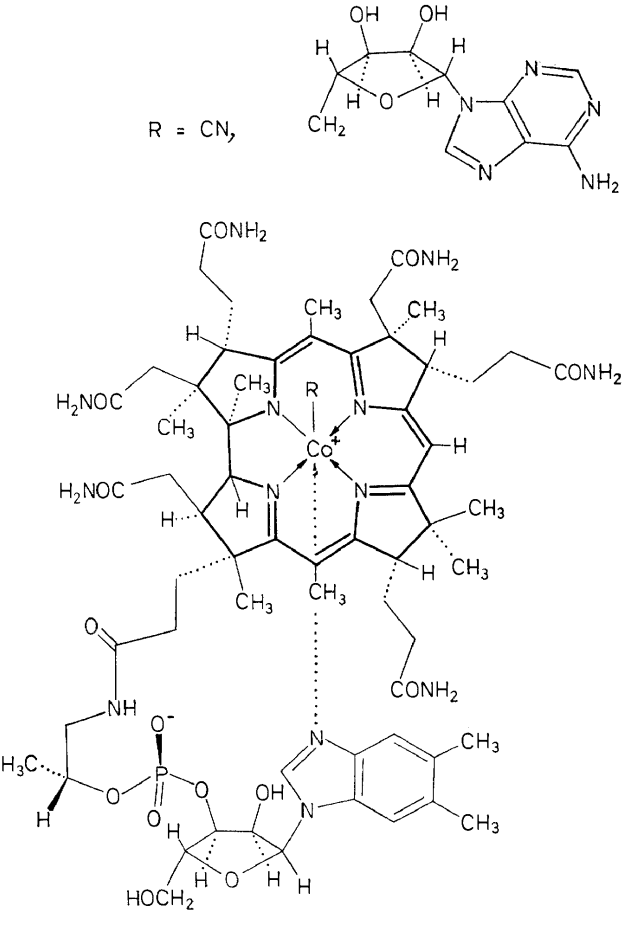
THE ROLE OF TRANSITION METALS IN THE CHEMICAL SYNTHESIS OF CORRINS

A. ESCHENMOSER

Organisch-chemisches Laboratorium ETH, Zürich, Switzerland

The problems involved in the structure and function of natural products related to vitamin B_{12} exemplify in a particularly striking way how research today is forced to ignore the classical boundaries between the various disciplines of chemistry.



I

Figure 1

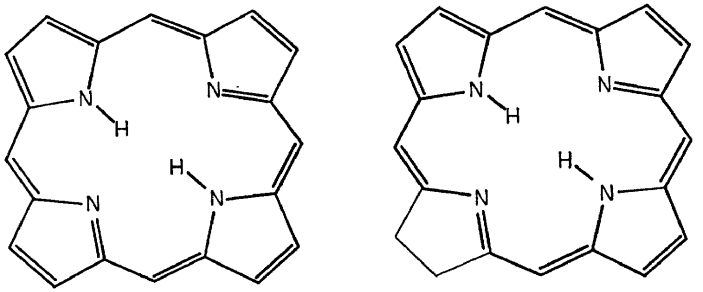
It was in organic laboratories of the pharmaceutical industry that the substance called cyanocobalamin (I, R = CN = vitamin B_{12}) was isolated and crystallized for the first time in 1948[1]. Enzymological studies in a biochemical laboratory had subsequently led to the discovery and isolation of B_{12}-coenzymes (*e.g.* I, R = 5′-adenosyl)[2], and by means of X-ray crystallography the chemical structure of these molecules had been revealed[3]. Ever since, biochemists, organic and inorganic chemists have been, still are and—presumably for quite a while—will be involved in interdisciplinary research directed to an understanding of the chemistry and the function of this class of compounds[4].

The inorganic asset of the cobalamines, the cobalt atom, being situated in the structural centre of these molecules, occupies also the centre of interest in many of the recent studies on the mechanism of B_{12}-action and there remains hardly any doubt, that cobalt will finally be shown to play a mechanistically central role in the various enzymic processes catalyzed by B_{12}-coenzymes.

Striking formal similarities do exist between the type of structural changes of substrates brought about in certain of these enzymic reactions and some of the known chemistry displayed by inorganic hydrido-cobalt-complexes. Moreover, the characteristic types of reactivity displayed *in vitro* by cobalamins have also been found in the chemical behaviour of simple model systems, such as *bis*-α-dioximino cobalt complexes, and the study of such model systems has expanded the chemical background knowledge about cobalt surrounded by planoid quadridentate ligands[5].

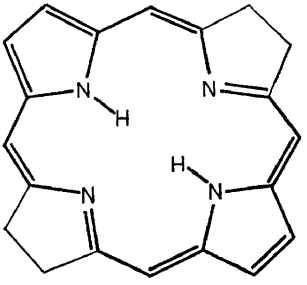
The structural environment of cobalt in B_{12}-compounds is the monoprotic, quadridentate, macrocyclic ligand system named corrin. It is the most recent member of that biogenetically closely related group of porphyrinoid ligands including the porphin (II) of the heme coenzymes, the chlorin (III) of the chlorophylls and the dihydrochlorin (IV) of bacteriochlorophyll, through which in conjunction with metal ions Nature has chosen to perform some of its fundamental molecular life processes. Structurally, the corrin ligand (V) differs from the more common porphin system in two important ways: its molecular periphery is completely saturated and two of its four five-membered rings are directly joined by a single bond between two tetrahedral carbon atoms. This goes in hand with a rather drastic difference in the electronic character of the two chromophors; the non-cyclic, linearly conjugated 14π-electron system of corrins is devoid of any close relationship to the pyrroloid aromatic character of porphins. The chemical and biochemical consequences of these differences, with respect to the capacity of ligands to tailor metal ion properties, are far from being understood or even explored.

This lecture is confined to what might be considered to be one of the prerequisites of a systematic exploration of corrin chemistry, the chemical synthesis of corrins. At first sight, the topic might appear to lie exclusively in the province of the organic chemist but, in fact, it does not. Corrin synthesis is one example which exemplifies how template effects of metal ions can expand the reach of organic synthesis; furthermore, in pinpointing specific synthetic goals it exemplifies how a systematic use of template effects can provide a feed-back to metal ion chemistry. Within the realm of

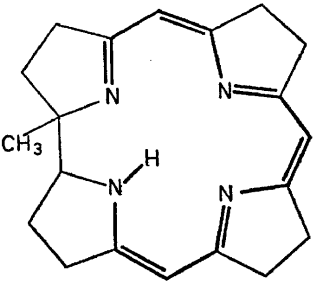


II

III



IV



V

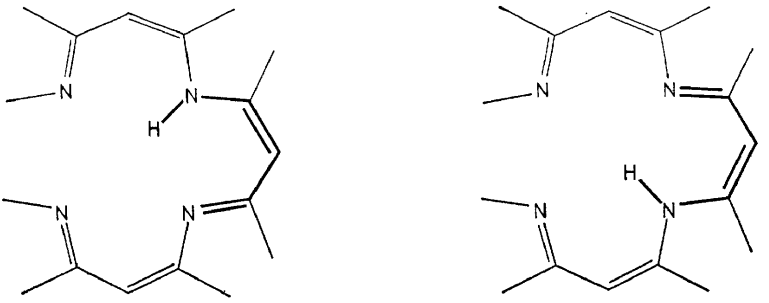
Figure 2

organic synthesis the use of metal templates is just a special case of a quite general trend in which one is trying to achieve higher orders of structural and stereochemical specificity in *intermolecular* reactions by prearranging reactive centres as covalently bound neighbouring groups and performing then the product forming steps *intramolecularly*. This, of course, is but a shadow of the strategy which Nature has so admirably perfected in enzymic synthesis.

Time will not allow me to deal here with the numerous other examples of metal template controlled reactions described in recent literature[6]; these have been reviewed by one of the active promotors of the field, Professor D. H. Busch, at the last coordination conference two years ago[7]. Yet, in a lecture on corrin synthesis special reference is due to the many important recent achievements on the synthesis of porphinoid and corrinoid complexes by Professor A. W. Johnson and his group in Nottingham[8].

The characteristic structural unit (VI) of the corrin chromophor is the vinylogous amidine system, as accentuated in the formulae *Figure 3*. This unit is simply the diaza-analogue of the β-keto-enol grouping, a most familiar ligand system in coordination chemistry.

Three general methods for the construction of such vinylogous amidine structures have emerged from the work on corrin and vitamin B_{12} synthesis; since these reactions will repeatedly appear during the lecture, they are abstracted in *Figures 4*, *5* and *6* and discussed here very briefly.



VI

Figure 3

(a) The condensation of enamines with iminoesters (Figure 4)[9]

These reactions are the result of the complementary nucleophilic and electrophilic reactivity of the β-carbon of enamines and the trigonal carbon of iminoesters groups; they can be effectively catalyzed either by base (deprotonation of the enamin-NH) or by protic acids (protonation of the iminoester nitrogen), but they seem to be rather sensitive to steric hindrance. The method profits strongly from the preparatively important fact that iminoesters can very mildly and quite generally be prepared by O-alkylation of the corresponding amide groups with Meerwein's trialkyl-oxonium salts[10].

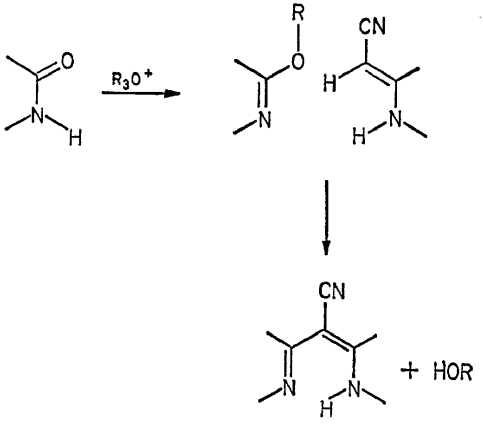


Figure 4

(b) The sulphide contraction method via oxidative precoupling (Figure 5)[11]

This reaction sequence is an illustration of that principle mentioned before, namely, the prearrangement of reactions centres as covalently bound neighbouring groups in order to achieve the desired synthetic step intramolecularly; here this step is a thioiminoester-enamide condensation.

One might say that the sulphur atom fulfils here the role of a bifunctional template. The choice of sulphur for this function was indicated by its easy

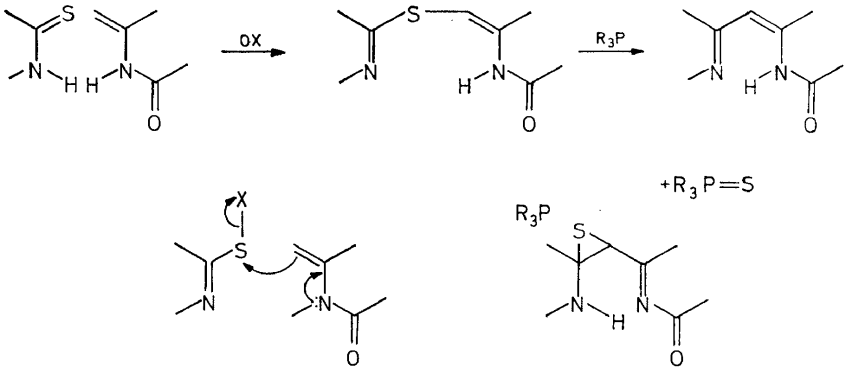


Figure 5

introduction (oxidative coupling of a thiolactam to an enamide *e.g.* by benzoylperoxide) as well as its facile removal (sulphur transfer from a hypothetical episulphide intermediate to a thiophile *e.g.* triphenylphosphine). This reaction sequence proves to be the method of choice in such cases where direct bimolecular iminoester condensations fail.

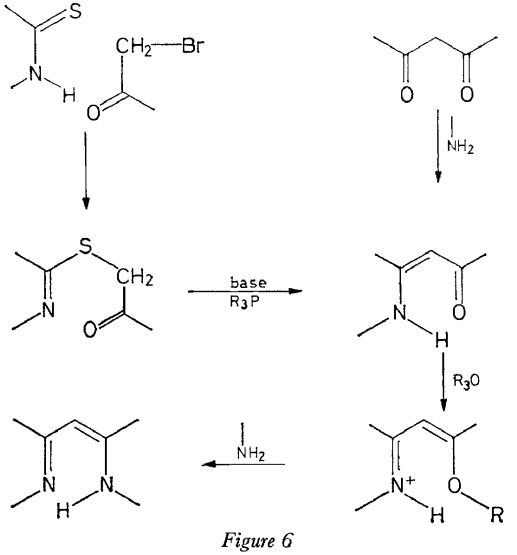
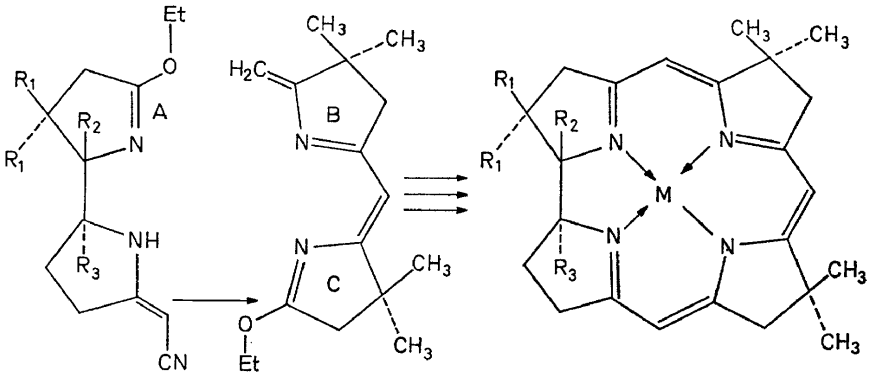


Figure 6

(*c*) *The sulphide-contraction method via alkylative precoupling* (*Figure 6*)[12]

Bromomethyl-carbonyl compounds alkylate the sulphur of secondary thiolactams with great ease. Subsequent treatment with a thiophile in the presence of an enolizing base removes the sulphur in a process analogous to the contractive sulphur transfer in method (b) and leads to corresponding β-amino-enone-derivatives. Alkylation with trialkyloxonium salts, followed by an alkoxy replacement with an amino group, forms vinylogous amidines. Incidentally, the last two steps provide in addition a general and simple route to vinylogous amidines from corresponding β-diketones since the transformation of the latter to β-amino-enones is a well known reaction.



R_1	R_2	R_3
H	H	H
H	H	CH_3
CH_3	CH_3	H

Figure 7

Figure 7 summarizes the final steps in our orginal approach to synthetic corrin complexes by which various cobalt (III)-, nickel(II)- and palladium-(II) complexes have been prepared during the last few years[13]. The final phase of the synthesis demands the accomplishment of two successive imino-ester-enamine condensations. The distribution of the four reactive centres in the two components VII and VIII is such that the structural specificity of the first condensation, that is the intermolecular one, is secured. This is the reaction between the two more reactive centres, namely the enamine system in Ring D after NH-deprotonation and the trigonal carbon of the conjugated iminoester group in Ring C.

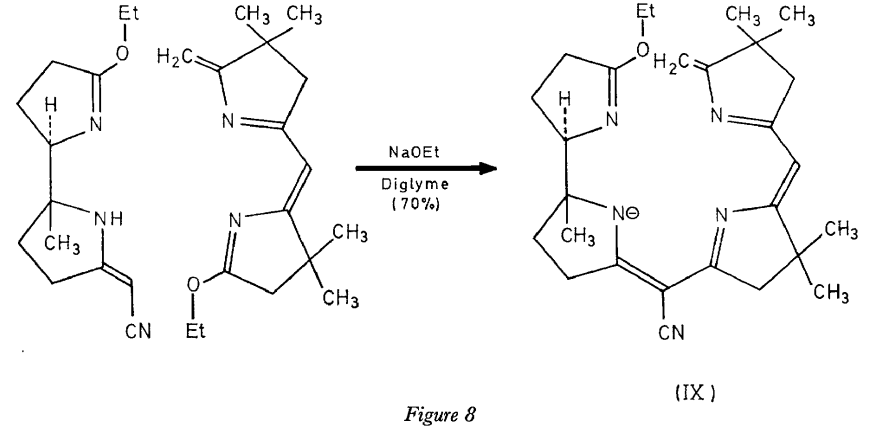


Figure 8

Such condensations proceed very smoothly leading to crystallized sodium salts of type IX. Here was the point where we had to call upon transition metals. Extreme configurational and constitutional lability of these condensation products in their free form precluded any extensive experimentation towards a direct closure of the macrocyclic ring. Not unexpectedly, exploratory experiments of this sort with either the free form, or the sodium or lithium salts had in fact ended in vain. A transition metal ion had to be inserted!

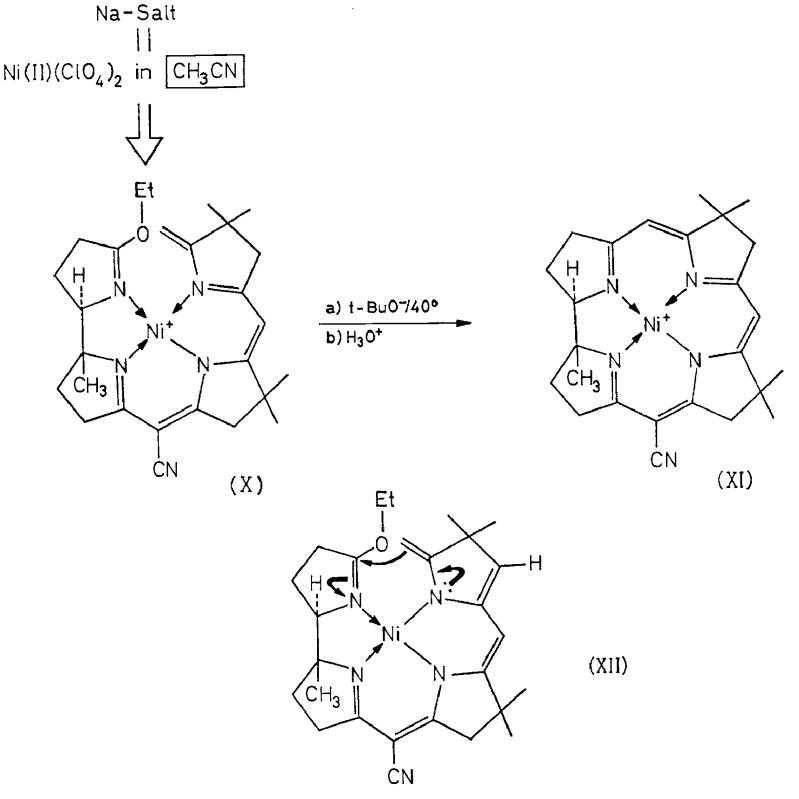


Figure 9

The beautifully crystalline and stable compound X formed by the reaction of the sodium salt IX in the pentamethyl series with nickel perchlorate in acetonitrile *or* aqueous ethanol shows all the expected properties of a square-planoid complex. The final iminoester condensation, the closure of the macrocyclic ring to the nickel corrin complex XI, only became a high yield process once it was realised that the nucleophilic reactivity of the methylene carbon needs additional electronic activation for its attack on the iminoester carbon of ring A. This activation is provided through deprotonation of one of the peripheric methylene groups in rings B or C by the strong base potassium *tert*-butoxide (*cf.* XII).

Thanks to the contributions of three crystallographic groups, those of

Professor J. Dunitz at ETH, Professor Dorothy Hodgkin in Oxford and Professor Galen Lenhert at Vanderbilt University, U.S.A., a number of corrin and corrinoid complexes prepared in our laboratory underwent X-ray analyses so the structural assignments of the complexes I am discussing in this lecture are on solid ground.

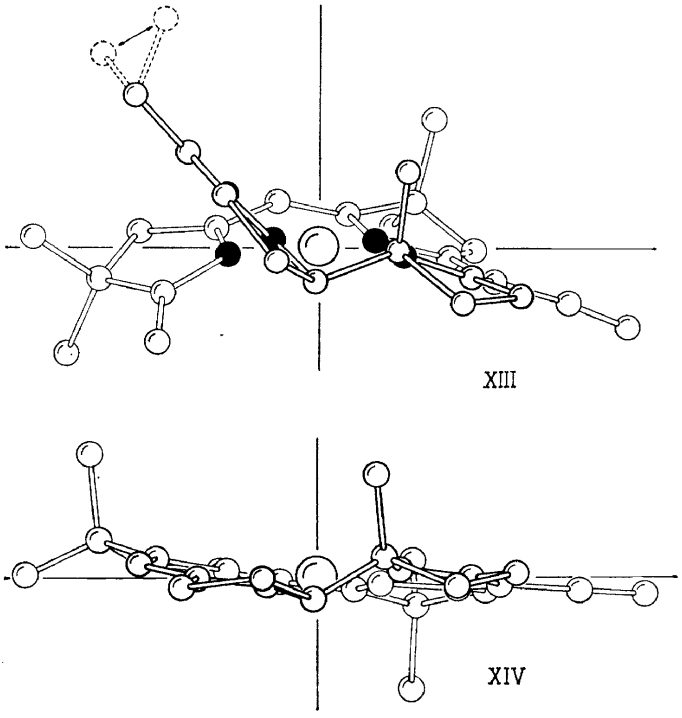


Figure 10

Figure 10 gives two examples from Professor Dunitz's laboratory[14], namely, side views on the models of the two nickel complexes before (XIII = X)[14a] and after (XIV = XI)[14b] cyclization. In the precorrinoid complex XIII the four nitrogens and the nickel ion lie approximately in the expected common plane and the two cyclization centres in ring A and B are juxtaposed and separated by a distance of about 3·4 Å which amounts to approximately twice the van der Waals radius of a trigonal carbon.

What happens when the sodium salt IX of the non-cyclized ligand is complexed with cobalt(II)-perchlorate in acetonitrile, that is, under conditions analogous to the nickel experiment, and subsequently oxidized to the tervalent state in acetonitrile?

Figure 11 shows the structure of the reaction product as it emerged from an X-ray analysis made in the Oxford laboratory[15].* The reaction looks

* This structure had also been proposed by Professor R. B. Woodward, Harvard University.

like a case of an inorganic metal ion teasing an organic chemist. The structure XV possesses a corrinoid chromophore without actually being a corrin. At some intermediate stage of the reaction an acetonitrile molecule, obviously complexed and thereby activated by the cobalt ion, undergoes an

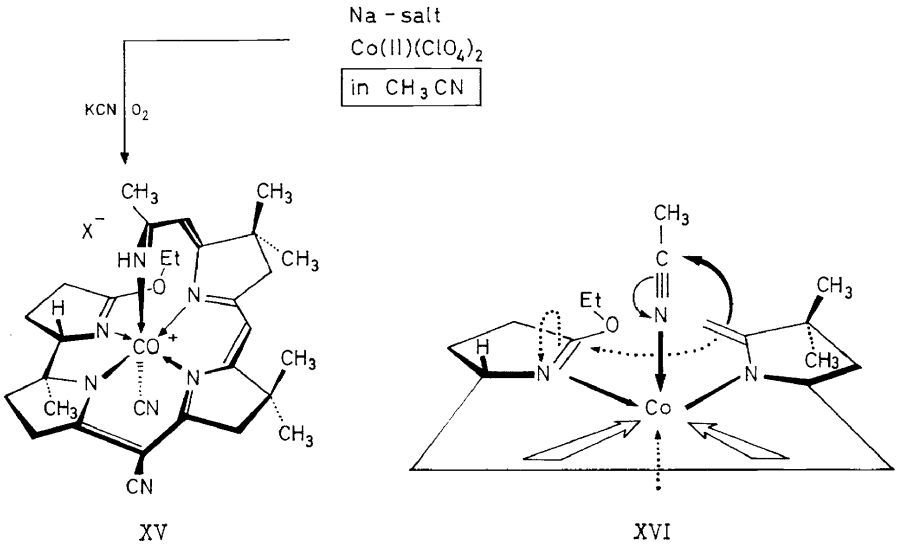


Figure 11

intramolecular electrophilic substitution at the neighbouring methylene group of ring B, a process originally expected to occur between the methylene group and the iminoester function of ring A (*cf.* XVI). Thereby, the amazing architecture of the quinquedentate ligand around the metal ion is erected (*Figure 12*). Whereas the nitrogen atoms of the four rings form an equatorial plane with the cobalt atom, the chromophoric part stemming from the acetonitrile is winding itself up to one of the axial positions giving rise, together with the cyanide ion, to a distorted octahedral geometry.

Obviously, complexing of the precorrinoid ligand with cobalt had to be carried out in the absence of acetonitrile.

In fact, in aqueous ethanol the reaction proceeds smoothly in the desired direction and the precorrinoid dicyano-cobalt(III)-complex XVII can subsequently be cyclized by a strong base in very high yield to the corresponding dicyano-cobalt(III)-corrin complex XVIII. (see *Figure 13*).

This then is the originally developed approach to corrin complexes of nickel, palladium and cobalt, a study which brought this class of compounds within the reach of organic synthesis and allowed the initiation of a systematic study of the specific properties of this ligand system[16]. Since this lecture is otherwise fully confined to aspects of synthesis, I shall not discuss here any of these properties with the exception of the following one. (*Figure 14*).

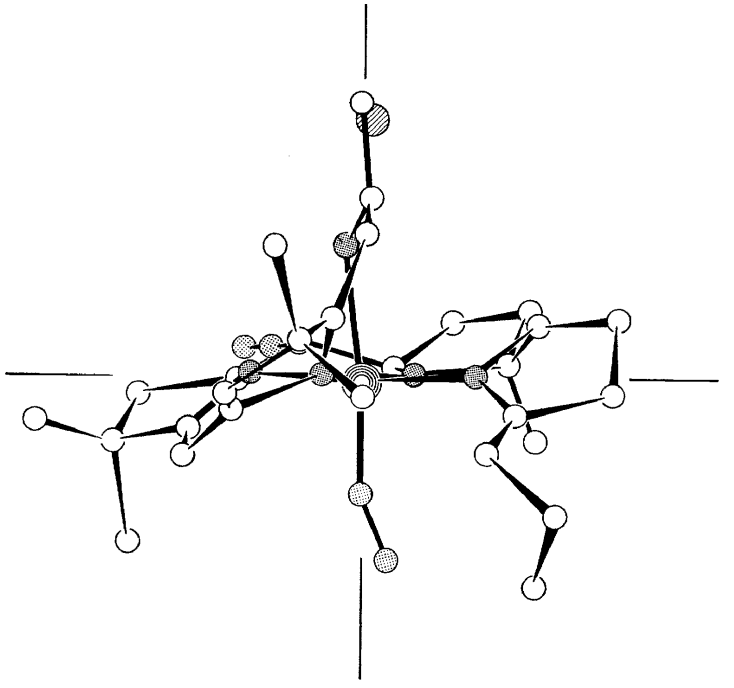
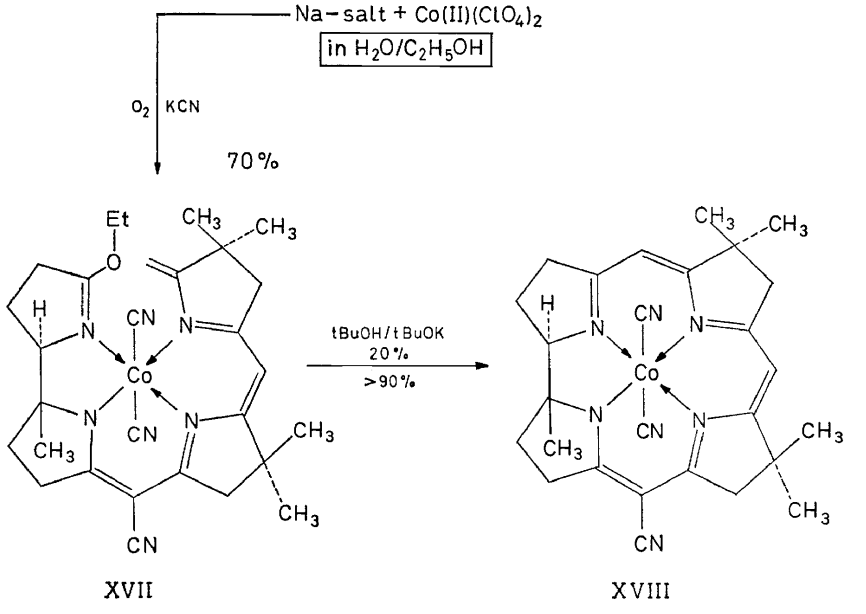


Figure 12



XVII XVIII

Figure 13

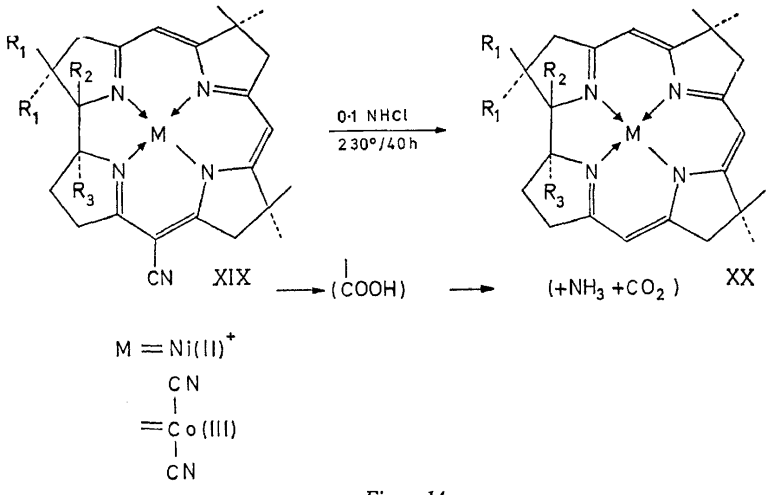


Figure 14

Neither in vitamin B_{12} derivatives, nor in synthetic corrin complexes has it been possible under either hydrolytic or reductive conditions to remove the metal ions, such as cobalt, nickel or palladium, without destruction of the ligand. This behaviour is exemplified by the preparative method for the hydrolytic removal of the cyano group bound to the chromophore in complexes of type XIX: the decyano complexes XX are isolated in high yields after extensive heating at over 200° in dilute mineral acid. The experimental results shown in *Figure 15* illustrate qualitatively that the high stability of

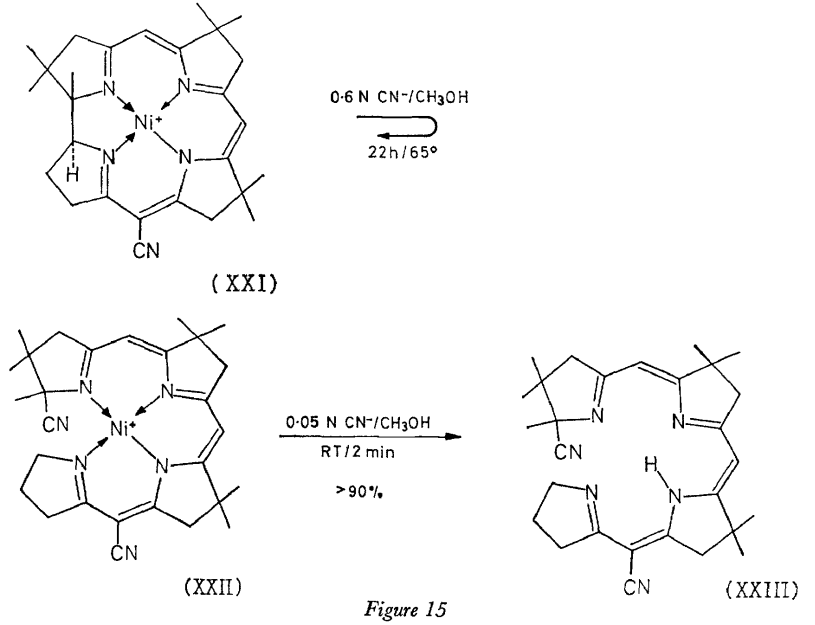


Figure 15

corrin complexes of nickel is not inherent in the thermodynamic of the chromophore—metal interaction, but is essentially kinetic in origin.

Whereas the nickel-corrin XXI does not give off the metal ion on treatment with excess cyanide ions at elevated temperatures, the corresponding complex XXII, which possesses the identical chromophore (and practically the same electronic spectrum) but lacks the covalent (C—C) bond between rings A and D, loses the nickel to the cyanide ion quantitatively within a few minutes at room temperature to give the free ligand XXIII. This may be considered to be a clear example of a lability difference reflecting the structural difference resulting from noncyclic versus macrocyclic chelation.

An intriguing question may be asked in passing: does Nature make use of the template capacities of cobalt in the biosynthetic construction of the corrin chromophore of vitamin B_{12}? First of all, there is no direct experimental evidence available with respect to this question, for the relevant structural details of corrinoid biosynthesis are still unknown[17]. On the other hand, the intuitively attractive *guess* that this might well be so has in a sense been hampered by the recent discovery of natural cobalt-free corrinoids in photosynthetic bacteria[18]. This important finding somehow hints at a biosynthetic pathway without the cobalt template participation, because the alternative would require the existence of an enzyme system with the most remarkable ability to circumvent, in removing the cobalt, that enormous kinetic barrier due to the macrocylic chelation.

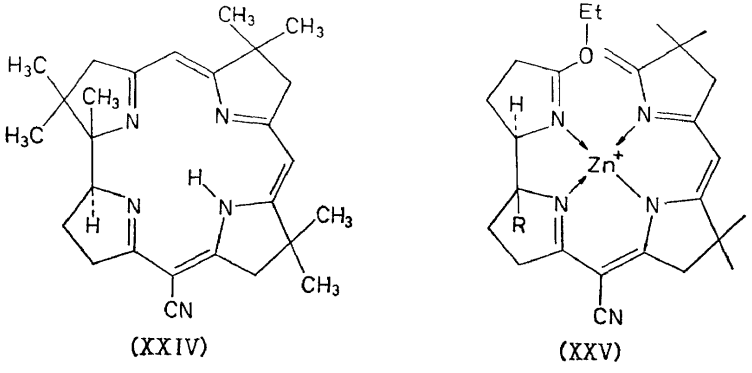


Figure 16

Can metal free corrins, *e.g.* XXIV, be synthesized chemically by the method described above? The answer is no: because the success of the final base catalyzed cyclization is tied to the template effect of such metal ions which form robust precorrinoid complexes and cannot, as yet, be removed after cyclization. Experiments directed to an iminoester cyclization of the labile zinc complex XXV failed. However, this very problem has been solved by recourse to the sulphide-contraction method via oxidative coupling[19].

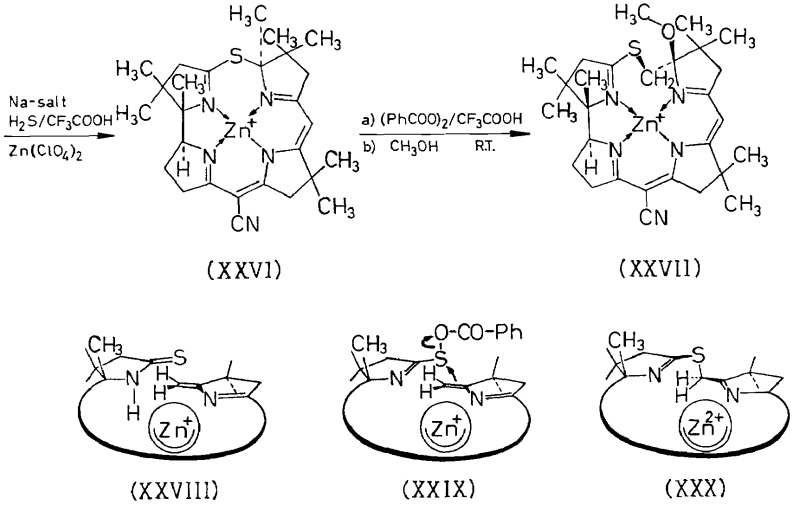


Figure 17

The starting material required for this reaction sequence would have been the precorrinoid thiolactam zinc complex. However, treatment of the precorrinoid sodium salt in the heptamethyl series with hydrogen sulphide in the presence of trifluoroacetic acid, followed by complexing with zinc(II)-perchlorate gave the macrocyclic thioiminoester isomer XXVI. Reaction with benzoylperoxide in methylene chloride in the presence of trifluoracetic acid brings about the desired oxidative coupling of the sulphur to the exocyclic carbon atom of the original methylene double bond of ring B. The crystalline derivative XXVII of the reaction product can be isolated after final treatment with methanol.

The formulae in *Figure 17* try to explain the rather intricate series of processes: trifluoroacetic acid presumably equilibrates the thioiminoester form of the starting material with the thiolactam isomer XXVIII, the latter is then attacked by benzoylperoxide to form the O-benzoate of the thiolactam-S-oxide XXIX and this—accelerated by the template effect of the zinc ion—reacts with the exocyclic enamine carbon of ring B to give XXX. Subsequent contact with methanol leads to the isolable addition product XXVII. Interestingly enough, the attack at the enamine double bond does lead to *addition* and not to *substitution*. In fact, considerations of molecular models clearly indicate that the double bond should not become restored in this exocyclic position as long as the lone pairs of the trigonal nitrogens of the rings A and B take part in coordination with the zinc ion, simply because the geometrical situation produced by the sulphur bridge is such that a double bond at this position could hardly be planar. Yet, restoration of that double bond is a prerequisite for the reaction to proceed towards the desired sulphide contraction. The situation is remarkable: the template zinc ion, which has rendered possible the spannings of rings A and B by the sulphur bridge, threatens to thwart the sulphide contraction step. Fortunately, the metal is actually no longer needed, the *sulphur template* can now take over,

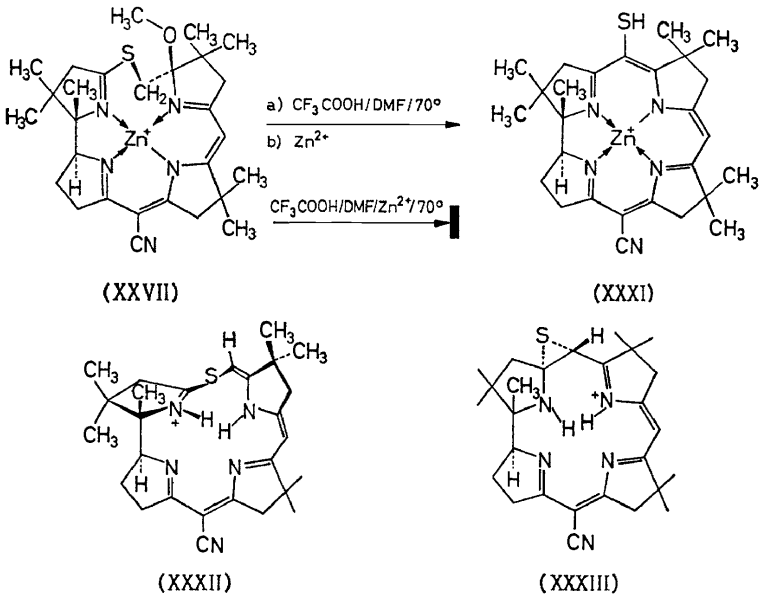


Figure 18

The treatment of the sulphur-bridge compound XXVII with trifluoroacetic acid in dimethylformamide at 70° brings about the sulphide contraction and produces the corrin chromophore (*cf.* XXXI), whereas the same treatment, *but in the presence of excessive zinc ions*, distinctly does not.

We assume that in the nucleophilic solvent DMF an acid-assisted decomplexation precedes the formation of an intermediate of type XXXII in which the molecule can now accommodate the exocyclic double bond on account of its higher flexibility as the metal free ligand. An intramolecular rearrangement via the hypothetical episulphide intermediate XXXIII leads to the mercapto-corrin derivative which is isolated as the crystalline zinc complex XXXI. From this point onwards the way to the metal-free corrin is clear*. (*Figure 19*).

Acid-catalyzed desulphurization with triphenylphosphine leads to the complex XXXIV which gives off the zinc ion with great ease during a few minutes treatment with trifluoroacetic acid in acetonitrile at room temperature, leading to the crystalline immonium salt XXXV of the metal free corrin. In view of the high stability of cobalt and nickel corrin complexes it was interesting to find that the neutral free ligand is a very labile, moderately basic molecule ($pK^*_{MCS} = 8{\cdot}6$) which surprisingly prefers to exist in the tautomeric form XXXVI. Paradoxically, the metal free corrin likes to be a non-corrin.

The metal template controlled, final cyclization between rings A and B is the characteristic feature of the corrin syntheses I have discussed so far.

* According to the n.m.r. spectra in $CDCl_3$ the zinc ion in the chlorides of the complexes XXXI and XXXIV is very probably pentacoordinated in $CHCl_3$ solution.

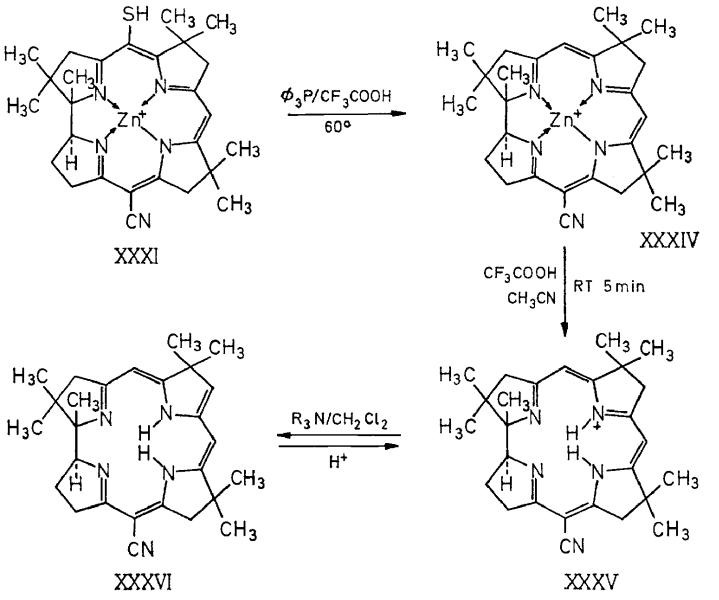


Figure 19

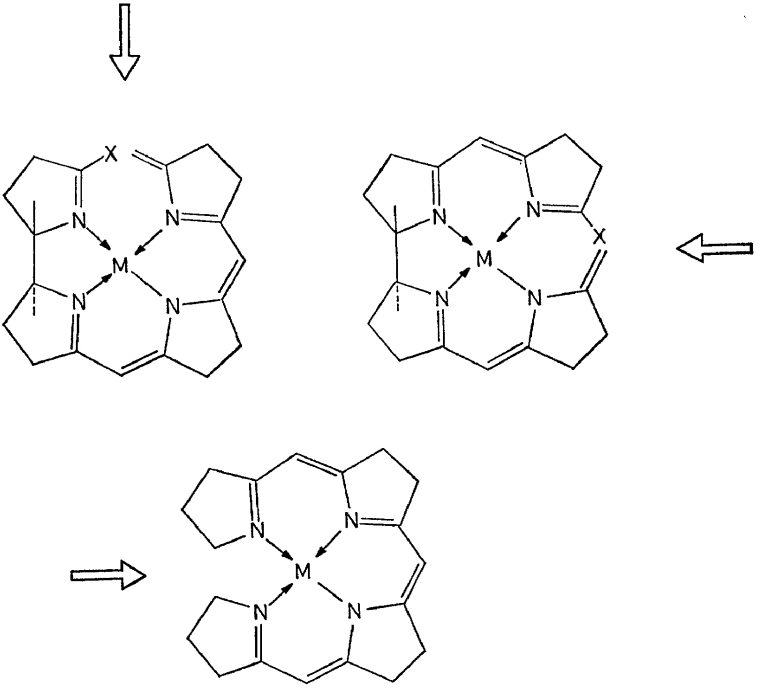


Figure 20

The chemical experience accumulated during the development of this approach, and the synthetic methods which emerged from it, would certainly make an analogous type of approach experimentally feasible, namely the one which would aim at a final cyclisation between rings B and C. Inevitably, both approaches demand the preparation of a precursor containing rings A and D and the solution of the stereochemical problem of joining these two rings together stereospecifically in a *trans* fashion.

To impose stereospecificity on a synthetic reaction is clearly a worthy task for a metal template. Let us consider therefore a third type of corrin synthesis, namely, the construction first of the chromophore by joining rings A, B, C and D together in a row to give a so-called A/D-seco-corrin, then the introduction of a metal ion, and finally a cyclization between rings A and D under both the constitutional and configurational control of the metal template. This type of approach would of course be reminiscent of the Nottingham synthesis of aromatic corrin analogues which include some dramatic metal ion assisted A/D-cyclizations in certain tetrapyrrolic systems to so-called corroles and tetradehydrocorrins[8].

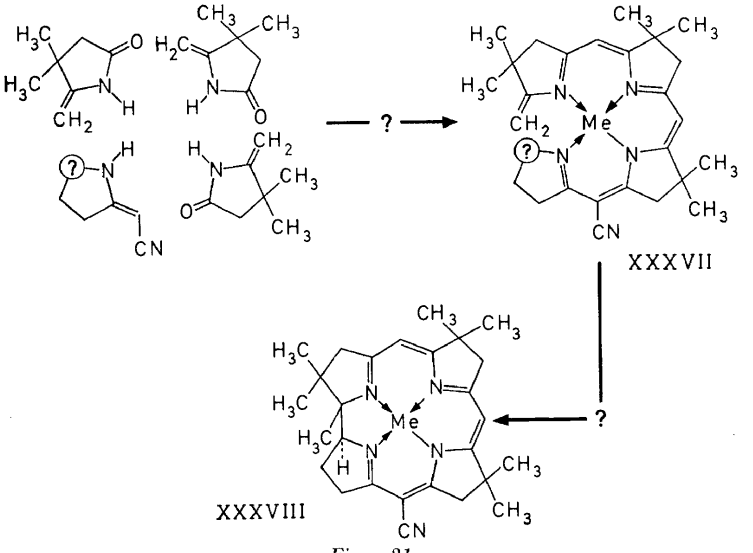


Figure 21

Figure 21 summarizes the strategy of what at the time—especially with a view to vitamin B_{12} itself—appeared to be a model of a kind of dream synthesis of corrin complexes. The experience which emerged from the recent attempts to realize this approach will now be discussed as the second part of my lecture. Thereby I shall not avoid the purely organic aspects as much as I tried to do before, but the metals will also come into their own.

The main problem at the outset of the project was the following: what type of reaction could possibly accomplish the A/D-ring closure of a A/D-seco-corrin XXXVII to a corrin complex XXXVIII? What kind of functional group should be introduced at the question mark position? Let us concentrate on the simplest of all answers, namely: no functional group at all.

As a matter of fact, the compound XXXVII ((?)=CH_2) is plainly isomeric with the corrin complex XXXVIII. The two systems differ only as regards the positions of a hydrogen atom and of a carbon-carbon bond. A cyclization would "simply" require the jump of a hydrogen atom from one position to the other and a corresponding reorganisation of that carbon–carbon bond.

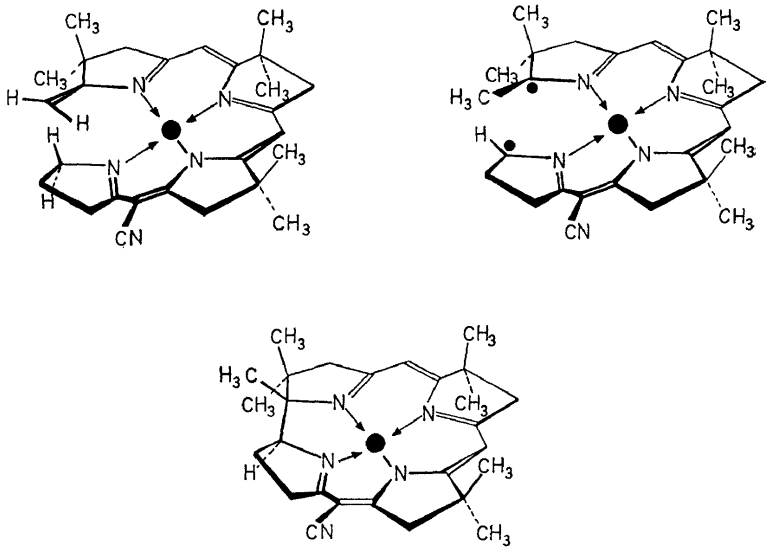


Figure 22

This kind of wishful formalism becomes immediately a serious and exciting problem as soon as we consider the geometry imposed on the ligand system by the central metal ion. In a square-planoid complex the chromophore would have to form a coil in which the aforementioned hydrogen comes to lie exactly below (or above) the exocyclic methylene double bond and where this hydrogen would be pushed into the π-cloud of this double bond. The chemical consequences of such a situation with respect to the cyclization delineated before can hardly be judged *a priori*. Therefore, the question has been subjected to an experimental test.

The process envisaged is a macrocyclic antarafacial 1,16,-hydrogen shift which would create a new conjugated 15-centre 16-electron π-system. This new π-system contains two formally non-bonding π-electrons—it cannot, in fact, be represented by a classical formula—and can gain the stabilization energy of a new carbon–carbon single bond by an antarafacial cyclization between rings A and D (*cf. Figure 22*).

What are the predictions to be drawn from the Woodward–Hoffmann rules[20] on the conservation of orbital symmetry with respect to these two hypothetical processes?

Figure 23 illustrates the symmetry of the frontier HMO-orbital π_9 of the 16-centred (16 + 1)-π-electron system relevant to the hydrogen shift in the electronic ground state. The analysis refers to the ligand π-system in which

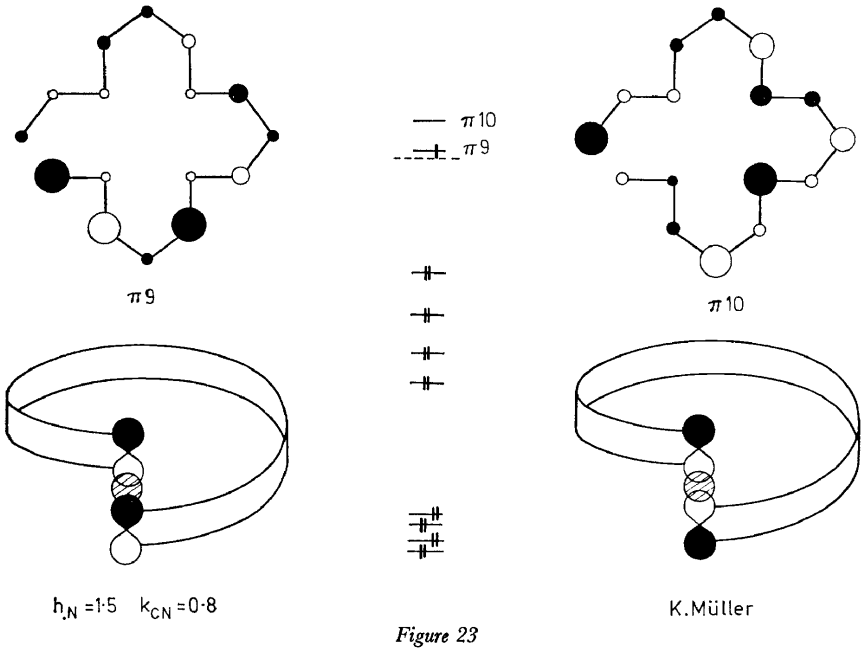


Figure 23

the metal orbitals are ignored. On its way from position 1 on the top side of the π-system to position 16 on the bottom side of the π-system the *s*-orbital of the hydrogen atom would change from a bonding into an antibonding frontier orbital interaction. As a Woodward–Hoffmann type conclusion, this hydrogen shift is therefore expected to be symmetry-forbidden thermally, but symmetry-allowed photochemically. *Figure 24* shows

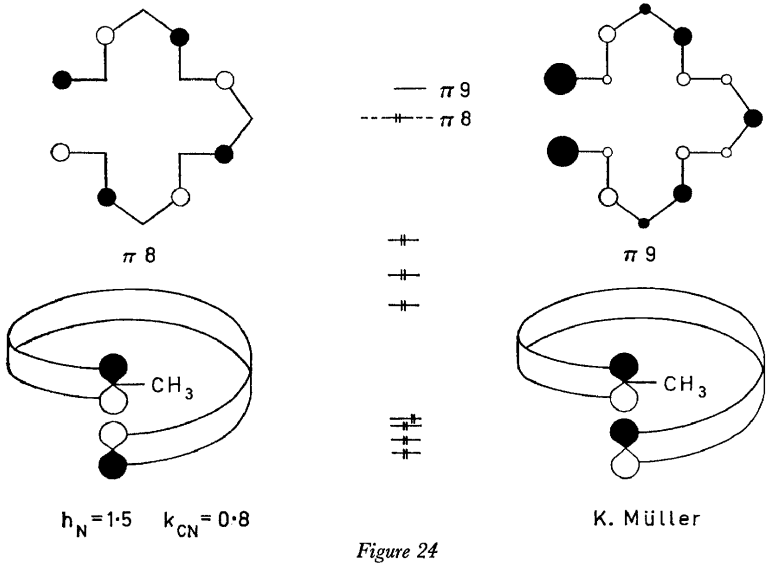


Figure 24

the analogous kind of analysis for the subsequent cyclization step. The symmetry of the frontier-orbital π_8 of the 15-centre 16-electron π-system does fit the requirement for a Möbius type 1,15-cyclization to be symmetry-allowed in the electronic ground state. It is worth mentioning here that the contrary would be true for the symmetry of the next higher orbital π_9.

Before discussing the crucial experiment, I would like to spotlight very briefly the synthetic steps leading to the A/D seco-corrin system.

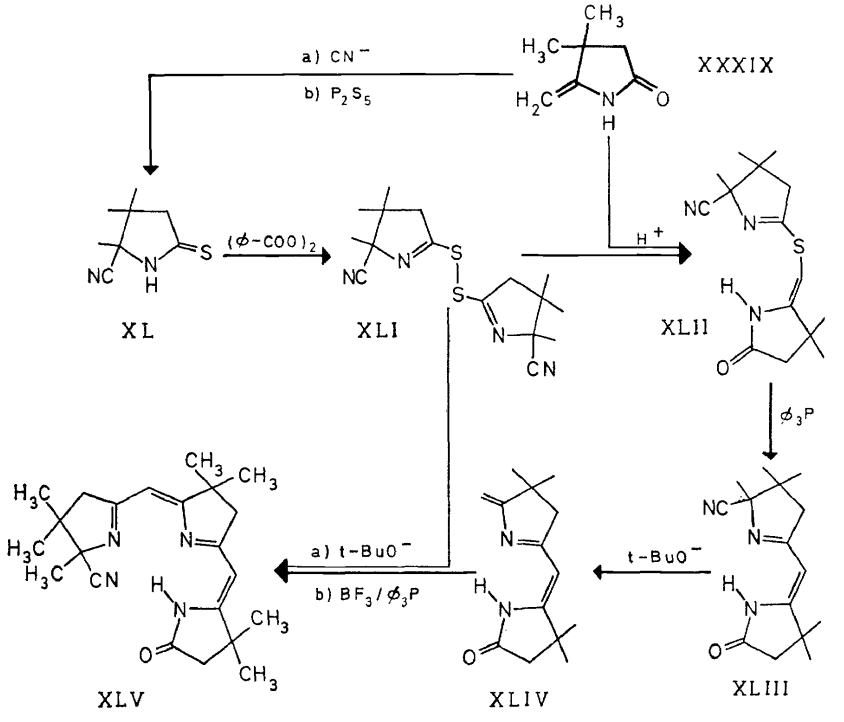


Figure 25

The reaction sequence developed for joining together three molecules of the monocyclic enamide XXXIX precursor to a tricyclic sesqui-derivative XLV containing the rings A, B and C is an illustrative example of the power of the sulphide-contraction condensation method described at the beginning. Oxidation of the cyano-protected thiolactam XL derivative with benzoyl-peroxide at ambient temperature leads to the dimeric disulphide XLI, which, under the influence of traces of acids, condenses readily and in high yield with the starting enamide to form a thio-bridged intermediate XLII. Heating with triphenylphosphine brings about the sulphide contraction (XLIII), and a subsequent treatment with base eliminates the protecting group (XLIV). A slight variation of the same condensation process adds on the third ring, the deviation being that the coupling of the bicyclic enamide with the disulphide is induced by base and not by protons, and that the sulphur contraction step has to be catalyzed by borontrifluoride.

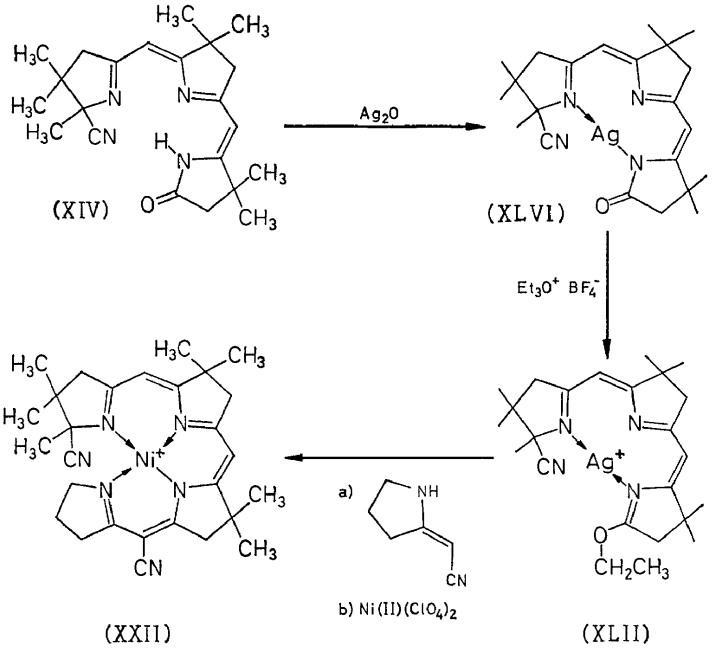


Figure 26

For a change, the fourth ring is introduced by way of the iminoester condensation method. Still, an illustrative complication had to be overcome: the necessary transformation of the lactam to the iminoester group *cannot* in this case be accomplished simply by alkylation of the free lactam with trialkyloxonium-tetrafluoroborate as usual, since concomitant N-alkylation intervenes strongly. Therefore, the ligand is first complexed with the digonally active silver ion to protect at least two nitrogen lone pairs against the alkylating agent. It was only with the help of the metal ion that the condensation step could again become routine (XLV → XLVII → XXII).

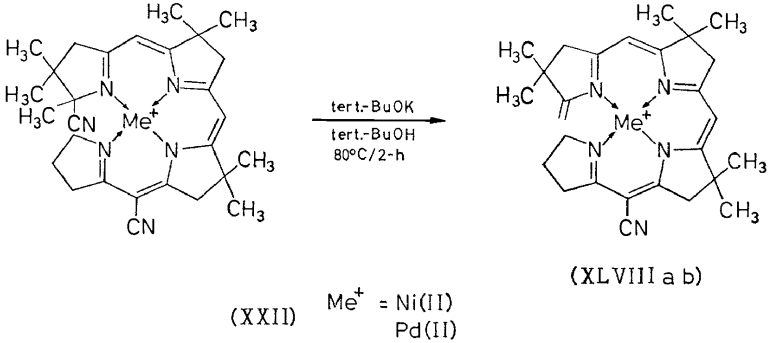
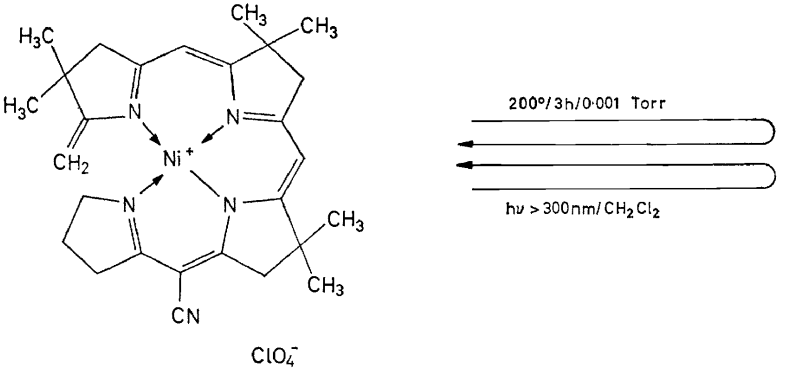


Figure 27

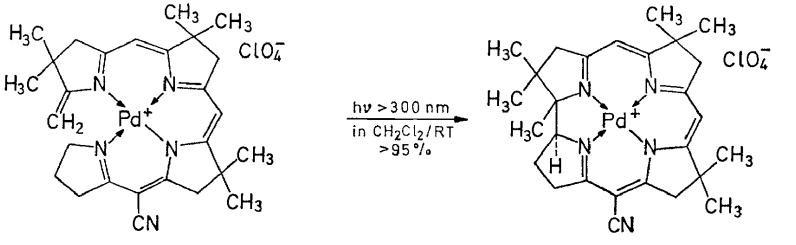
We have seen earlier in this lecture that the nickel(II) seco-corrin complex XXII loses the metal to cyanide ion with extreme ease. The free ligand XXIII is a crystalline compound, available for complexing with various metal ions. From *Figure 27* we notice the removability of the cyanide protecting group from both the nickel(II) and palladium(II) complex by treatment with strong base, doubtlessly induced by deprotonation at one of the peripheric methylene positions. Both complexes XLVIII a, b show a close similarity in the character of their electronic and vibrational spectra, both are diamagnetic in chloroform solution and therefore of square-planoid structure. At this stage then we are back to the crucial question: does that macrocyclic hydrogen jump occur?



(XLVIII a)

Figure 28

The verdict of the experiment had to be accepted neither thermally, that is on heating up to 200°, nor photochemically under various conditions did the nickel(II) complex perchlorate XLVIIIa disclose any tendency to undergo this type of reaction.



XLVIIIb

Figure 29

Yet, the corresponding palladium(II) complex XLVIIIb does undergo the cyclization photochemically with fabulous ease even in sunlight, leading to the palladium(II)-corrin complex XLIX in over 95 per cent yield. The constitution and configuration of this complex are rigorously established

by independent synthesis via the classical (AD + BC)-approach, the configuration at the AD-junction in this heptamethyl series being settled by Professor Galen-Lenhert's X-ray analysis[21] of the corresponding dicyanocobalt(III) complex. Significantly, no indication could be found that the A/D-cyclization of the palladium complex can be induced thermally.

The palladium(II)-ion has—as is well known—an inherently stronger tendency towards square planar coordination than the nickel(II)-ion. We presume that the dramatic difference in the behaviour of the two secocorrin complexes towards cyclization is a consequence of this property. Relevant X-ray analyses will have to clarify this question. It would be the second case in corrinoid synthesis that the template palladium (II)-ion reveals itself as being superior to the homologous nickel(II)-ion as regards the imposition of square-planoid geometry on a quadridentate organic ligand system, the other example being the recently described synthesis of a palladium(II)-corphin complex[22].

On the other hand, new and more incisive questions arise with respect to the cyclization involving hydrogen transfer. Nothing is yet known about the nature of the photoreactive species involved, whether or not the two processes of hydrogen transfer and carbon–carbon bond formation are separated by an intermediate as originally presumed or whether the properties of such an intermediate are determined by the metal ion, so that effects other than purely geometrical ones control the cyclization process. Finally, further experimental information about complexes with metals other than those two mentioned has also to be awaited.

The role of transition metals in the chemical synthesis of corrins is more than just adding a touch of "inorganic elegance" to organic synthesis—"leave elegance to tailors and cobblers", a physicist once said—it is a vital role in the sense that perhaps no synthetic corrin would as yet exist without recourse to metal templates. Beside the purely topological function of *arranging the proximity* of reaction centres, metal ions have served this purpose as follows:

(i) by *stabilizing* labile organic intermediates and thereby facilitating their isolation and characterization,

(ii) by *activating* organic ligands electronically for base-catalyzed processes,

(iii) by subjecting organic ligands to heavy *steric strain* so that they perform strain-releasing reactions which they would otherwise certainly never undergo,

(iv) *by protecting* organic coordination sites against the detrimental attack of aggressive alkylation reagents,

(v) and, last but not least—by converting the organic chemists involved in this work to genuine admirers of the depth, potentials and wonders of *transition metal chemistry.*

Organic synthesis is still a largely empirical branch of chemistry and progress in this field is most intimately dependent on the experimental skill and scientific abilities of those men who are too young to give lectures, but who do the work. Out of the group of doctoral students and postdoctoral fellows who have produced the results I have discussed in this lecture, I would like to mention here the names of those whose contributions have not yet, or only partially, been published: B. Golding, P. Löliger and P. Dubs (sulphide contraction method); A. Fischli and H. U. Blaser (metal free

corrin); J. Schossig, M. Roth; P. Wehrli, D. Miljkovic and Y. Yamada (A/D-corrin synthesis). I express here my appreciation to all of them.

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References

[1] E. Lester Smith and L. F. J. Parker. *Proc. Biochem. Soc., Biochem. J.* **43**, VIII (1948); E. L. Rickes, G. Brink, F. R. Koniuszy, T. N. Wood and K. Folkers. *Science* **107**, 396 (1948); B. Ellis, V. Petrow and G. F. Snook. *J. Pharm. Pharmacol.* **1**, 60 (1949).

[2] H. A. Barker, R. D. Smyth, H. Weissbach, J. L. Tookey, J. N. Ladd and B. E. Volcani. *J. Biol. Chem.* **235**, 480 (1960).

[3] D. C. Hodgkin, A. W. Johnson and A. R. Todd. *Spec. Publ. Chem. Soc.* **B**, 109 (1955); D. C. Hodgkin. *Progr. Chem. Org. Nat. Prod.* **15**, 167 (1958); P. Galen Lenhert and D. C. Hodgkin. *Nature* **192**, 937 (1961).

[4] R. Bonnett. *The Chemistry of the Vitamin B_{12} Group, Chem. Revs.* **63**, 573 (1963); E. L. Smith. *Vitamin B_{12}*, 3rd. Ed. Methuen, London (1965); F. Wagner. *Vitamin B_{12} and Related Compounds, Ann. Rev. Biochem.* **35/I**, 405 (1966).

[5] G. N. Schrauzer. *Accounts Chem. Res.* **1**, 97 (1968).

[6] D. H. Busch. *The Significance of Complexes of Macrocyclic Ligands and Their Synthesis by Ligand Reactions, Rec. Chem. Progress* **25**, 107 (1964); D. St. C. Black and E. Markham. *Effect of Chelation on the Synthesis of Organic Macrocycles, Rev. Pure and Appl. Chem.* **15**, 109 (1965); J. P. Collman. *Reactions of Ligands Coordinated with Transition Metals* in R. L. Carlin, *Transition Metal Chemistry* **2**, 2 (1966).

[7] D. H. Busch. *Helv. Chim. Acta*, Fasc. extraord. Alfred Werner **1967**, 174.

[8] A. W. Johnson. *Chemistry in Britain*, **1967**, 253.

[9] A. Eschenmoser, *Pure App . Chem.* **7**, 297 (1963); E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro and R. Scheffold. *Angew. Chem.* **76**, 393 (1964); *Angew. Chem. internat. Edit.* **3**, 490 (1964).

[10] H. Meerwein, G. Hinz, P. Holfmann, E. Kroning and E. Pfeil. *J. Prakt. Chem.* **147**, 17 (1937); H. Meerwein, E. Battenberg, H. Gold, E. Pfeil and G. Willfang. *J. Prakt. Chem.* **154**, 83 (1939).

[11] This method originated from the work on the synthesis of vitamin B_{12} (B. Golding and P. Löliger); *cf.* A. Eschenmoser, *XI Corso Estivo di Chimica*, 1967, Accademia Nazionale dei Lincei, Conferenze, 1968, 181; P. Löliger, Diss. ETH (1968); P. Wehrli, *Diss*, ETH (1968).

[12] P. Dubs. *Diss.* ETH (1968); *cf.* E. B. Knott, *J. chem. soc.* **1955**, 916.

[13] (a) A. Eschenmoser, R. Scheffold, E. Bertele, M. Pesaro and H. Gschwend. *Proceed. Royal Soc.* **A288**, 306 (1965); (b) I. Felner, A. Fischli, A. Wick, M. Pesaro, D. Bormann, E. L. Winnacker and A. Eschenmoser. *Angew. Chem.* **79**, 863 (1967), *Angew. Chem. Internat. Ed.* **6**, 864 (1967).

[14] (a) M. Dobler and J. D. Dunitz. *Acta Crystallographica* **21**, A 110 (1966); (b) J. D. Dunitz and E. F. Meyer jr.. *Proceed. Royal Soc.*. **A 288**, 324 (1965).

[15] B. Kamenar, P. F. Hoskins and C. K. Prout. *Proceed. Royal Soc.* **A 288**, 293 (1965); B. Kamenar, C. K. Prout, T. N. Waters and J. M. Waters. *J. chem. Soc.* **A 1967**, 2081.

[16] D. Borman, A. Fischli, R. Keese and A. Eschenmoser. *Angew. Chem.* **79**, 867 (1967); *Angew. Chem. Internat. Ed.* **6**, 868 (1967); E. L. Winnacker. *Diss.* ETH (1968).

[17] *cf.* D. Shemin and R. C. Bray. *Ann. New York Acad. Sci.* **112**, 615 (1964).

[18] J. I. Toohey. *Proc. Nat. Acad. Sci. USA* **54**, 934 (1965); *Feder. Proceed.* **25**, 1628 (1966).

[19] A. Fischli and A. Eschenmoser. *Angew. Chem.* **79**, 865 (1967); *Angew. Chem. Internat. Ed.* **6**, 866 (1967).

[20] R. B. Woodward and R. Hoffmann. *J. Am. Chem. Soc.* **87**, 395, 2511 (1965); R. Hoffmann and R. B. Woodward. *Accounts Chem. Res.* **1**, 23 (1968).

[21] Private communication from Professor P. Galen Lenhert.

[22] A. P. Johnson, P. Wehrli, R. Fletscher and A. Eschenmoser. *Angew. Chem.* **80**, 622 (1968); *Angew. Chem. Internat. Ed.* **7**, 623 (1968).