ROBERT ROBINSON LECTURE*

Post-B_{12} Problems in Corrin Synthesis

By A. Eschenmoser
EIDGENÖSSISCHE TECHNISCHE HOCHSCHULE ZÜRICH, CH-8006 ZÜRICH, SWITZERLAND

1 Introduction

To deliver a Robert Robinson Lecture is a great honour for me, and I would like to express my gratitude and appreciation to the members of the Council of the Chemical Society. I only regret that this must be the first in the series of Robert Robinson Lectures to be given without Sir Robert in the audience.

Organic chemists will not cease to be aware of Robinson's extraordinary contributions to their science; nor should they forget his continuing influence on their own thinking. When one but looks, this influence is easily detected in our own research, in fact, in work that is directly related to the topic of this lecture to be given in Sir Robert's memory.

Figure 1 is reproduced from a lecture presented at the I.U.P.A.C. Congress

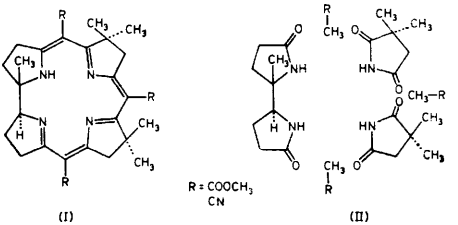


Figure 1 *Our work starts from the transparent formalism that a corrin derivative of type* (I) *is at the same oxidation level as the assembly of structures* (II). *From this point of view, the problem of constructing the double bond system of the corrin nucleus emerges as a reversal of formal hydrolytic processes, that is to say, as a series of stepwise carbon–carbon condensations between imide or lactam carbonyl groups and suitably activated carbon bridge components*

in London in 1963.[1] The reproduction illustrates the essence of the retrosynthetic concept that served as the starting point for the work which led to synthetic

* The present text is an extended version of the lecture delivered on April 9, 1976 at the Annual Meeting of the Chemical Society in Glasgow. The English of the manuscript has undergone extensive corrective measures by Professor C. Wintner (Haverford College, Pennsylvania, U.S.A.) who, fortunately for the author, chose to spend his sabbatical year at the E.T.H.

[1] A. Eschenmoser, 'Studies on the Synthesis of Corrins', *Pure Appl. Chem.*, 1963, **7**, 297.

corrins in 1964.[2] In retrospect, it is clear that it was specifically this concept of 'equality of oxidation levels' that steered our experiments at the very beginning into channels which were basically correct and fruitful.

Was this concept in synthetic planning new in its time? Not at all! In fact, it was brilliantly implemented half a century before by Robinson when he conceived (together with Lapworth) his unforgettable synthesis of tropinone[3] (see facsimile in Figure 2).

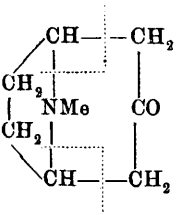


Figure 2 *By imaginary hydrolysis at the points indicated by the dotted lines, the substance may be resolved into succindialdehyde, methylamine, and acetone, and this observation suggested a line of attack of the problem which has resulted in a direct synthesis* (R. Robinson, 'A Synthesis of Tropinone', *J. Chem. Soc.*, 1917, 762)

Robinson's tropinone synthesis must be considered as one of the first—perhaps as *the* first—*modern* synthesis in organic chemistry; it is a solitary forerunner of the modern era of natural product synthesis that came to bloom so vigorously some 30 years later. Furthermore, it illustrates the process by which the science and art of organic synthesis was handed down to our time, a process exceeding the range of fully and clearly expressed teaching. For it has been almost exclusively by *example* that the art of synthetic planning has been passed on; only very recently have systematic efforts been launched to rationalize and articulate, and then to harness in computer programs[4] what had largely been beyond explicit knowledge before. 'Disconnecting carbon–carbon bonds' by 'imaginary hydrolysis' has always been an underlying part of the synthetic chemist's *intuitive* planning, just as it is today one of the basic elements of retrosynthetic analysis. This lecture presents a good opportunity to remember that it is to men like Robert Robinson that we owe such seemingly simple, but fundamental, ways of looking at target molecules in organic synthesis.

It is now just about four years ago that the decade-long joint efforts of Woodward's group at Harvard and ours at the E.T.H. came to their conclusion

[2] A. Eschenmoser, R. Scheffold, E. Bertele, M. Pesaro, and G. Gschwend, *Proc. Roy. Soc.*, 1965, **A288**, 306; 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.*, 1964, **76**, 393 (*Angew. Chem. Internat. Edn.*, 1964, **3**, 490).

[3] R. Robinson, *J. Chem. Soc.*, 1917, 762.

[4] E. J. Corey, *Pure Appl. Chem.*, 1967, **14**, 19; *Quart. Rev.*, 1971, **25**, 455.

in the execution of two total syntheses of cobyric acid[5] and hence, in a formal sense,[6] of vitamin B_{12}. Figure 3 recalls the event. The two approaches represent two vastly different types of corrin synthesis, the one culminating in closure between rings A and B through imino-ester–enamine condensation (A/B-route), the other in a final photochemical secocorrin→corrin cyclization between rings A and D (A/D-route).

Corrinoid synthesis based on (A→D) ring closures had been pioneered by Johnson and his school in their extensive work on the 'pyrrole approach' to synthetic corrinoids.[7,8] In view of what I am going to discuss in this lecture, I would like to point out here what Professor Johnson has made abundantly clear over the years, namely that his synthetic work on corrins was initiated and pursued always with one eye looking to the problem of vitamin B_{12} biosynthesis. The question 'How does Nature make the corrin nucleus of vitamin B_{12}?' has now shifted into the focus of interest in the chemistry of natural corrinoids, and we see it under very active investigation in a number of bioorganic laboratories.[9]

Can the work done on the *chemical* synthesis of vitamin B_{12} be extended to make a contribution to the problem of vitamin B_{12} *biosynthesis*? This question began to motivate and direct our activity in the field of corrin chemistry soon after the smoke on the battlefield of total synthesis had disappeared. The major stimulus came from the synthetic step shown in Figure 4,[10] the (A→D) ring closure in the photochemical route[5b] to cobyric acid.

The beauty of the spectral changes that accompany this reaction reflects

[5] (*a*) R. B. Woodward, *Pure Appl. Chem.*, 1968, **17**, 519; 1971, **25**, 283; 1973, **33**, 145; (*b*) A. Eschenmoser, *Quart. Rev.*, 1970, **24**, 366; 23rd I.U.P.A.C. Congress, Boston, *Pure Appl. Chem. Suppl.*, 1971, **2**, 69; *Naturwiss.*, 1974, **61**, 513; (*c*) W. Fuhrer, P. Schneider, W. Schilling, H. Wild, J. Schreiber, H. Maag, N. Obata, A. Holmes, and A. Eschenmoser, *Chimia* (*Switz.*), 1972, **26**, 320; W. Fuhrer, 'Totalsynthese von Vitamin B_{12}: der photochemische Weg', Thesis E.T.H. Zürich, Prom. Nr. 5158, Juris-Verlag, Zürich, 1973; H. Maag, 'Totalsynthese von Vitamin B_{12}: Dicyanocobalt(III)-cobyrinsäure-hexamethylester-f-amid', Thesis E.T.H. Zürich, Prom. Nr. 5173, Juris-Verlag, Zürich, 1973; W. Schilling, 'Totalsynthese von Vitamin B_{12}: Darstellung von Zwischenprodukten und partialsynthetische Endstufen', Thesis E.T.H. Zürich, Prom. Nr. 5352, Jursis-Verlag, Zürich, 1974.

[6] Cobyric acid from natural sources had been converted into vitamin B_{12} in 1960; see W. Friedrich, G. Gross, K. Bernhauer, and P. Zeller, *Helv. Chim. Acta*, 1960, **43**, 704; M. A. Wuonola and R. B. Woodward (personal communication) have recently (March 1976) accomplished this conversion starting with *synthetic* cobyric acid (prepared *via* the A/B-route), thus promoting the synthesis of vitamin B_{12} from a formal to an actual one.

[7] A. W. Johnson, 'Synthetic Approaches to the Corrin Nucleus' in 'Vitamin B_{12} and Intrinsic Factor', Enke Verlag, Stuttgart, 1962, p. 1.

[8] D. Dolphin, R. L. N. Harris, J. L. Huppatz, A. W. Johnson, and I. T. Kay, *J. Chem. Soc.* (*C*), 1966, 30; A. W. Johnson, *Chem. in Britain*, 1967, **3**, 253; A. W. Johnson and W. R. Overend, *Chem. Comm.*, 1971, 710; *J.C.S. Perkin I*, 1972, 2681; A. W. Johnson, *Chem. Soc. Rev.*, 1975, **4**, 1; *Phil. Trans. Roy. Soc.*, 1976, **B273**, 319.

[9] (*a*) A. I. Scott, *Tetrahedron*, 1975, **31**, 2639 and papers cited therein; (*b*) A. R. Battersby, M. Ihara, E. McDonald, J. R. Stephenson, and B. T. Golding, *J.C.S. Chem. Comm.*, 1973, 404; 1974, 458; (*c*) C. E. Brown, D. Shemin, and J. J. Katz, *J. Biol. Chem.*, 1973, **248**, 8015; (*d*) H. C. Friedman, 'Biosynthesis of Corrinoids' in 'Cobalamin, Biochemistry and Pathophysiology', ed. B. M. Babior, Wiley-Interscience, New York, 1975, p. 75.

[10] Figure 4 is taken from the thesis of W. Fuhrer.[5c] The cyclization of the cadmium complex leads (under the conditions indicated) to the metal-free corrin ligand; rapid decomplexation is induced by the buffered reaction medium as soon as the ligand has cyclized.

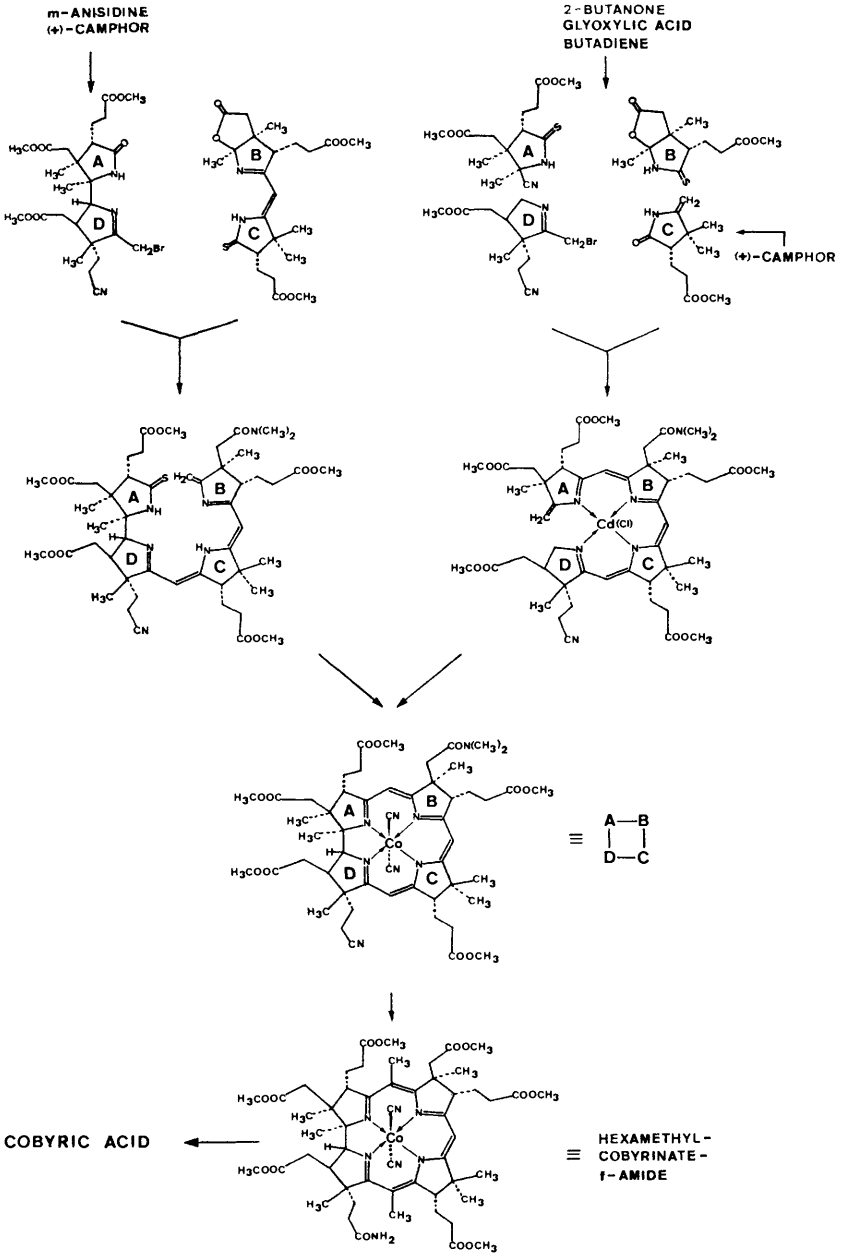

m-ANISIDINE
(+)-CAMPHOR
2-BUTANONE
GLYOXYLIC ACID
BUTADIENE
(+)-CAMPHOR
COBYRIC ACID
HEXAMETHYL-
COBYRINATE-
f-AMIDE

Figure 3

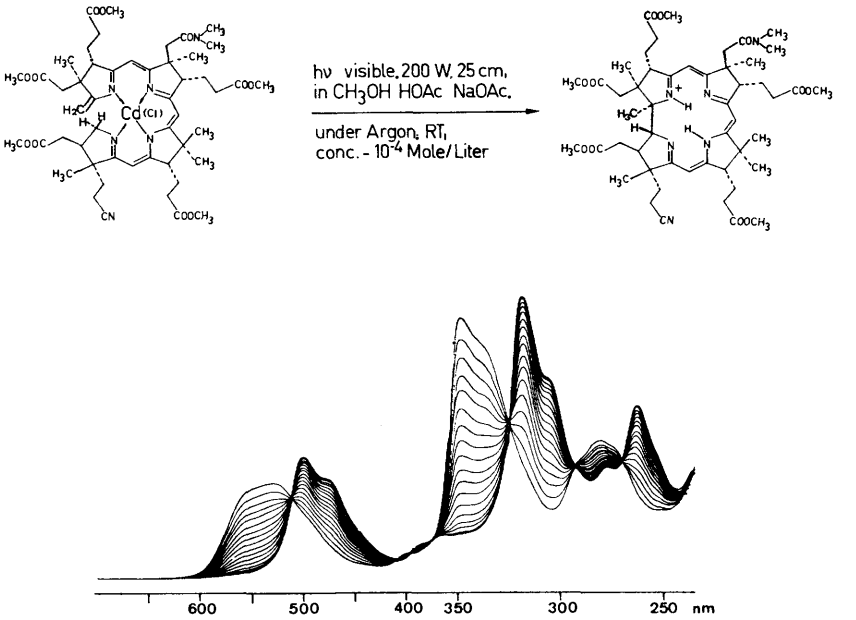


Figure 4

some of the delight that this synthetic step has given us. In the case of the conformationally flexible cadmium complex the reaction proceeds in high preparative yield and leads to the natural A/D-configuration of the corrin nucleus with a stereoselectivity of 95%.[10] Could this step have any structural relationship to what happens in cobyric acid biosynthesis? If Nature builds the corrin nucleus *via* an (A→D) ring closure—as had originally been postulated[7] and then chemically exemplified by Johnson in his work on the pyrrole road to corrinoids[8]—would Nature perform this ring closure before or after the methylation steps, or, perhaps, somewhere in between? What types of pathway are—from the purely chemical point of view—available to Nature for such a ring closure?

Such questions formed the background of our post-B_{12} work in corrin synthesis, and I would like to summarize in this lecture what we have found.[11] But as my story unfolds, let us keep something in mind. Of all that architecture and organic synthesis have in common, one thing is this: for the works of both, explicit goals are usually set, but after the works are done, their *raison d'être* often lies within themselves.

The three leading questions that directed this work are illustrated in Figure 5. They were:

[11] For recent advances and current problems in synthetic corrin chemistry, also consult the work of R. V. Stevens *et al.* on the 'isoxazole approach' towards synthetic corrinoids; see R. V. Stevens, *Tetrahedron*, 1976, **32**, 1599 and papers cited therein.

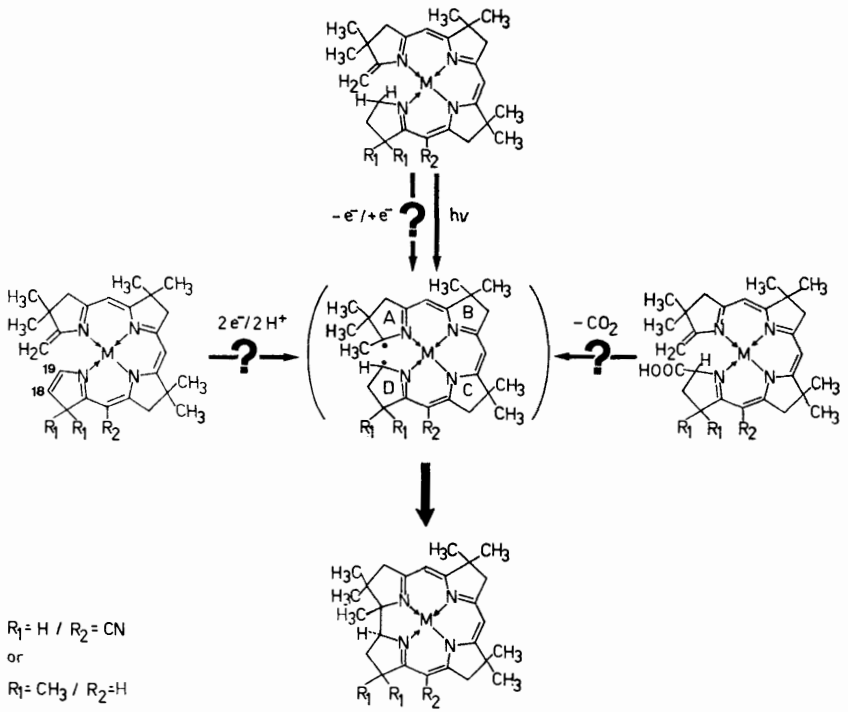


Figure 5

(i) Can the act of light excitation in the photochemical A/D-secocorrin→corrin cycloisomerization be replaced by a redox process in the dark?

(ii) Will Δ^{18}-dehydro-A/D-secocorrin complexes undergo a reductive (A→D) ring closure in acidic medium?

(iii) Is there a decarboxylative pathway from 19-carboxy-A/D-secocorrin complexes to corrin complexes?

The unifying feature of these three potential ring-closure processes is a common formal intermediate, namely the (constitutionally) same 16π-electron system that represents the presumed—but experimentally so far elusive—intermediate in the photochemical A/D-secocorrin→corrin cycloisomerization. The π-system of this 'intermediate' is a ($\pi \rightleftharpoons \sigma$)-valence tautomer of the corrin π-system, and it could be anticipated that any reaction sequence arriving at it would, by doing so, discharge itself by stereospecific formation of the corrin ring. It became evident that contemplation of the various possible ways of forming this '1,19-secocorrin biradical' actually constitutes a powerful conceptual approach for recognizing a whole variety of new potential routes to corrins.

Out of this variety we should—so we felt originally at least—concentrate experimentally on routes whose chance of being related to the biosynthetic route was not *a priori* nil. However, what all these investigations did *not* aim at was simply to extend the number of A/D-secocorrin→corrin ring closures for preparative purposes; it seemed unlikely that we would beat the method of light-induced ring closure, which had proven itself on numerous occasions to be by far the cleanest and most delightful step we had ever encountered in our work.

2 The Photochemical A/D-Secocorrin→Corrin Cycloisomerization[13,14]

Before presenting the results on the problem of a redox simulation of the photochemical A/D-secocorrin→corrin ring closure it seems appropriate to outline present knowledge about the photoreaction itself. Since 1969[12, 5b] this process has been the target of mechanistic investigations by Wild,[13] Bühler,[14a] and Neier[14b] in our laboratory, as well as the object of studies in the laboratories of Dunitz,[15] Quinkert,[16] and Thomson.[17] Figure 6 summarizes some of the relevant findings and conclusions.

The occurrence of the photocyclization is intimately dependent on the nature of the central metal ion. The ligand complexed with electronically 'innocent' metal ions such as lithium, magnesium, zinc, or cadmium rapidly cyclizes under

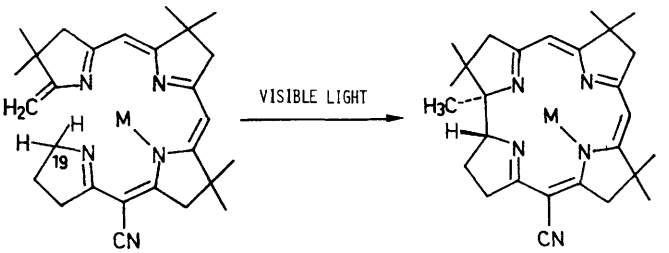


Figure 6 *The reaction proceeds with* M = Li, MgCl, ZnCl, CdCl, Pd^+, *or* Pt^+, *but not with* M = H, Cu^+, Ni^+, $Co(CN)_2$, *or* MnCl
The 19,19-*dideuterio*-Pd^{II} *complex cyclizes slower than the protium analogue; one deuterium atom migrates to the methylidene carbon*
Oxygen and specific triplet quenchers thwart the cyclization of the zinc and cadmium complexes
The cyclization of the zinc and cadmium complexes is strongly sensitized by the cyclization product (and by the synthetic precursor of the educt)

[12] Y. Yamada, D. Miljkovic, R. Wehrli, B. Golding, P. Löliger, R. Keese, K. Müller, and A. Eschenmoser, *Angew. Chem.*, 1969, **81**, 301 (*Angew. Chem. Internat. Edn.*, 1969, **8**, 343).

[13] H. J. Wild, 'Die Synthese von Corrin-Komplexen durch photochemische A/D-Cycloisomerisierung', Thesis E.T.H. Zürich, Prom. Nr. 4848, Juris-Verlag, Zürich, 1972.

[14] (*a*) N. Bühler, 'Synthetische und mechanistische Studien zum Aufbau corrinoider Metallkomplexe durch lichtinduzierte A/D-Cycloisomerisierung', Thesis E.T.H. Zürich, Prom. Nr. 5154, Juris-Verlag, Zürich, 1973; (*b*) R. Neier, Thesis E.T.H. Zürich (to appear 1977).

[15] M. Currie and J. D. Dunitz, *Helv. Chim. Acta*, 1971, **54**, 98.

[16] A. Syldatk and G. Quinkert, unpublished work; *cf.* A. Syldatk, Thesis Techn. Univ. Braunschweig, 1974.

[17] M. Gardiner and A. J. Thomson, *J.C.S. Dalton*, 1974, 820.

strict exclusion of oxygen in essentially quantitative yields at room temperature; the complexes of the heavy transition-metal ions platinum and palladium (quantum yield 0.008 in chloroform at 20 °C[16,14a]) cyclize also, but more slowly; however, the reaction does not take place at all with the complexes of the light transition-metal ions cobalt(III), nickel(II), or copper(II).[13] These metal ions with unfilled *d*-shells are apparently very effective in quenching the excitation of the chromophore system.[17] The rate-limiting step in the transformation is the sigmatropic shift of a hydrogen atom from the methylene group (position 19) in ring D to the exocyclic methylidene carbon at ring A. This has been spectroscopically documented in the case of the specifically labelled 19,19-dideuteriosecocorrin palladium complex, which cyclized approximately seven times more slowly than the protium analogue.[14a] Oxygen and specific non-singlet quenchers[18] thwart the cyclization of the zinc and cadmium complexes. The outcome of one such experiment is illustrated in Figure 7.[14b] Action spectra[14] (see Figure 8) as well as kinetic analyses revealed that the cyclization of the zinc and the cadmium complexes proceeds predominantly *via* sensitization by the cyclization product. This phenomenon is accompanied by another which is equally remarkable, namely that no luminescence could be detected with secocorrin complexes such as those of magnesium, zinc, and cadmium[16] under conditions where the corresponding corrin complexes fluoresce strongly.[17] The origin of this difference in luminescence behaviour is not simply to be related to the higher rigidity of the macrocyclic ring system of the corrin compared with the secocorrin system; the 1-cyano-1-methyl derivative of the cadmium secocorrin complex (see Figure 9) fluoresces even more efficiently than the corresponding corrin complex. We are left with the idea that it may be specifically the structural element of the methylidene double bond at ring A of the secocorrin system which causes the excited chromophore to lose its singlet excitation energy by non-radiative decay before a structurally identifiable photochemical process, an emission, or an intersystem crossing can set in.[19]

The combined observations made so far on the cyclization and luminescence properties of the secocorrin and corrin complexes make sense if one assumes that the crucial sigmatropic hydrogen shift proceeds while the secocorrin chromophore system is in a triplet state;[14] this state appears *not* to be populated *via* light excitation of the secocorrin complex, because a non-radiative internal conversion process (involving a non-isomerizing deformation of the methylidene group?) of the lowest singlet excited state occurs too rapidly. However, the photoreactive state appears to be efficiently populated *via* triplet-state transfer from the cyclization product. The lifetime of the lowest excited singlet state of the corrin complex—in contrast to that of the secocorrin system—apparently

[18] *E.g.* 1,4-Dichloro-2,3-diazabicyclo[2,2,2]oct-2-ene 2,3-dioxide; *cf.* E. F. Ullman and P. Singh, *J. Amer. Chem. Soc.*, 1972, **94**, 5077; P. Singh and E. F. Ullman, *ibid.*, 1976, **98**, 3018.

[19] The non-radiative decay is not brought about by a simple rotation around the axes of the methylidene double bond: recent experiments by Neier[14b] in our laboratory with methylidene-monodeuteriated cadmium complexes revealed no evidence for an efficient light-induced *exo–endo*-isomerization.

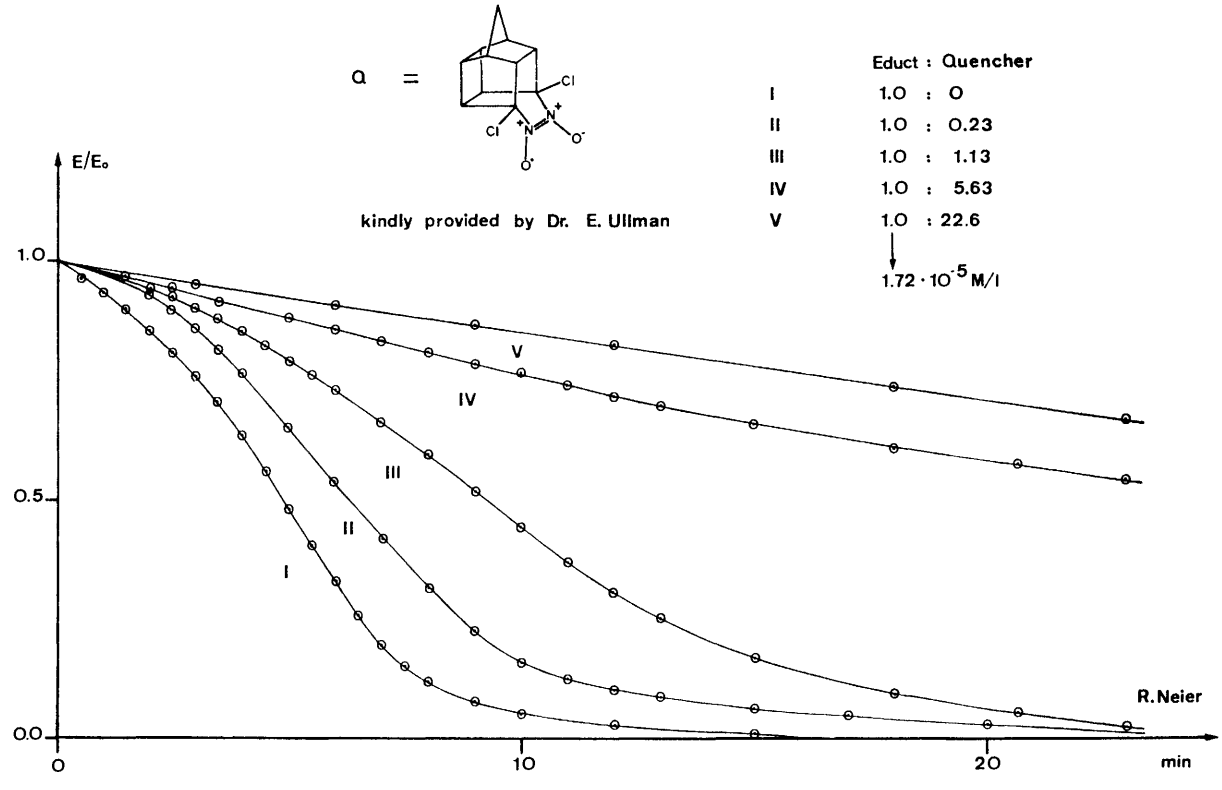

Cyclisation of Cd-complex in the presence of Q (EtOH / RT / 510 nm)
Q =
Cl
Cl
N+
N+
O-
O
kindly provided by Dr. E. Ullman
Educt : Quencher
I 1.0 : 0
II 1.0 : 0.23
III 1.0 : 1.13
IV 1.0 : 5.63
V 1.0 : 22.6
1.72 · 10-5 M/l
E/E0
1.0
0.5
0.0
0
10
20
min
R.Neier
I
II
III
IV
V

Figure 7

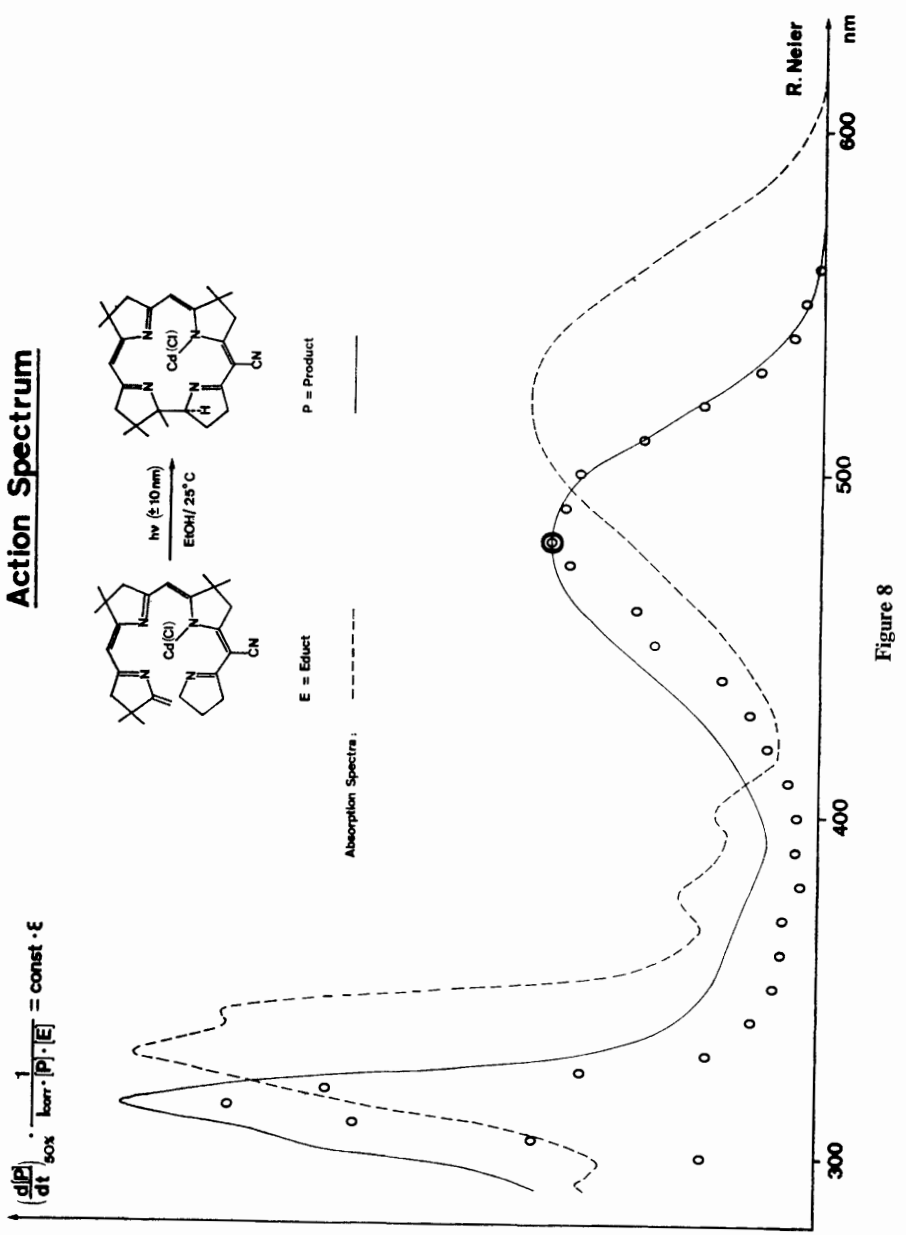
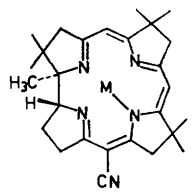
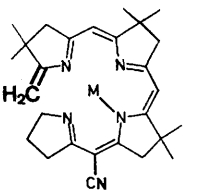

Action Spectrum
$\left(\frac{d[P]}{dt}\right)_{sox} \cdot \frac{1}{k_{corr} \cdot [P] \cdot [E]} = \text{const} \cdot \varepsilon$
Cd(Cl)
CN
hν (± 10 nm)
EtOH/ 25°C
E = Educt
P = Product
Absorption Spectra:
R. Neier
300
400
500
600
nm

Figure 8



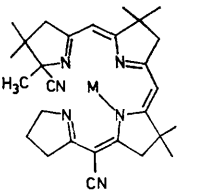
M = H(H⁺)
Li
Mg(Cl)
Zn(Cl)
Cd(Cl)

fluoresce and
(M=Zn, Cd) sensitize
cyclisation



M = Mg(Cl)
Zn(Cl)
Cd(Cl)

do not
fluoresce



M = Cd(Cl)

fluoresces and
sensitizes
cyclisation

Figure 9

is long enough to allow strong fluorescence as well as intersystem crossing to the triplet[20] and, eventually, sensitization of the secocorrin reactant.

The crude overall picture which we presently have of the photochemical A/D-secocorrin→corrin cycloisomerization (see Figure 10) indicates a much higher complexity of this synthetic step than we originally envisaged. It may even be that a good portion of luck kindly assisted our original finding[13] that secocorrinoid zinc, cadmium, and magnesium complexes cyclize smoothly to corrins: today we know that, at least in the cadmium series, it is not only the closed

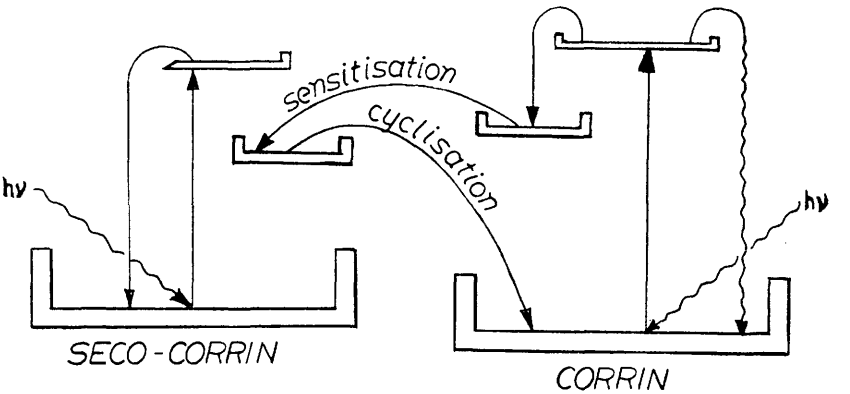


Figure 10

[20] Phosphorescence (in addition to fluorescence) of the cadmium(II)–corrin triplet has been detected by Thomson[17] at 77 K.

cyclization product that sensitizes the reaction but also the open 1-cyano-1-methylsecocorrin complex (see Figure 9), which has a methyl group instead of a methylidene group on ring A. Traces of compounds that have the methylidene double bond in protected form may well play a preparatively important role in the cyclization of those complexes which show an 'induction period'.[21] Such traces may have survived from the preparation of the 1-methylidene-secocorrin complexes[22] and/or they may be formed from them by addition of HX molecules (X = OH, OR, *etc.*) to the (highly nucleophilic and—after protonation —electrophilic) methylidene double bond. The preparative success of the photochemical cyclization of 1-methylidene-1,19-secocorrin complexes with closed-shell metal ions seems to hinge not only on the fact that these compounds create their own sensitizers as the forward reaction proceeds, but also on their ability to give rise to (or to contain) traces of contaminants which, by virtue of their also being sensitizers, bring the cyclization process off the ground. Quite obviously, in the field of secocorrin photochemistry there is no dearth of questions which await and deserve additional and more quantitatively oriented experimental investigation.

3 Studies on a Redox Simulation of the Photochemical A/D-Secocorrin→Corrin Ring Closure[23,24]

Our experimental involvement in the redox chemistry of A/D-secocorrins originated with the belief that 1-methylidene-1,19-secocorrin complexes might represent ideal systems for demonstrating the preparative feasibility of what one might call the redox simulation of a photochemical reaction in the dark (Figure 11).

Recombination of a secocorrin cation radical with an electron from a strong reductant is not necessarily expected to lead back directly to the secocorrin in its electronic ground state; the electron on its way to that ground state may more probably make its 'first halt' in a lowest excited state of the π-system and thereby induce those structural changes which one observes after a corresponding photoexcitation or photosensitization of the secocorrin complex. That electronically excited π-states can be accessible through alternating one-electron oxidation/reduction processes is known, as shown by the phenomenon of electroluminescence;[25] a corresponding type of 'no-light photochemistry' must necessarily exist. Any type of redox process that amounts to the substitu-

[21] Such 'induction periods' have been shown to occur in the cyclization of the chloro-zinc, chloro-cadmium, and chloro-magnesium complexes, but *not* with the (much more slowly cyclizing) palladium and platinum complexes.[13–15] The cyclization of the palladium complex is likewise *not* quenched by oxygen as the former cyclizations very efficiently are.

[22] 1-Cyano-1-methylsecocorrin complexes are intermediates in the synthesis of the 1-methylidenesecocorrin complexes.[12,13]

[23] B. Kräutler, A. Pfaltz, R. Nordmann, K. O. Hodgson, J. D. Dunitz, and A. Eschenmoser, *Helv. Chim. Acta*, 1976, **59**, 924; K. O. Hodgson and J. D. Dunitz, *Helv. Chim. Acta*, 1976, **59**, 1898; R. Nordmann, Thesis E.T.H. Zurich (to appear).

[24] B. Kräutler, 'Versuche zu einer Redox-Simulation der photochemischen A/D-Secocorrin→Corrin-Cycloisomerisierung', Thesis E.T.H. Zürich (to appear in 1977).

[25] D. M. Hercules, *Science*, 1964, **145**, 808; *Accounts Chem. Res.*, 1969, **2**, 301; R. E. Visco and E. A. Chandross, *J. Amer. Chem. Soc.*, 1964, **86**, 5350.

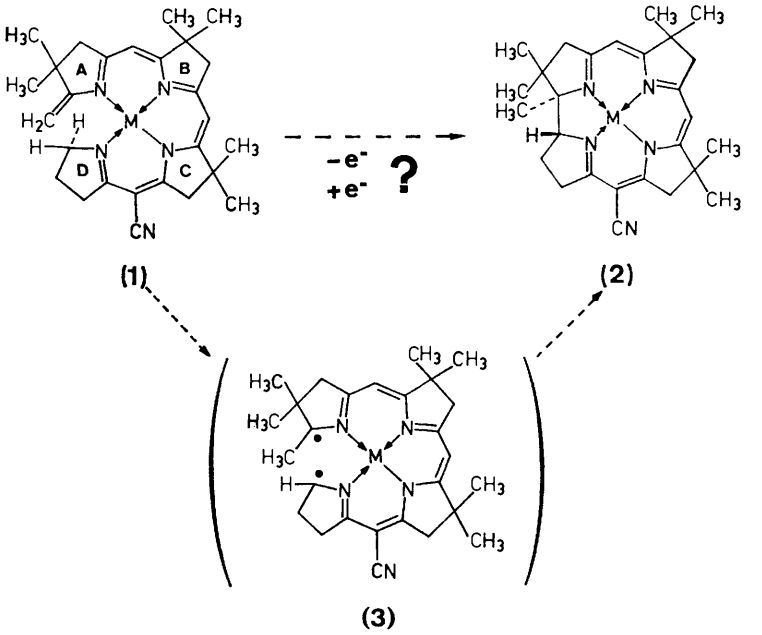
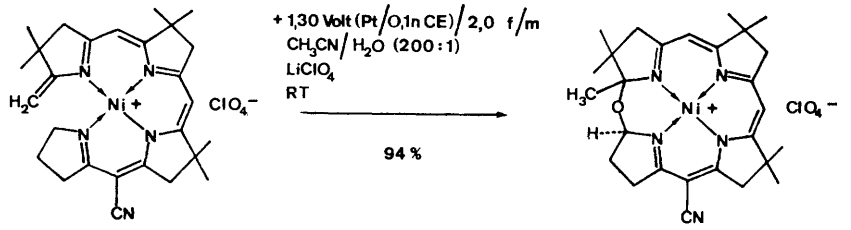


Figure 11

tion of a light excitation step by dark reactions would *per se* deserve attention, not least with respect to its potential in biosynthetic chemistry.

The expectation expressed in Figure 11 was eventually substantiated experimentally, but in a manner that was different from the one originally envisaged. Whereas the initial hypothesis induced our electrochemical studies on secocorrins, it did not really come to its crucial experimental test, because of the surprising experimental findings which interfered and eventually led to the results summarized in Figure 12. The techniques and theory of electrochemistry were introduced into our laboratory by Kräutler whose work this is,[24] and who deserves special acknowledgement for it.

Electrochemical oxidation of the nickel(II) 1,19-secocorrinate in *moist* acetonitrile solution produces, in a two-electron oxidation process under the conditions indicated in Figure 12, the cyclized secocorrin oxide in almost quantitative yield. The structure of the oxidation product was determined in an *X*-ray analysis by Hodgson and Dunitz.[23] Labelling experiments on the mechanism of this reaction (see Figures 12 and 13) convincingly showed the A/D-bridge oxygen to stem from water. No incorporation of water protons into the product occurs; instead, one of the hydrogen atoms of the methylene group at ring D position 19 cleanly moves to the methylidene carbon at ring A during the oxidation. Cyclic voltammetry of the reaction of both the 19,19-diprotium and the



in "dry" CH_3CN : yield < 24 %

in $CH_3CN/H_2{}^{18}O$ (200:1) : complete incorporation of ^{18}O

in CH_3CN/D_2O (20:1) : no D-incorporation detectable (NMR, MS)

Figure 12

19,19-dideuterium complexes (see Figures 14 and 15) revealed that the crucial hydrogen transfer proceeds as the rate-determining step after the transfer of the first electron; the evidence for this is as follows.[26]

The oxidation wave of the protium complex at room temperature and low potential sweep rate is irreversible. It shows a peak potential around +1.25 V, corresponding approximately to the consumption of two electrons, and is accompanied by the oxidation wave (+1.43 V) of the oxidation product, *i.e.* the oxido-complex (see Figure 14). At high potential sweep rate this accompanying wave of the oxidation product is not present, and the peak current corresponds to the transfer of one electron only; the same is observed at low potential sweep rate *and* low temperature. The behaviour of the 19,19-dideuterium complex under identical conditions is characteristically different: at room temperature and low potential sweep rate the accompanying product wave is hardly discernible, and the peak current is much less than in the case of the diprotium complex. This peak-current isotope effect[27] at room temperature is operative over a whole range of potential sweep rates (see Figure 15); not surprisingly, it tends to disappear at very high rates and—over the whole range of rates—at low temperature.

A tentative skeleton for the mechanism of formation of the secocorrinoid oxide complex is drawn in Figure 16. The crucial step of the sequence, the sigmatropic cation radical isomerization, would be followed by a fast nucleo-

[26] For a more detailed discussion and characterization of the mechanism of the electrochemical oxide formation see refs. 23 and 24.

[27] *Cf.* also the isotope effect in the preparative yield of the dideuterio-oxide complex (Figures 12 and 13).

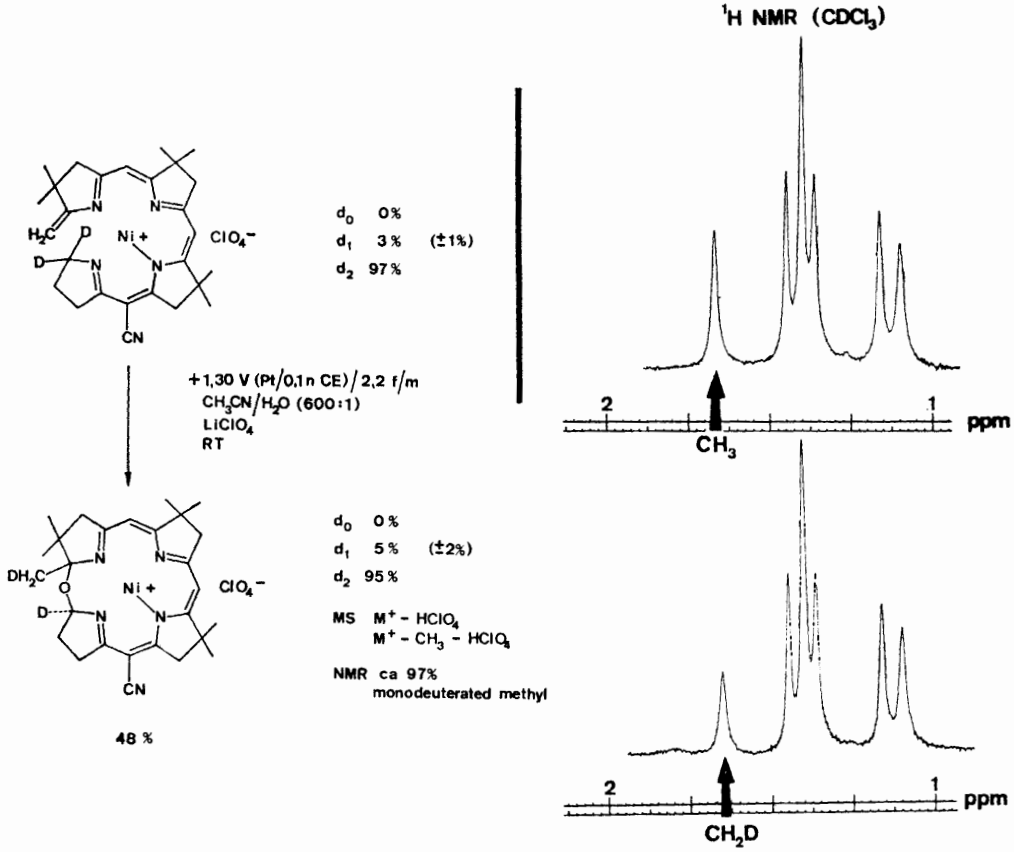

^{1}H NMR ($CDCl_3$)
d_0 0%
d_1 3% (±1%)
d_2 97%
+1,30 V (Pt/0,1n CE)/2,2 f/m
CH_3CN/H_2O (600:1)
$LiClO_4$
RT
d_0 0%
d_1 5% (±2%)
d_2 95%
MS $M^+ - HClO_4$
$M^+ - CH_3 - HClO_4$
NMR ca 97%
monodeuterated methyl
48 %
2
1
ppm
CH_3
2
1
ppm
CH_2D

Figure 13

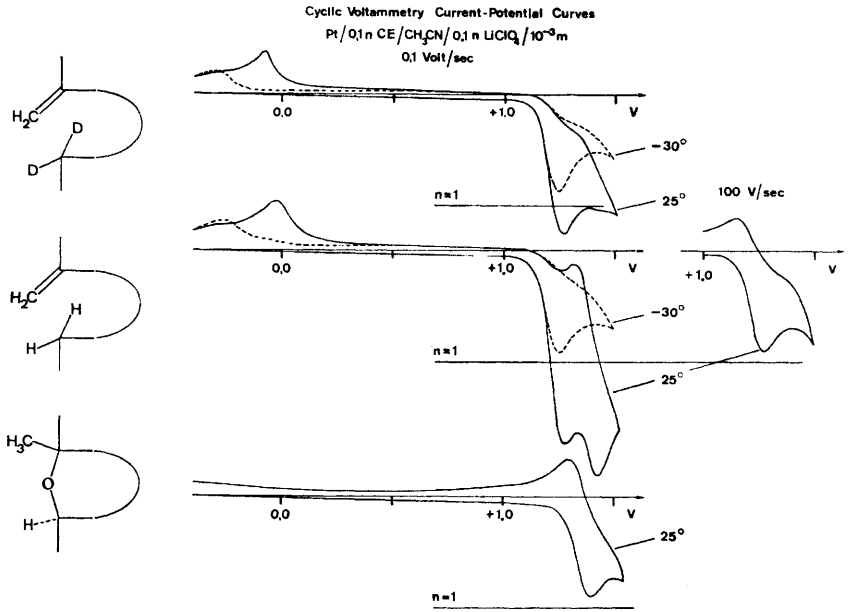


Figure 14

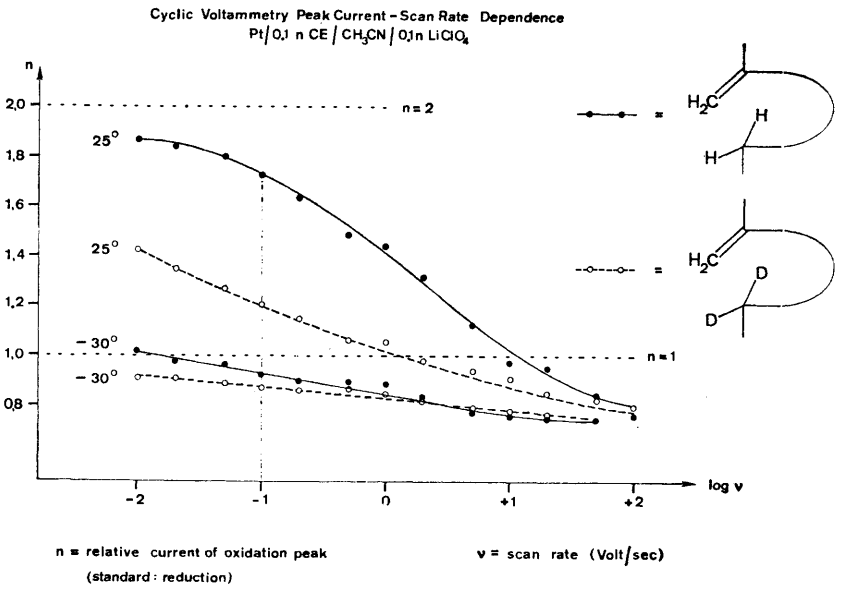


Figure 15

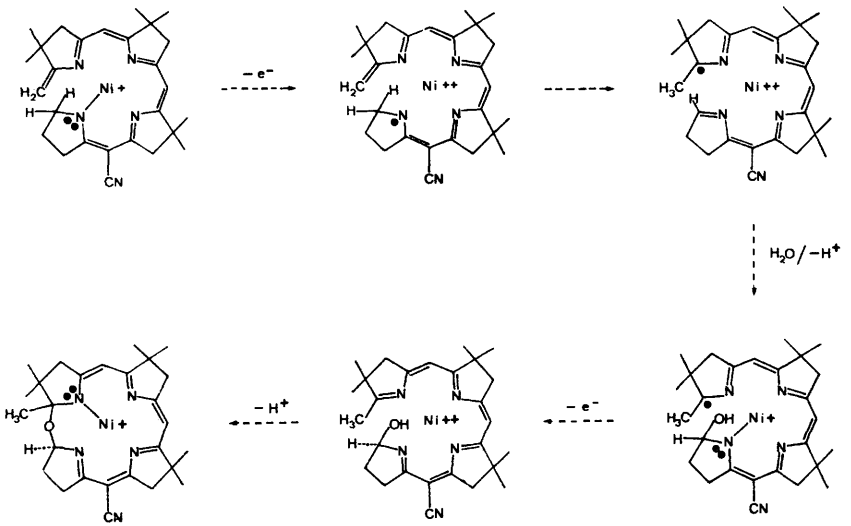


Figure 16

philic addition of a water molecule and then (after loss of an oxygen-bound proton) by the second electron transfer; a final internal nucleophilic addition would close the oxide ring. The next more detailed version of this scheme would—according to recent observations—have to include (reversible) dimerization equilibria involving the two isomeric cation radicals. Derivatives of a methylidene–methylidene dimer of the initial radical have in fact been isolated in preparative oxidation experiments at -30 °C in 'dry' acetonitrile; the assumption of a fast (but reversible) formation of such dimers seems to provide a rationale for the two curious aspects of the cyclic voltagrams, namely the irreversibility characteristics of the oxidation wave at -30 °C where no hydrogen shift occurs and the occurrence of the back-reduction wave around 0 to -0.3 V.[26]

The formation and sigmatropic rearrangement of a secocorrinoid cation radical are specific neither for the nickel(II) complex nor for the method of electrochemical oxidation. Figure 17 shows the outcome of oxidation experiments with trisphenanthrolineiron(III) perchlorate ($E_{\frac{1}{2}} = +0.99$ V);[23] they gave the same oxide complex as the electrochemical oxidation. Furthermore, the electrochemical formation of an oxide complex analogous to the one in the nickel(II) series has also been observed with the corresponding chlorozinc(II) complex.[24]

The easy accessibility of the nickel(II) secocorrinate oxide would appear to make this compound a potentially useful intermediate for a synthetic entry into dehydrocorrinoids. However, explorative experiments carried out in conjunction with the problem of a synthesis of Δ^{18}-dehydrosecocorrin complexes (see Section 4) showed that the oxide bridge is quite inert towards acid-catalysed ring-opening. Until now, the most valuable experiment in this series was the

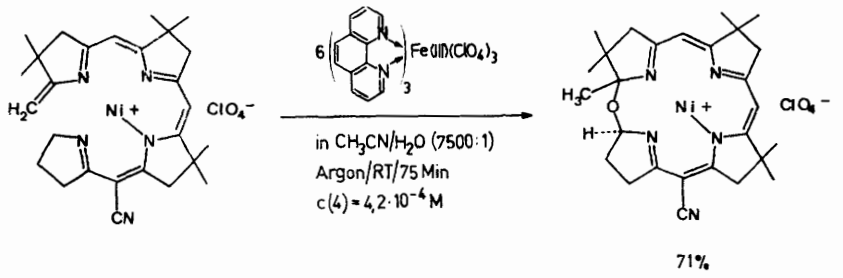


Figure 17

thermolytic treatment of the chloride salt[28] under the conditions indicated in Figure 18. It led to the neutral nickel(II) D-pyrrolocorrinate, a new member

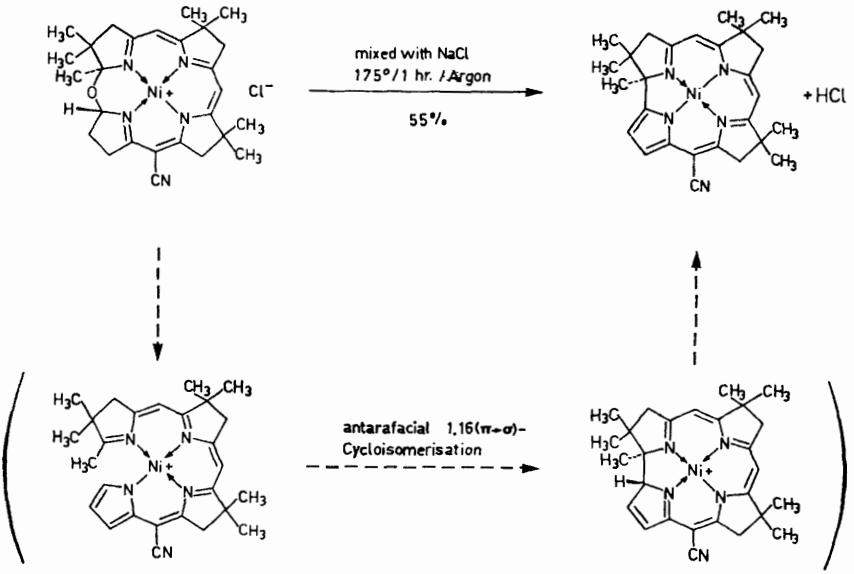


Figure 18

in the family of dehydrocorrins obtained synthetically so far.[29] The reaction quite probably proceeds *via* the two intermediates indicated in the Figure; thus, it may represent the first model transformation for the electrocyclic

[28] The chloride ion expectedly acts as a weak base in this reaction; the perchlorate complex remains unchanged at the same temperature.

[29] The structure has been confirmed in an *X*-ray analysis carried out in the laboratory of Prof. K. O. Hodgson, Stanford University.

1,16-($\pi \rightarrow \sigma$)-cycloisomerization that recently has been explicitly proposed by Scott[30] to be the type of ring closure that might occur in the biosynthesis of vitamin B_{12}.

As the story of oxide formation unfolded, it became clear that the unforeseen cation radical rearrangement, having denied us our original version of a redox ring closure, now offered an alternative opportunity (see Figure 19). If water

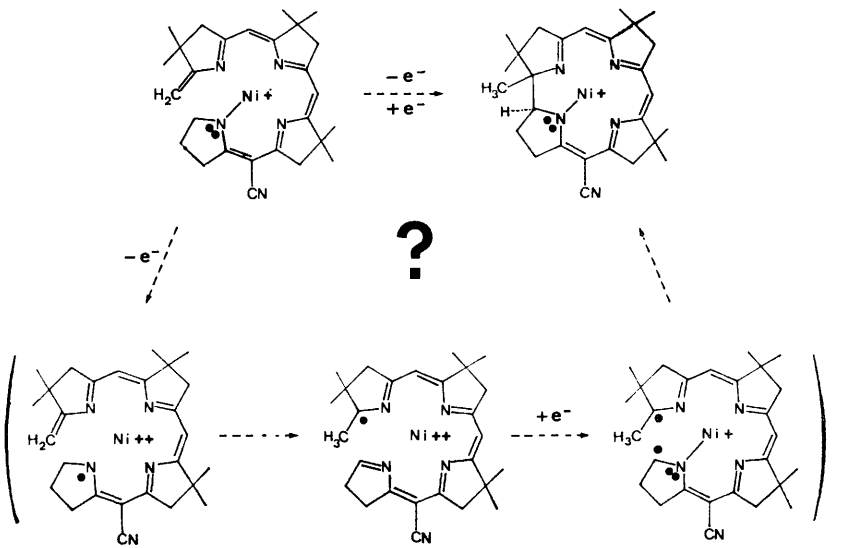


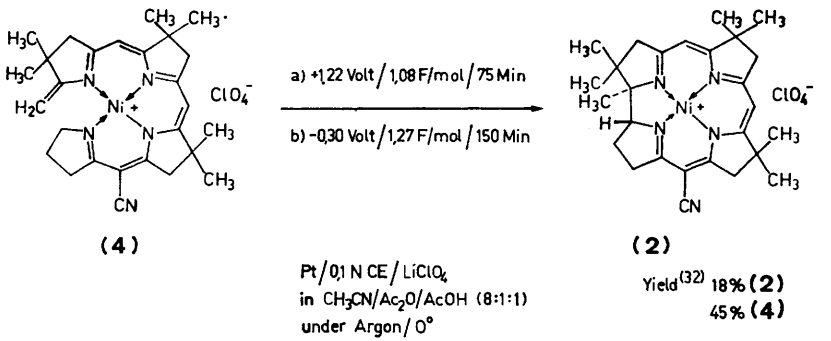
Figure 19

(or any comparable nucleophile) were rigorously excluded from the medium in which the secocorrin cation radical forms, it might be possible to return one electron to the rearranged cation radical *subsequent* to the hydrogen shift. The formal result of such a reduction step would again be the legendary '1,19-secocorrin biradical'. Therefore, its valence tautomer, the cyclic corrin, should become the final product of the oxidation–reduction sequence.

Preparative electrochemical oxidation of nickel(II) secocorrinate in the anhydrous solvent mixture (acetonitrile–acetic anhydride–acetic acid) consumed—in contrast to the analogous experiments in moist acetonitrile—only about one electron equivalent. Subsequent reduction led to a reaction mixture from which both starting material and the corresponding corrin complex[31] were isolated in crystalline form (see Figure 20). This result demonstrates that a redox simulation

[30] A. I. Scott, *Heterocycles*, 1974, **2**, 125; *Science*, 1974, **184**, 760; *Tetrahedron*, 1975, **31**, 2639.

[31] Note that the nickel(II) secocorrinate does *not* cyclize under the influence of light; *cf.* Section 2 and refs. 5*b* and 12.



(4) (2)

Figure 20

of the photochemical A/D-secocorrin→corrin cycloisomerization is in fact experimentally feasible. However, we have good reasons (see above) to reckon with the occurrence of a reaction network in this oxidation–reduction process that is more complex than would appear from the straightforward reaction sequence of the working hypothesis drawn in Figure 19. More work on this problem is necessary.[32]

What is the takehome lesson of these electrochemical studies on A/D-secocorrin complexes? We think it to be the finding that the 1,16-sigmatropic hydrogen shift, the crucial process in the photochemical A/D-secocorrin→corrin cycloisomerization, is not a specific property of the electronically excited π-system; it seems to occur comparably well in the corresponding cation radical. In a way, it appears that the parallel in chemical behaviour between the photoexcited secocorrin and the secocorrin cation radical can lessen our ignorance regarding the nature of the photochemical process. Confining ourselves to a qualitative frontier orbital point of view, we would *now* say that the hydrogen shift in the photoreactive excited state of the secocorrin is more an affair of the π-system's half-emptied HOMO than of its half-filled LUMO.[33] In boldly venturing into an analogy between the photochemical and the redox versions of the cyclization reaction we would assign to the photoexcited LUMO electron the function of a powerful (intramolecular) reductant 'for the second step', and as one of the major differences between the two versions we would propose the absence (?)

[32] The reappearance of starting material in the reaction product is presumably related to the (thermally and reductively) reversible dimerizations of the cation radicals involved. Recently, Kräutler has been able to raise the yield of corrin to 40% (in addition to 48% starting material) by replacing the acetic anhydride–acetic acid mixture by acetic anhydride–trifluoroacetic acid.

[33] The opposite would seem to be indicated by a formalistic application of the Woodward–Hoffmann rules to the photochemically induced hydrogen shift. HMO estimates[14,24] indicate that the shift would be strongly *endothermic* if it had to start from the secocorrin's electronic ground state, *exothermic* from a secocorrin excited state, but essentially *isothermic* in the secocorrin cation radical [the rise of the singly occupied HOMO (π_8)—see Figure 21—is approximately compensated by a fall of the doubly occupied orbital π_4].

of a time gap between the 'oxidation step' and the 'reduction step' when the reaction is induced by photosensitization (see Figure 21). Would there, perhaps, be intuitional strength to be gained for the synthetic organic chemist were he more disposed to relate the 'physical' phenomena of photoexcitation and sensitization with the 'chemical' phenomenon of oxidation–reduction?

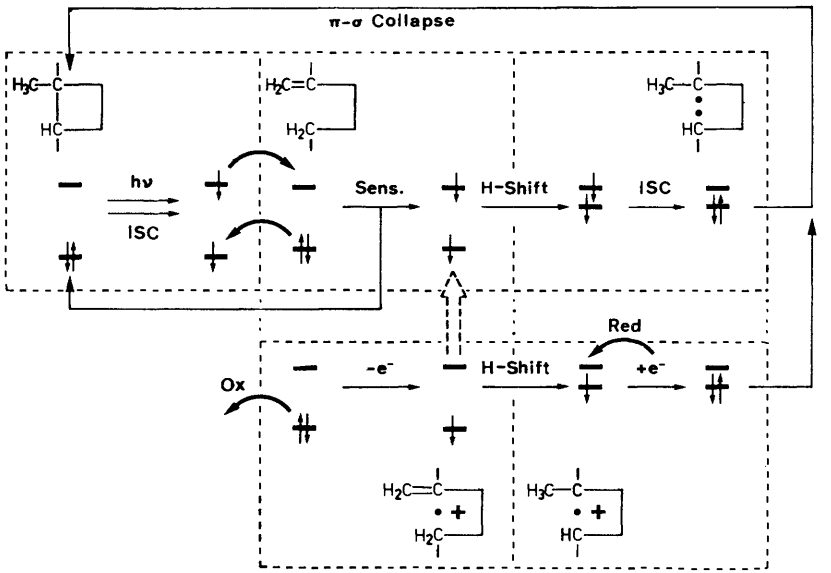


Figure 21

4 Synthesis and Reductive Cyclization of a Δ^{18}-Dehydro-1,19-secocorrin Complex[34,35]

If one analyses the question of how Nature would have to proceed in a biosynthesis of cobyric acid in order to go from urogen III (see discussion in Section 5) to the corresponding methylated A/D-secocorrin system of the type discussed in the foregoing section, one easily comes across the Δ^{18}-dehydro-A/D-secocorrin structure as one lying along the route of such a hypothetical reaction sequence.[36] That a dehydrosecocorrin system could give rise to the '1,19-secocorrin biradical' by reduction in a protonating medium has been indicated in the Introduction (see Figure 5); Figure 22 shows this in more detail. Protonation at the methylidene carbon (known to be the preferred site of nucleophilic attack in A/D-secocorrins[14]) followed by the delivery of the first electron, protonation at the other end position of the chromophore (position 18), and finally

[34] A. Pfaltz, B. Hardegger, P. M. Müller, S. Farooq, B. Kräutler, and A. Eschenmoser, *Helv. Chim. Acta*, 1975, **58**, 1444.
[35] A. Pfaltz, Thesis E.T.H. Zürich (to appear).
[36] *Cf.* Figure 31 (p. 408).

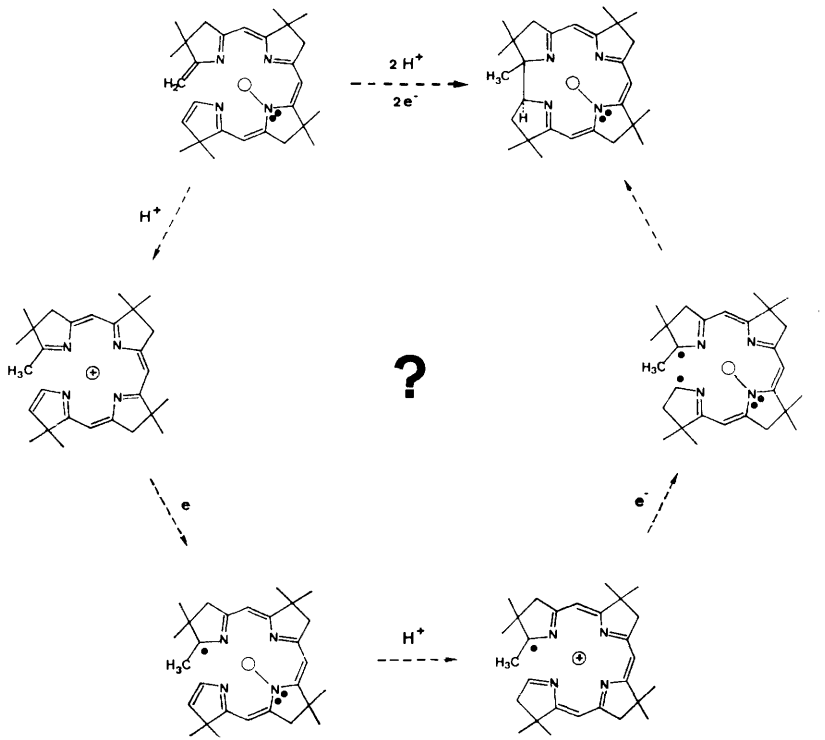


Figure 22

transfer of the second electron: such could be the sequence of events that would constitute a reductive Δ^{18}-dehydro-A/D-secocorrin→corrin cyclization.

The experimental test of this working hypothesis required a preparation of Δ^{18}-dehydro-A/D-secocorrins, a task that turned out to be more difficult than presumed;[37] it eventually found a satisfactory and informative solution in the *de novo* synthesis summarized in Figure 23.

The special variant of the method of sulphide contraction, which was used in this synthesis to couple the AB- with the CD-component, stems from the work on the photochemical route of the B_{12} synthesis[5b,5c] and had already been applied to simpler corrinoid systems at an earlier occasion.[38] The novel aspect of the reaction sequence is the use of the reagent *trans*-2,3-diphenyl-1-aminoaziridine[39]

[37] B. Hardegger, 'Untersuchungen in der Corrinreihe und eine neue Methode zur Reduktion der Lactamgruppe', Thesis E.T.H. Zürich, Prom. Nr. 5347, Juris-Verlag, Zürich, 1974.

[38] E. Götschi, W. Hunkeler, H.-J. Wild, P. Schneider, W. Fuhrer, J. Gleason, and A. Eschenmoser, *Angew. Chem.*, 1973, **85**, 950 (*Angew. Chem. Internat. Edn.*, 1973, **12**, 910); P. M. Müller, S. Farooq, B. Hardegger, W. S. Salmond, and A. Eschenmoser, *Angew. Chem.*, 1973, **85**, 954 (*Angew. Chem. Internat. Edn.*, 1973, **12**, 914).

[39] D. Felix, R. K. Müller, U. Horn, R. Joos, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, 1972. **55**, 1276.

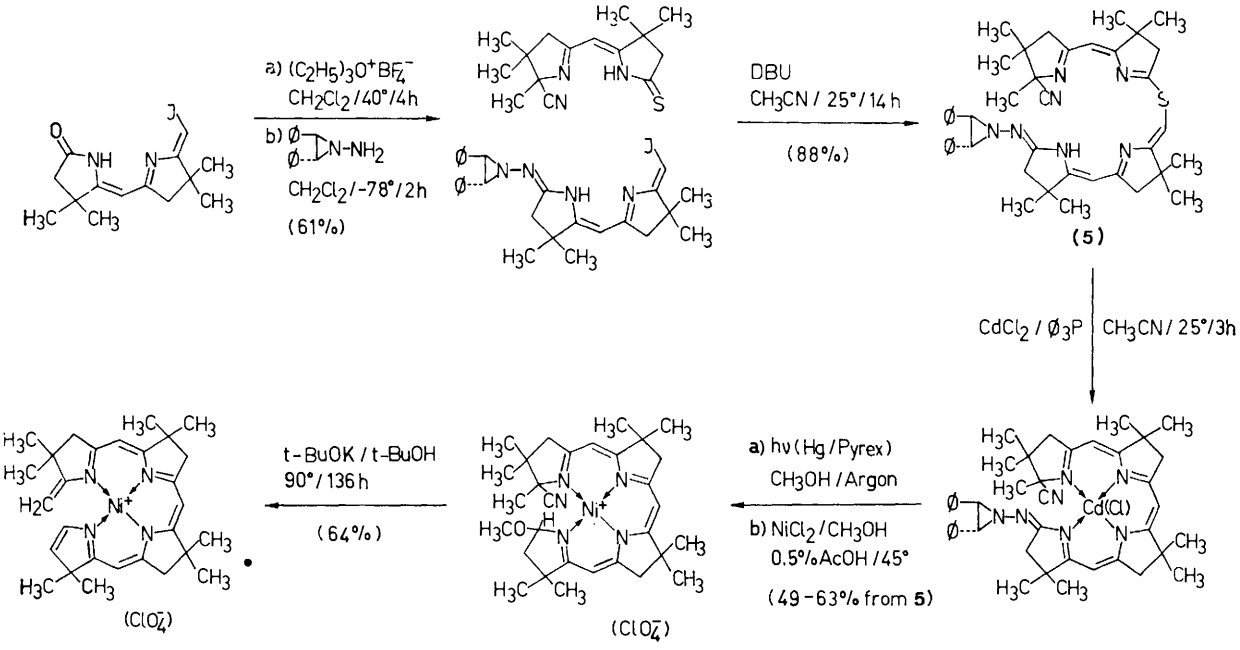

a) $(C_2H_5)_3O^+BF_4^-$
CH_2Cl_2 / 40° / 4h
b) Ø-N-NH$_2$
CH_2Cl_2 / -78° / 2h
(61%)
DBU
CH_3CN / 25° / 14 h
(88%)
(5)
$CdCl_2$ / $Ø_3P$ | CH_3CN / 25° / 3h
a) hν (Hg / Pyrex)
CH_3OH / Argon
b) $NiCl_2$ / CH_3OH
0.5% AcOH / 45°
(49 - 63% from 5)
t-BuOK / t-BuOH
90° / 136 h
(64%)
(ClO_4^-)
(ClO_4^-)

Figure 23

to achieve the reduction of the lactam function in ring D. Irradiation of the tetracyclic amidrazone cadmium complex with u.v. light in methanol at room temperature led to smooth elimination of molecular nitrogen and stilbene, and left a semi-reduced product that was isolated and crystallized as the two diastereomeric 19-methoxy-1,19-secocorrin-nickel(II) complexes. This photolytic reduction process is a variant of the Bamford–Stevens[40] reaction; it may serve a purpose in delicate cases where more conventional methods for the semi-reduction of lactam or imide functions fail, as was the case in the present example.[41]

The nickel(II) Δ^{18}-dehydro-1-methylidene-1,19-secocorrinate is indeed easily and specifically protonated at the methylidene carbon[42] and displays, as expected, a much less negative reduction potential in the presence of acids than in unprotonated form (see Figure 24). Electrochemical reduction in acetonitrile in the

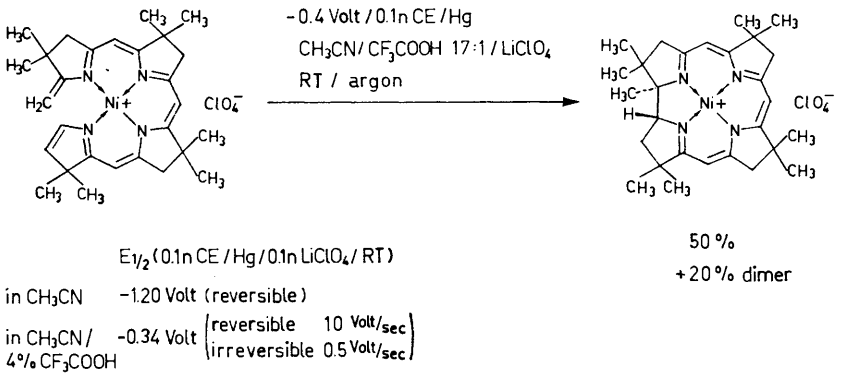


Figure 24

presence of trifluoroacetic acid led to the consumption of slightly less than two electron equivalents and smoothly gave the corresponding corrin complex; the concomitant formation of a corrinoid dimerization product[35] restricted the yield. No further experiments in support of the mechanistic scheme of Figure 22 have been carried out; the preparative result obtained amply fulfilled the purpose of the investigation, namely to show that there is indeed a smooth reductive pathway from Δ^{18}-dehydrosecocorrins to corrins.

5 Decarboxylative Cyclization of a Nickel(II) A/D-Secocorrinate-19-carboxylic acid[35]

While the work discussed above was proceeding, major developments occurred in the field of vitamin B_{12} biosynthesis. First of all, it was finally demonstrated that urogen III, the intermediate on the way to all natural porphinoids, is indeed

[40] W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 1952, 4735.
[41] For more examples see ref. 37.
[42] As shown by the u.v. and ^{1}H n.m.r. spectra in trifluoroacetic acid.[34]

a precursor of the vitamin.[43] The greatest impact, however, came from a discovery made in the laboratory of the pioneer in the field of vitamin B_{12} biosynthesis, Shemin,[44] as well as in Scott's laboratory:[45] ^{13}C-experiments of these workers revealed—probably to everyone's surprise—that the angular methyl group at ring A of vitamin B_{12} does *not* stem from the urogen III *meso*-carbon (circled CH_2 in Figure 25) but instead from methionine, as do all the other 'extra methyl

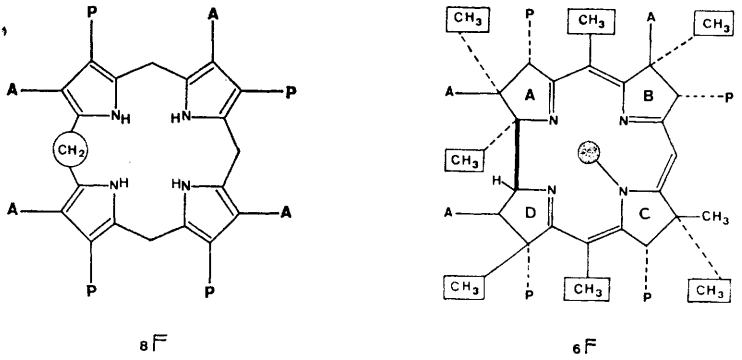


Figure 25

groups' (squared CH_3's) of the vitamin's corrin nucleus.[46] Once again, Nature does not simply do what would have appeared to be most economical from the chemist's point of view.

It was this remarkable aspect of vitamin B_{12} biosynthesis that made us wonder whether it might be possible to induce an A/D-secocorrin→corrin cyclization through the departure of a one-carbon unit from position 19 of an appropriate A/D-secocorrin derivative. If one had the (strongly nucleophilic) methylidene carbon at ring A in *protonated* form and, at the same time, a carboxy-group at position 19 in a *deprotonated* state, then departure of carbon dioxide might ensue, leaving behind a conjugated π-system that is, once again, the elusive '1,19-secocorrin biradical' (see Figure 26). The position of the carboxy-group

[43] (*a*) A. I. Scott, C. A. Townsend, K. Okada, M. Kajiwara, and R. J. Cushley, *J. Amer. Chem. Soc.*, 1972, **94**, 8269; (*b*) A. I. Scott, C. A. Townsend, K. Okada, and M. Kajiwara, *ibid.*, 1974, **96**, 8054; A. I. Scott, C. A. Townsend, K. Okada, M. Kajiwara, R. J. Cushley, and P. J. Whitman, *ibid.*, 1974, **96**, 8069; (*c*) A. I. Scott, N. Georgopapadakou, K. S. Ho, S. Klioze, E. Lee, S. L. Lee, G. H. Temme, C. A. Townsend, and I. M. Armitage, *ibid.*, 1975, **97**, 2548; (*d*) A. R. Battersby, M. Ihara, E. McDonald, F. Satoh, and D. C. Williams, *J.C.S. Chem. Comm.*, 1975, 436; (*e*) H. O. Dauner and G. Müller, *Hoppe-Seyler Z. physiol. Chem.*, 1975, **356**, 1353.

[44] C. E. Brown, J. J. Katz, and D. Shemin, *Proc. Nat. Acad. Sci. U.S.A.*, 1972, **69**, 2585; see also ref. 9*c*.

[45] A. I. Scott, C. A. Townsend, K. Okada, M. Kajiwara, P. J. Whitman, and R. J. Cushley, *J. Amer. Chem. Soc.*, 1972, **94**, 8267; see also ref. 43*b*.

[46] R. C. Bray and D. Shemin, *Biochim. Biophys. Acta*, 1958, **30**, 647; *J. Biol. Chem.*, 1963, **238**, 1501.

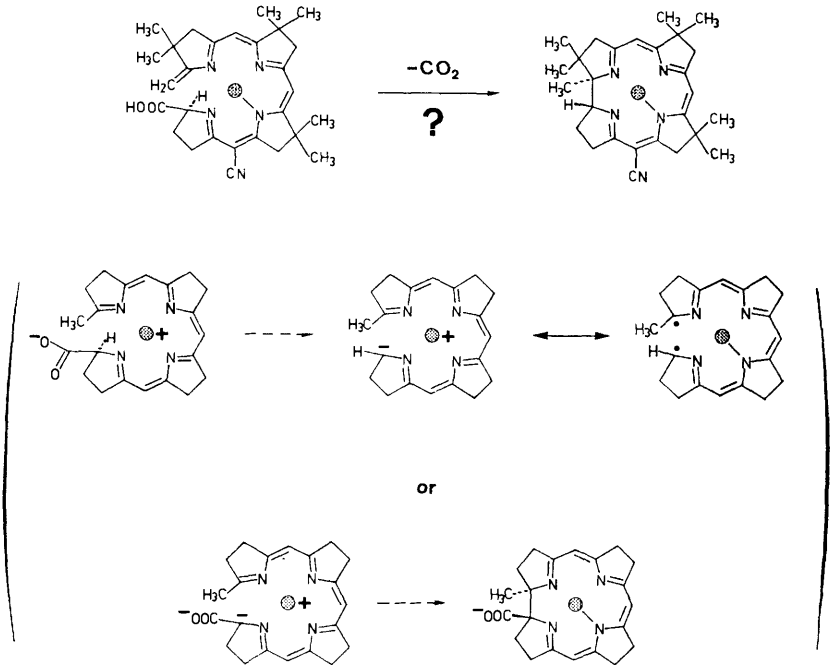


Figure 26

relative to the nitrogen centres of the π-system after methylidene protonation is not one where conventional β-ketimine-type activation for decarboxylation could come into play. Rather, it is a position from which an anionic decarboxylation would lead to an ylide structure; the ionic representations of the '1,19-secocorrin biradical' are, in fact, ylide structures.[47] By this reasoning, protonation of the methylidene carbon would be a prerequisite for decarboxylation; without protonation the chromophore will stay enaminoid, a much less electrophilic π-system, and one that would not be expected to support the decarboxylation.[48]

If ylide formation *via* decarboxylation after methylidene protonation is accepted as a possible pathway for a secocorrin→corrin ring closure, then there is also a closely related pathway to be considered: ylide formation through *deprotonation* at C-19 after methylidene protonation (see Figure 26). This mode of ring closure would lead to the corrin-19-carboxylic acid and ought to be easily recognized by the isolation of this acid. At the time we felt rather sure in our conviction that the enaminoid (nucleophilic) π-system of the *corrin*

[47] For a more revealing way of describing such systems, see L. Salem, *J. Amer. Chem. Soc.*, 1974, **96**, 3486.

[48] This reasoning was based on the conjugative destabilization to be expected when the enaminoid (nitrogen) lone pair of the chromophore becomes linearly conjugated with the carbanionoid lone pair that would emerge from decarboxylation; see, however, footnote 60.

chromophore would not assist the decarboxylation of a carboxylate group in this position (see above).

'Stimulative support' for the belief in the existence of a decarboxylation to the 'secocorrinoid ylide' came just in time from an unexpected direction[49a] (see Figure 27). In experiments aimed at a preparation of the elusive L-proline en-

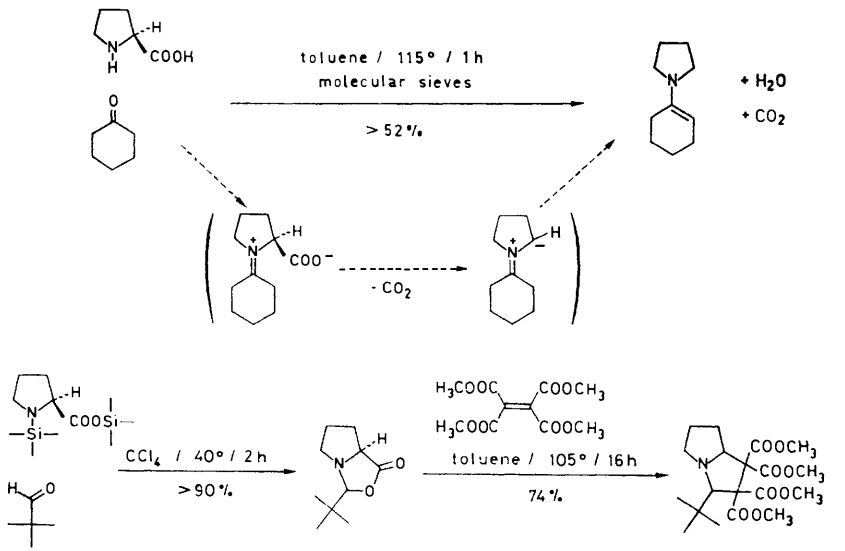


Figure 27

amine derivative of cyclohexanone we observed smooth and clean[50] formation of the pyrrolidine enamine derivative when a suspension of L-proline in a toluene solution of cyclohexanone was heated in the presence of molecular sieves. This reaction must represent an example of an iminium-carboxylate→ylide decarboxylation.[51] The result of the closely related decomposition of the lactone derived from L-proline and pivalaldehyde, formulated in Figure 27,[49b] bolsters this contention.

In subjecting the hypothesis of the decarboxylative A/D-secocorrin→corrin

[49] (*a*) Unpublished work by A. Treasurywala (1974) in our laboratory; (*b*) unpublished work by A. Treasurywala and C. Angst (1975); *cf.* C. Angst, Diplomarbeit E.T.H. Zürich, 1975.

[50] The reaction went essentially to completion; the yield mentioned in Figure 27 refers to the isolation of a distilled, 'spectroscopically pure' sample of the (highly sensitive) enamine.[49a]

[51] A literature search revealed that this type of reaction had in fact been observed before, although investigated mostly with aromatic carbonyl compounds; *cf.* T. Curtius and G. Lederer, *Ber. deutsch. chem. Gesellschaft*, 1886, **19**, 2462; G. Rizzi, *J. Org. Chem.*, 1970, **35**, 2069 and literature cited therein; *cf.* also the role of 'non-stabilized' ylide intermediates in the isomerizations of Atisine and Garrya alkaloids; *cf.* S. W. Pelletier and L. H. Keith in 'The Alkaloids XII', ed. R. H. F. Manske, Academic Press New York, 1970, p. 166.

cyclization to an experimental test we were fortunate to have had the required type of model compound essentially in our hands already. Some time ago, as a part of the project of making optically active corrin complexes, Bühler[52] had carried out the synthesis summarized in Figure 28. Besides showing how the

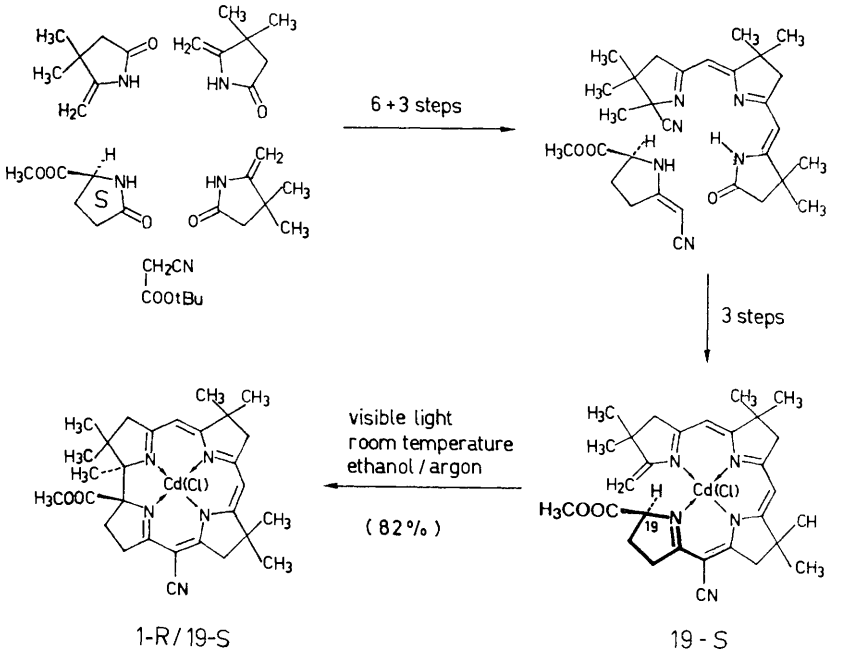


Figure 28

required 19-carboxy-derivatives of A/D-secocorrins (as well as of the corresponding corrins[53]) were made, this scheme may serve here as an example of the general route which we like to choose in our laboratory from the variety of routes available when we have to synthesize a given derivative in the corrin series today.[54,55]

19-Carboxy-derivatives of secocorrinoid zinc, cadmium, palladium, and nickel complexes were prepared and used as substrates in a search for decarboxylative

[52] Unpublished work.[14a]

[53] The absolute configuration of the pyroglutamic acid starting material determines by steric control the sense of helicity in the secocorrin complex. The photochemical cyclization proceeds with retention of configuration.[14a]

[54] For the detailed sequence of steps see refs. 12, 5*b*, and 38, and for experimental procedures see the theses of H. J. Wild,[13] N. Bühler,[14] and E. Götschi.[55]

[55] E. Götschi, 'Über den Aufbau corrinoider Systeme mit der Sulfidkontraktionsmethode', Thesis E.T.H. Zürich, Prom. Nr. 4986, Juris-Verlag, Zürich, 1973.

cyclization.[56] The search, not unexpectedly, turned out to be rather difficult, in as far as these substrates revealed a complex spectrum of reactivities in various directions. The successful experiments were made by Neier and Pfaltz[35] in the nickel series. Figure 29 describes the conditions leading to decarboxylative

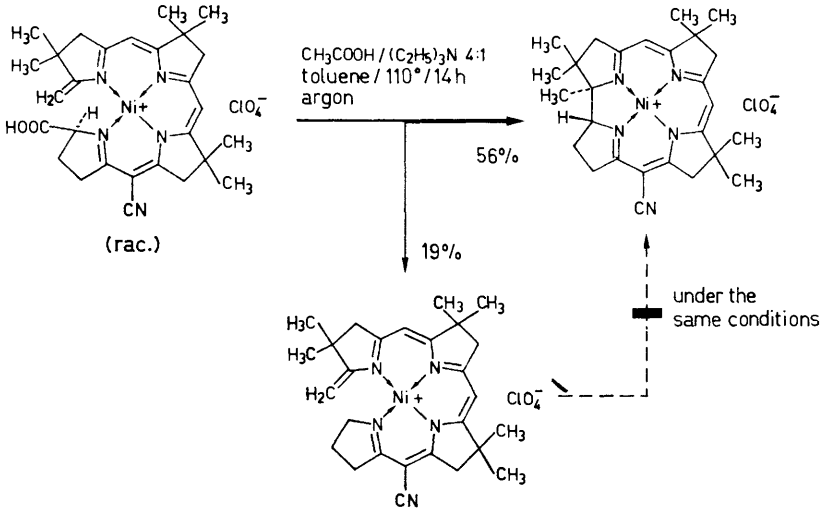


Figure 29

cyclization of the 19-carboxy-1-methylidene-1,19-secocorrin nickel(II) complex. These reaction conditions reflect the working hypothesis which we followed in order to hit the mechanistic path we had in mind: a weak base for keeping a part of the substrate carboxyl deprotonated, an external carboxylic acid[57] for reversibly protonating the methylidene carbon, and finally a non-polar solvent for encouraging CO_2 formation from the carboxylate anion.

What we found surprising (and originally disturbing) in the outcome of these experiments was the fact that decarboxylated but uncyclized material always appeared among the reaction products, in addition to the desired corrin. This *could* mean that the expectation, according to which decarboxylation should have a chance only after protonation of the methylidene carbon, is unwarranted and that a cyclized 19-carboxycorrin complex could equally well decarboxylate. If so, then the formation of a (19-decarboxy)corrin complex by decarboxylative cyclization would, as such, not constitute evidence for the operation of the cyclization mechanism for the sake of which the investigation on the problem

[56] Unpublished work of N. Bühler[14] and K. Hirai.

[57] The formally appealing intramolecular proton transfer from the carboxy-group to the methylidene carbon would require the carboxy-group to point inside the helix; however, there is hardly any doubt that it prefers the *exo*-configuration for steric reasons.

of a decarboxylative A/D-secocorrin→corrin ring closure had actually been undertaken. Therefore, racemic nickel(II) 1,2,2,7,7,12,12-heptamethyl-15-cyano-corrinate-19-carboxylic acid (prepared *via* photochemical cyclization of the seco acid followed by transcomplexation[35]) was subjected to the conditions used in the decarboxylative cyclization experiments (4:1 acetic acid-triethylamine in toluene; argon, 110 °C, 4 h). The decarboxylated corrin complex was isolated in 80% yield! A systematic search for the mildest possible reaction conditions that would induce this 'forbidden' decarboxylation led to the dramatic observation presented in Figure 30. In the presence of excess 2:3 acetic acid–triethyl-

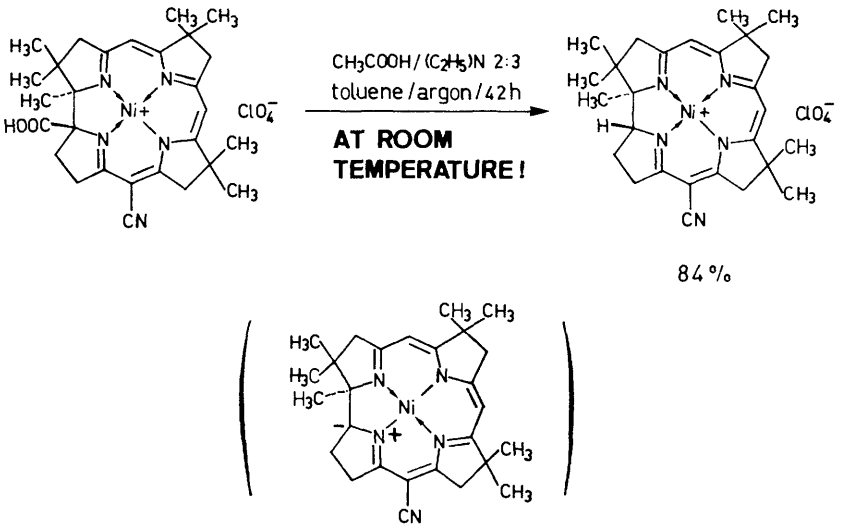


Figure 30

amine in toluene solution under strict exclusion of oxygen decarboxylation proceeds within seven days even at room temperature![58]

The lessons that this admittedly surprising result taught us were at least threefold. First, the observations quite clearly indicated that the ring-closure step in the decarboxylative cyclization of Figure 29 by no means need be induced by the decarboxylation step; cyclization might equally well precede decarboxylation, Complementary experiments will have to settle this question of mechanism.[59] Secondly, a hitherto unknown and unexpected chemical

[58] No reaction occurs under these mild conditions with the corresponding 19-carboxyseco-corrinate. The 19-carboxycorrinate is stable in hydroxylic solvents at room temperature.

[59] The results of preliminary deuteriation experiments point to the deprotonation → cyclization → decarboxylation pathway; when the reaction was carried out with *O*-deuteriated acetic acid and prematurely interrupted, the isolated corrin complex (*ca.* 20%) contained deuterium in position 19 whereas the recovered educt carboxylic acid (*ca.* 60%) did not (^{1}H n.m.r.).

feature of the corrin ligand appears to have been revealed, namely that corrinium ylides of the type shown in Figure 30 may prove to be accessible intermediates, capable of mediating reactions of corrin complexes at the angular position in ring D.[60] Finally, and perhaps most important to us, the observations—having so irrefutably demolished some of our cherished preconceived notions about the behaviour of corrinoid systems—triggered a drastic change in our attitude towards the goals we ought to pursue with this work in the future. Some aspects of this change are dealt with in the concluding section.

6 Outlook

In the course of our post-B_{12} work on corrin synthesis we gradually gained the impression that one could increase the number of secocorrin→corrin (A→D) cyclizations without too much difficulty. In fact, the situation 'threatened' to develop into what one might call the 'prostaglandinization' of corrin synthesis! Originally our attitude was to circumvent that 'menace' by attempting to confine our experimentation to potentially biomimetic modes of (A→D) ring closure which were at the same time—so to say—'chemically non-trivial'.[61] The experiences described in the preceding section eventually led us to a diametrically opposite attitude, namely to judge a given ring-closure variant with respect *neither* to its potential biosynthetic interest, *nor* to such things as 'chemical trivialness' or synthetic usefulness. Rather, we should seek and welcome *all* variants as part of a whole emerging spectrum of (A→D) ring closures, a spectrum that ranges from the original pyrroloid cyclizations of Johnson *et al.*[8] to the photochemical A/D-secocorrin→corrin cycloisomerization. Every additional experimentally documented A/D-secocorrinoid→corrinoid cyclization would strengthen our growing conviction that, from the point of view of synthesis, the corrin ring structure should be looked at very much as the more common porphyrin ring system is viewed already, namely as inherently accessible rather than as particularly demanding.

Today (A→D) cyclization pathways are known, or can be safely assumed, to exist at all the various structural levels of secocorrinoids that differ from each other in the degree to which their four rings are methylated. The circle in Figure 31 presents a collection of such structures, to some extent arbitrarily selected for the sake of illustration, using present knowledge—as well as uncertainty—about B_{12} biosynthesis.[9] Pathways to corrinoid structures have already been documented in model systems for those structures of the circle which are labelled

[60] The ease of formation of such ylide intermediates may depend strongly on the metal ion that co-ordinates the ligand. The argument mentioned in footnote 48 is probably vitiated by the influence of the electrophilic nickel ion.

[61] As 'non-trivial' from a chemical point of view we had considered—biased as we were—any cyclization pathway that would proceed through the '1,19-secocorrin biradical'. In retrospect it seems appropriate to mention that in discussions with my colleague D. Arigoni he had fervently opposed such an attitude; he may thus have contributed to our change of mind.

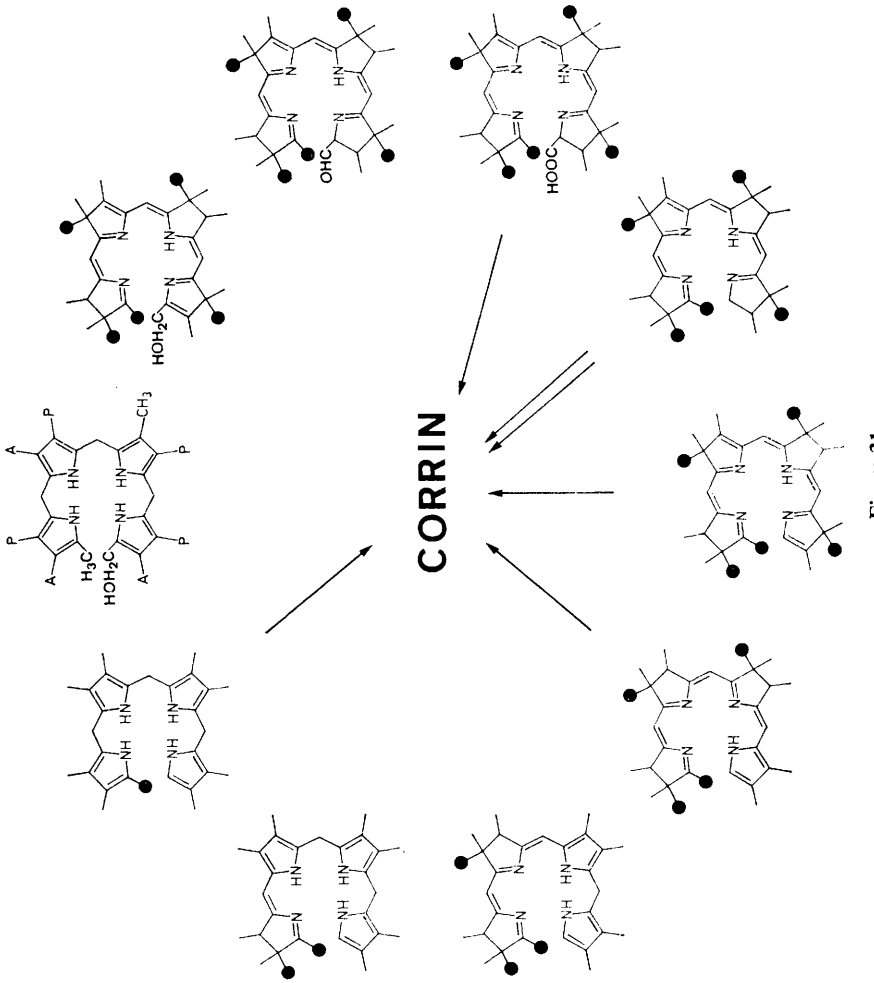


Figure 31

with an arrow.[62] We have little doubt that, for the others, (A→D) cyclization pathways *can* (and will) also be documented. It almost looks as if formation of the corrinoid ring system becomes a *not improbable* event, once a porphinoid precursor has been generated and has entered the channel of the secocorrinoid structures. Recent findings[44,45] on B_{12} biosynthesis seem to teach us that descendants of porphobilinogen enter this channel through the replacement of a *meso*-methylene group by a methyl group; such—in effect reductive—substitution barricades the road to the porphinoids.

Just how recent in the evolutionary scale of natural product structures is the corrin nucleus? This would seem to be the basic question behind these considerations on the adequate place for the corrin system in a 'hierarchy of synthesis'. The work on the chemical synthesis of corrinoids *via* (A→D) ring closures seems to bring up more and more emphatically the possibility that this ring system could be—from the point of view of its chemical accessibility—an *elementary* type of natural product, and perhaps one of the remaining tasks of synthetic corrin chemistry will be what we might call the 'demystification of the vitamin B_{12} structure'. We have looked up to this 'holy' molecule since its appearance on the chemical scene 20 years ago, seeing it as an overwhelming manifestation of living Nature's unexcelled potential for synthesis. *Now* we should raise the question as to whether vitamin B_{12} is in fact a surviving descendant of an archaic type of structure that even may have had a chance of being formed under abiotic conditions *before* having been functionally selected and structurally developed by living systems. In other words: Is vitamin B_{12} an object for research in prebiotic chemistry? Conspicuously enough, the molecule of coenzyme B_{12} (see Figure 32) contains, apart from the corrin nucleus, building blocks which already *are* considered as archaic and which are imagined to have been ingredients of prebiotic organic matter. Is it conceivable that corrin-like structures could have been ingredients too? What then would be the palette of elementary, *i.e.* potentially prebiotic, synthetic pathways out of which the *contemporary* biosynthetic pathway to the vitamin could have emerged and developed? To provide experimental groundwork for dealing with questions of this sort is the task of —as well as an opportunity for—organic synthesis.[63]

[62] The arrow at the upper left refers to Johnson's (A→D) cyclization to tetradehydro-corrinoids,[8] the others to work described in this article; see also Scott's[30] proposal in context with the arrow at the lower left. The 1,19-secocorrinoids of Figure 31 are uniformly formulated as their metal-free 1-methyl tautomers; see in this context the recent findings of M. Imfeld, C. A. Townsend, and D. Arigoni, *J.C.S. Chem. Comm.*, 1976, 541; A. Battersby, R. Hollenstein, E. McDonald, and D. C. Williams, *ibid.*, 1976, 543; A. I. Scott, M. Kajiwara, T. Takahashi, I. M. Armitage, P. Demou, and D. Petrocine, *ibid.*, 1976, 544.

[63] It has been stated in the literature that, from the microbiological point of view, the biosynthesis of vitamin B_{12} appears to be a phylogenetically old property which had originated very early in bacterial history and possibly had preceded haem biosynthesis; *cf.* K. Decker, K. Jungermann, and R. K. Thauer, *Angew. Chem.*, 1970, **82**, 153 (*Angew. Chem. Internat. Edn.*, 1970, **9**, 138); I. De Ley and K. Kersters, in 'Comprehensive Biochemistry', ed. M. Florkin and E. H. Stotz, Vol. 29B, Elsevier, New York, 1975, p. 1, 29. I thank Professor A. I. Scott for pointing out these literature references to me and for informing me of a relevant discussion in N. Georgopapadakou, 'Biosynthetic Studies on 6-Methylsalicylic Acid and Vitamin B_{12}', Ph.D. Thesis. Yale University, 1975.

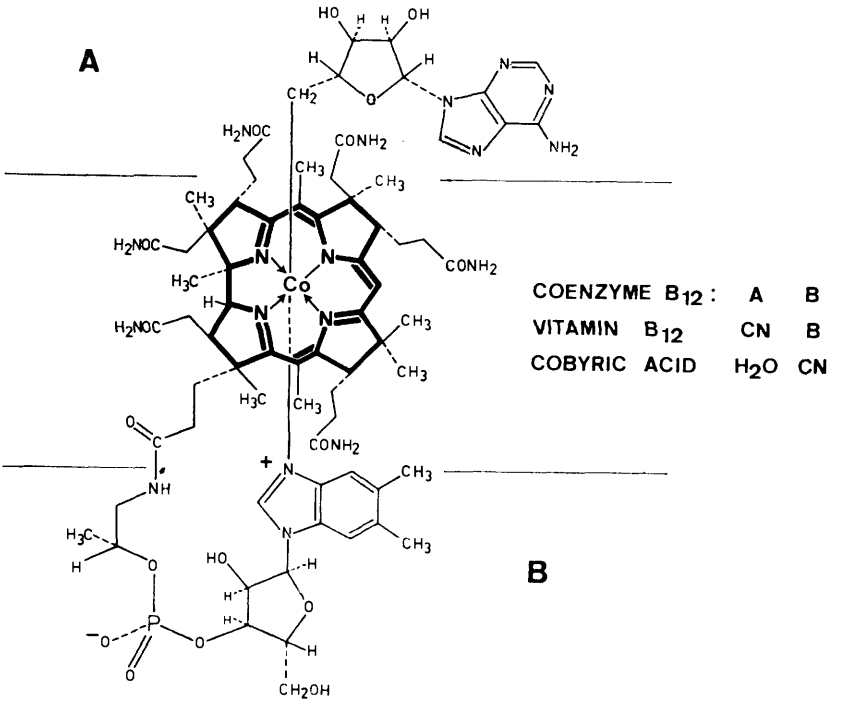


Figure 32

It is now a century and a half since Wöhler's synthesis of urea initiated the process of demystification of the substances produced by living systems. Is this process still going on, and does it represent a hidden but important function that organic synthesis still has to fulfil in our own time?

The following is the list of my collaborators who did the work described in this review: Dr. Yasuji Yamada, Hans Wild, Niklaus Bühler, Reinhard Neier, Bernhard Kräutler, Andreas Pfaltz, René Nordmann, Dr. Salem Farooq, Peter Müller, Bruno Hardegger, Dr. Koichi Hirai, Dr. Adi Treasurywala, and Christoph Angst (see also references). Financial support came from the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung.

I would like to thank Professor Claude Wintner for his kind and very valuable help in preparing the manuscript.