where one of the glycine methylene protons appears to be extracted in preference to the other before condensation to serine occurs. The problem is to organise the chiral bias so that one proton is extracted in preference to the other or that D_2O adds D^+ to the carbanion at one position in preference to the other. In complexes of the type,



although the methylene protons are non-equivalent, there is no discrimination between their rates of exchange in aqueous base. However, the introduction of a chiral N centre bound to the metal and adjacent to the methylene protons changes the situation radically. The complex ion Λ-N-benzylglycinatobis(ethylenediamine)cobalt(III)$^{3+}$ stereospecifically coordinates the benzyl glycine (12) in the configuration shown.



(4) (1)

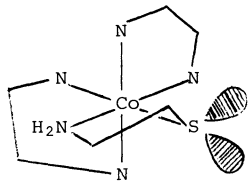
The other configuration where the benzyl group abutts on the en chelate is too sterically hindered to be observed. Clearly the chiral Co centre directs and maintains the stereo-chemistry at the N centre regardless of whether the proton on the N atom is exchanging or not. In base the glycinate protons exchange and other studies indicate that removal of H^+ leads to a planar carbanion.(11)Assuming this is true in this instance, the 4:1 ratio of

diastereoisomeric product must arise from preferential addition of D_2O on one side of the planar carbanion. Equilibrium studies on analogous diastereoisomeric *N*-methyl alanine chelate (13) indicate the stable conformer is that with the methyls *trans* to each other. We infer therefore that D_2O will add in preference to the carbanion *trans* to the benzyl group. Although the stereospecificity is not as great as we hoped it would be, the experiment demonstrates the potential of such reagents to do stereospecific deuteration reactions.

Some comment on the labilisation of the chelated amino acid seems warranted. Binding the COO^- group to the metal ion will clearly enhance the acidity of the α-*C* protons. The metal appears to be somewhat less effective than R^+ (R = CH_3, C_2H_5 etc.) in this respect but the additional electron withdrawing contribution comes from binding the amine group to the metal also. The dual effect then allows the α-*C* proton to be exchanged readily at pH 12 (11).

Stereospecific oxidation of coordinated RS^-

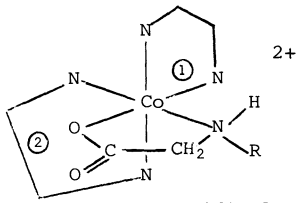
Chelated cysteamine in the bis(ethylenediamine)cobalt(III) complex shown below can be oxidised with a variety of oxidants at the sulphur centre to the coordinated sulfenate ion.



Clearly there are two sites for the oxidation and there is a sharp preference (4:1) for one site over the other with H_2O_2 as oxidant.

Each chelated sulfenate ion now has a chiral S centre which is stable to racemisation (14) and which retains a substantial degree of its nucleophilic capacity. The coordinated sulfenate moiety reacts readily with CH_3I to methylate the sulphur centre and generate the sulfoxide stereospecifically with the sulphur bound to the metal centre.

The origin of the stereospecific oxidation follows from our understanding of the variation in the stability of isomers in analogous complexes with similar configurational characteristics. For example, complexes of the type

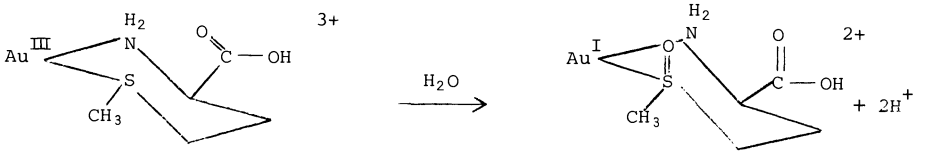


appear to coordinate the chiral N centre stereospecifically (12,15) in the configuration shown. The specificity has been analysed in terms of the non-bonded interactions between the substituent R (= CH_3, CH_2–⬡) and the atoms of the remaining chelate rings (12,15) for the two configurations possible at the N centre. In the orientations where R is poised over the ethylenediamine chelate ① a substantial interaction occurs between the non-bonded atoms in the manner described for the chiral glycine problem. It follows that H_2O_2 will prefer to approach the sulphur atom along the direction of least interaction with this en chelate to give the most abundant isomer.

Since the bound sulfenate ion (14) is stable to racemisation, alkylation to the sulfoxide is inevitably stereospecific. In basic aqueous conditions the Co-S bond is cleaved to give the hydroxo complex which in acidic conditions subsequently rechelates the sulfoxide complex to give the O-bound isomer and a six-membered chelate ring.(16)

The chemistry described above is probably related to the stereospecific oxidation of methionine by Au(III) salts to the sulfoxide (17). A reasonable explanation of the specificity arises from a consideration of the conformation of the chelate formed by

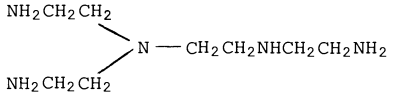
coordinating the N and S donor atoms:



The chair Au(III) chelate would prefer equatorial orientations for the carboxyl and CH_3 groups and the $2e^-$ change induced at S by the Au(III) ion allows $\overset{2+}{-S-}$ to capture water and release $2H^+$. The oxygen addition thereby has to be induced in the axial position. Clearly conformational factors of this type in metal catalysed organic reactions could be generally useful.

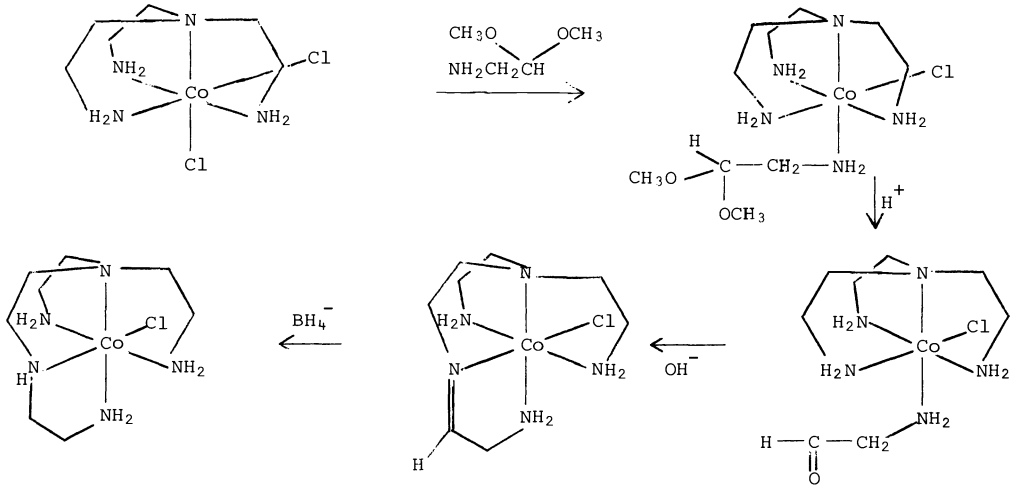
Regiospecific synthesis of a bifurcated multidentant amine cobalt(III) complex

The synthesis of the amine



3-(2-aminoethyl)1,8diamino 3,6-diazaoctane by regular organic methods proved to be difficult at least in our hands but a ready solution to the problem presented itself after we had come to understand some of the advantages of coordinated nucleophiles (18).

Quadradentate tris-(2-aminoethyl)amine (tren) readily complexes to give the $[Co(tren)Cl_2]^+$ ion which reacts stereospecifically with aminomethylacetal $NH_2CH_2C(OCH_3)_2H$ to give $[Co(tren)(acetal)Cl]^{2+}$ isomer shown below. Treatment of the acetal with acid gives the

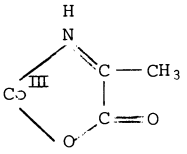


coordinated amino acetaldehyde complex which at pH 5 (25°) condenses regiospecifically at the amine centre *trans* to the bound Cl^-, (3×10^{-3} sec^{-1} $\mu = 1.0$ $NaClO_4$). The stable chelated imine is formed by elimination of H_2O from the carbinolamine (7×10^{-4} sec^{-1}). The specificity for the site of condensation arises because the amino group *trans* to the bound Cl^- is much more acidic than the other two amino groups *cis* to bound Cl^-. Reduction of the chelated imine with BH_4^- is very rapid (<30 sec) to give the saturated quinquidentate amine.

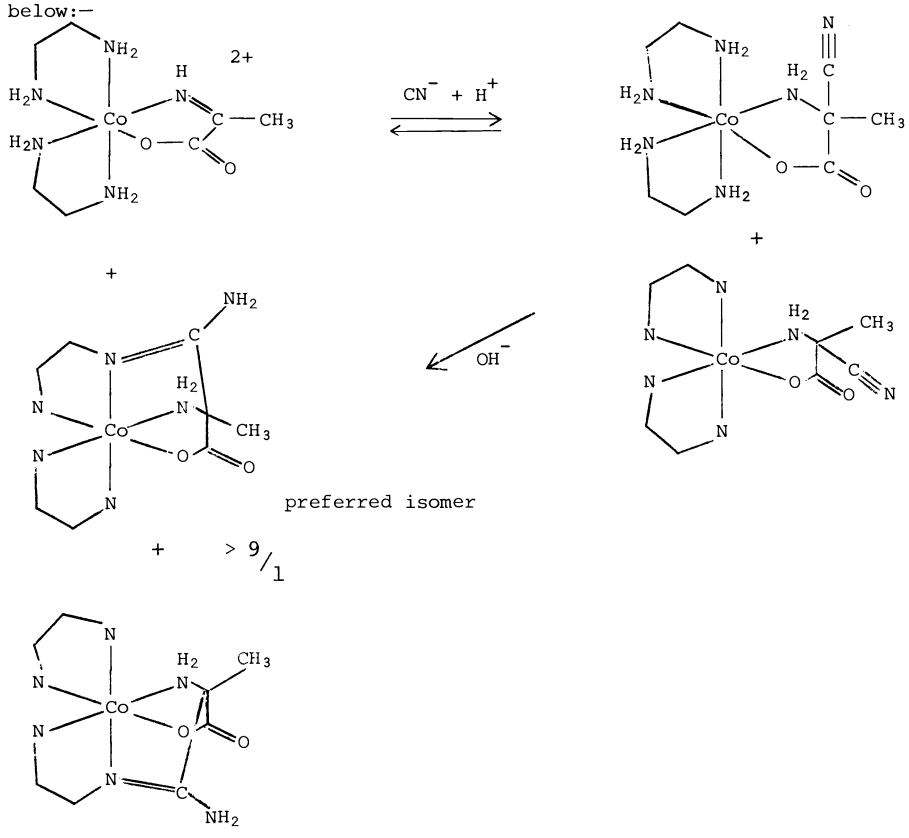
The site of condensation is not important in terms of producing the bifurcated amine but, of course, it is crucial in the production of one of the three possible complex diastereoisomers. Clearly substituent effects such as this will be important in directing synthesis in coordination complexes. The other interesting feature of this chemistry is the protection of the amine group in aminoacetone so that the polymerisation problems usually encountered with this reagent are avoided. The overall yield in the sequence of reactions is greater than 90%.

Stereospecific addition of CN^- at a chelated imine

Imines bound to some metal ions are activated to attack by nucleophiles (19,20) provided the donation from the metal *d* electrons to the empty π^* orbitals of the imine is not substantial (21). A good example of an activated chelated imine is that derived from pyruvato-imine bound to the Co(III) ion:—

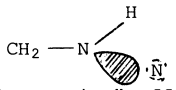
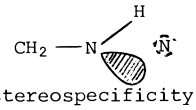


In this condition the imine is susceptible to very rapid addition of carbanions such as $\bar{C}H_2NO_2$ (19) and $(-)CH(COCH_3)_2$ (20). Presumably the activity arises because the metal ion imparts some iminium character on the chelate. At the same time the metal prevents protonation of the imine and stabilises the imine chelate. For example species of this type are stable in 6 M HCl. Cyanide ion should add in the same manner as the carbanions and we have investigated this reaction using the pyruvato imine bis(ethylenediamine)cobalt(III) ion (22) shown below:—



It is likely that CN^- adds reversibly at the imine centre. Other studies would indicate that there is little preference for addition on one side of the planar chelate relative to the other even though the Co(III) centre is chiral. The stabilities of analogous amino acid complexes (12) and the reduction of the chelated imine by the BH_4^- ion both show little specificity (23). However, the subsequent reaction of coordinated amide ion with the amino acid nitrile is another matter. Once formed, the amidine quadradentate is stable to both acid and base. Moreover, the least stable configuration is the preferred product. The strain in the bound amidine moiety $-CH_2-N=C(NH_2)-C$ for this isomer is much greater than that of the kinetically less-preferred product where the amidine moiety $-CH_2-N=C(NH_2)-C$ is close to being planar. The strain difference is reflected in the equilibrium position for the two isomers which lies heavily towards the isomer least favoured by the kinetic route.

Both CN^- and OH^- appear to be involved in the rate law and the involvement of CN^- could be accommodated by a pre-equilibrium. After addition of CN^- to the imine, OH^- abstracts a proton from the amine and the coordinated amide ion attacks the nitrile to generate the amidine. The stereospecificity of the condensation presumably arises from this amide attack and the preference of one site over the other needs some explanation. Dreiding models of the anticipated activated complexes indicate a substantial difference between the two orientations. These are depicted (on the following page) looking down the -CN axis at the orientation of the groups around the bound amide ion. In the orientation which leads to the preferred isomer the deprotonated orbital points directly at the nitrile C atom. In the orientation which leads to the least abundant isomer, the nitrile orientation is between the N proton and the deprotonated orbital. We presume it is this

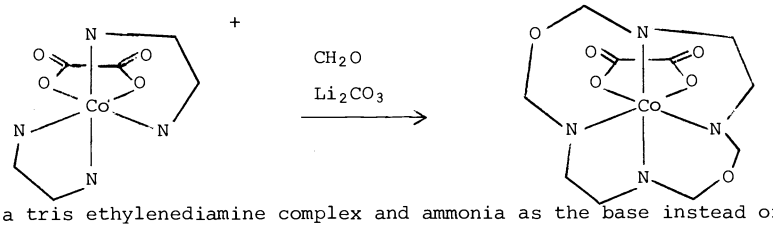



"orbital steering" effect which accounts for the stereospecificity. In terms of the energetics, of course, only a difference of about 1.3 kcal/mole in the free energies of activation would be enough to accommodate the results.

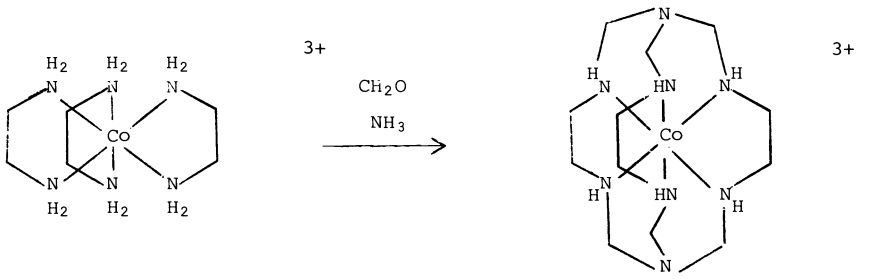
Chiral metal ion cages

The construction of large fused ring systems like the cryptates (24) requires rather sophisticated organic synthesis and it has occurred to a number of chemists that the problem might be simplified by coordinating a metal ion so that the problem is reduced to linked small ring synthesis. This strategy has now been applied to the synthesis of the nitrogen analogues of the polyether cryptates (25).

The synthesis arose from coordinated imine chemistry of the type described previously (19,20) and the discovery of the synthesis of a dioxa cyclam quadradentate on a metal centre (26), *i.e.*

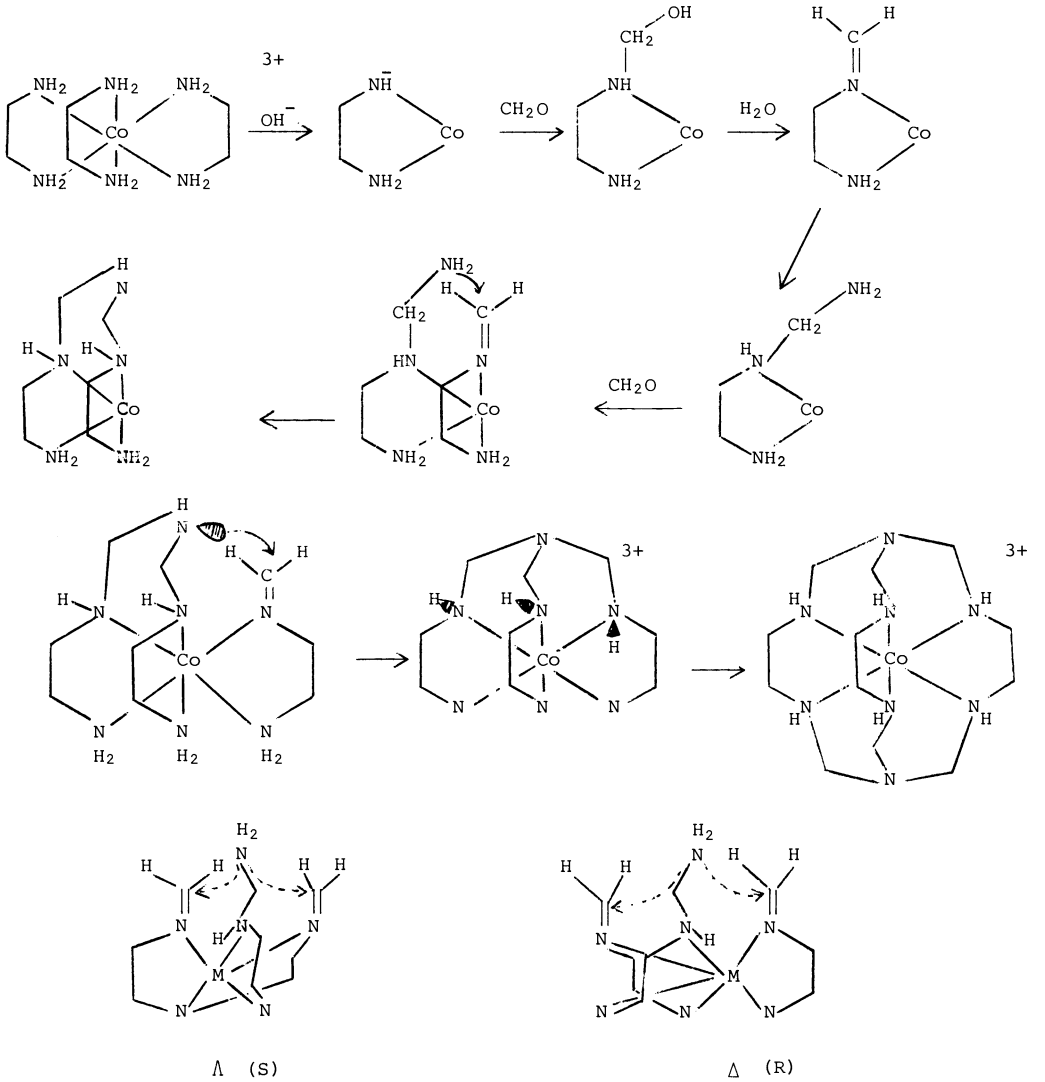


Using a tris ethylenediamine complex and ammonia as the base instead of OH^-, the prospect of making a trigonal cap was conceived and achieved as follows:—



The cage confers interesting properties on the metal compared with the parent tris(ethylenediamine). For example, Co^{2+} does not exchange with the Co(II) cage in 24 hrs at 25° even though Co^{2+} usually exchanges its ligands on the microsecond time scale. Moreover, the Co(II) complex retains its chirality at least over two hours without measurable racemisation.

The chirality of the complex is of special interest from the point of view of stereospecificity since it has seven chiral centres yet if the synthesis is conducted with one chiral form of the tris(ethylenediamine) complex, only one isomer is produced of the 64 possible. This extraordinary specificity needs some examination and to do that the mechanism of synthesis has to be considered in some detail. The first step is obviously the condensation of formaldehyde with the bound ethylenediamine and this requires deprotonation of the bound amine centre followed by attack of the coordinated amide ion at the carbonyl centre to generate the carbinolamine. Elimination of water leads to the coordinated imine which is then susceptible to addition of ammonia to give the gem diamine shown. Addition of another CH_2O unit to give another imine is followed by intramolecular attack by the gem diamine to make the first six-membered ring. Addition of another CH_2O molecule to give another imine group and another intramolecular attack, this time by the ring secondary amine group, leads to the synthesis of the first cap. The process is then repeated to complete the cage. Clearly the ammonia-formaldehyde reaction competes with the process but using an excess of these reagents the condensation can be made almost quantitative with respect to the tris(ethylenediamine)complex. The specificity is decided by the chirality of the parent tris(ethylenediamine)complex since this decides the orientation of the gem-diamine and subsequent additions of the amino group to the adjacent imine. Unless the gem-diamine is oriented in the apical position, condensation to give the cap is prohibited. The Δ or Λ configuration of the ethylenediamine chelates then decides the orientation of the secondary proton if the amino methylene moiety is required to be apical Λ(S) or Δ(R).



Λ (S) Δ (R)

These are some of the best examples of stereospecificity organised by the metal ions which we have encountered. Further studies will ascertain whether the origins of the specificity are as described but it is clear that substituents on the metal can direct the site of the condensation and that the metal constrains the intramolecular cyclisations to modify the effects anticipated from the regular organic chemistry. The activating effects of the metal ion, the use of coordinated nucleophiles, the possibility of specificity and the protecting and organising capacity of the metal centre should all be useful for inorganic and organic synthesis.

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