108. Electrofugal Fragmentation of Alkylcobalamin Derivatives Using Cob(I)alamin and Heptamethyl Cob(I)yrinate as Catalysts[1])

by **Albert Fischli**

Pharmaceutical Research Department, *F. Hoffmann-La Roche & Co. Ltd.*, CH-4002 Basle

(17.VII.81)

Summary

The cob(I)alamin- (**1**(**I**)) and the heptamethyl cob(I)yrinate- (**2**(**I**)) catalyzed transformation of an epoxide to the corresponding saturated hydrocarbon **3** → **4** → **5** is examined (see *Schemes 1* and *3–5*). Under the reaction conditions, the epoxyalkyl acetate **3** is opened by the catalysts with formation of appropriate (β-hydroxyalkyl)-corrinoid derivatives (**13**, **14**, **17**, **18**, see *Schemes 12* and *14*). Triggered by a transfer of electrons to the Co-corrin-π system, the Co,C-bond of the intermediates is broken, generating the alkenyl acetate **4** (*cf. Schemes 12* and *14*) following an electrofugal fragmentation (*cf. Schemes 2* and *12*). The double bond of **4** is also attacked by the catalysts, leading to the corresponding alkylcorrinoids (**15**, **19**, see *Schemes 12* and *14*) which in turn are reduced by electrons from metallic zinc, the electron source in the system, inducing a reductive cleavage of the Co,C-bond with production of the saturated monoacetate **5** (see *Schemes 2*, *5* and *12*). In the cascade of steps involved, the transfer of electrons to the intermediate alkylcorrinoids (**13–15**, **17–19**, see *Schemes 12* and *14*) is shown to be rate-limiting. Comparing the two catalytic species **1**(**I**) and **2**(**I**), it is shown that the ribonucleotide loop protects intermediate alkylcobalamins to some extent from an attack by electrons. The protective function of the ribonucleotide side-chain is shown to be present in alkylcobalamins existing in the base-on form (*cf. Chap. 4* and see *Scheme 14*).

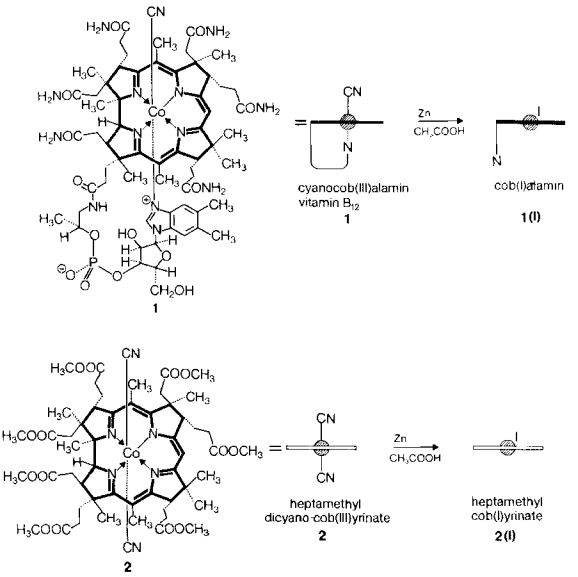
1. Introduction. – The transformational possibilities considering a fission of the Co,C-bond in alkylcobalamins, accessible *e.g.* from cob(I)alamin (s. *Scheme 1*) and appropriate electrophiles, can be represented as shown in *Scheme 2*[2]). The well-known homolytic cleavage, induced by light or heat [2c], produces an alkyl radical and cob(II)alamin. Recombination reactions of a radical with the scavenger cob(II)-alamin [4–6] as well as irreversible cleavage of the Co,C-bond [5] [7] [8] by light

[1]) 9th Communication in the series Cob(I)alamin as Catalyst; for the 8th communication see [1].

[2]) The five possible forms **a**–**e** of an alkylcobalamin in acidic solution, arising from the known equilibrium between octahedral [2a] and tetragonal-pyramidal [2b] [3] complexes and from the

0018-019X/82/4/1167-24$01.00/0

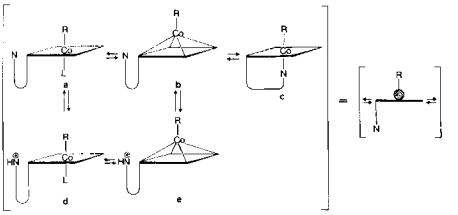
Scheme 1



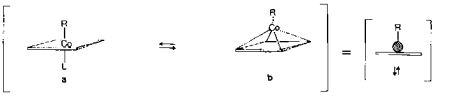
have been observed. Up to now, under the conditions applied[3]), olefins have been reduced with catalytic amounts of the Co(I)-corrinoids **1(I)** and **2(I)** (s. *Scheme 1*) without formation of products generated by a homolytic fission of the Co, C-bond. During studies of the saturation of trisubstituted double bonds leading to optically active products, very little influence of light was detected on the enantiomeric excess of the saturation products [9]. The homolytic fission of the Co, C-bond is therefore not a product-forming reaction under the conditions applied.

---

possibility of protonation of the dimethylbenzimidazole terminus when the nucleotide loop is uncoordinated, are represented by a formula with two lateral double-arrows:

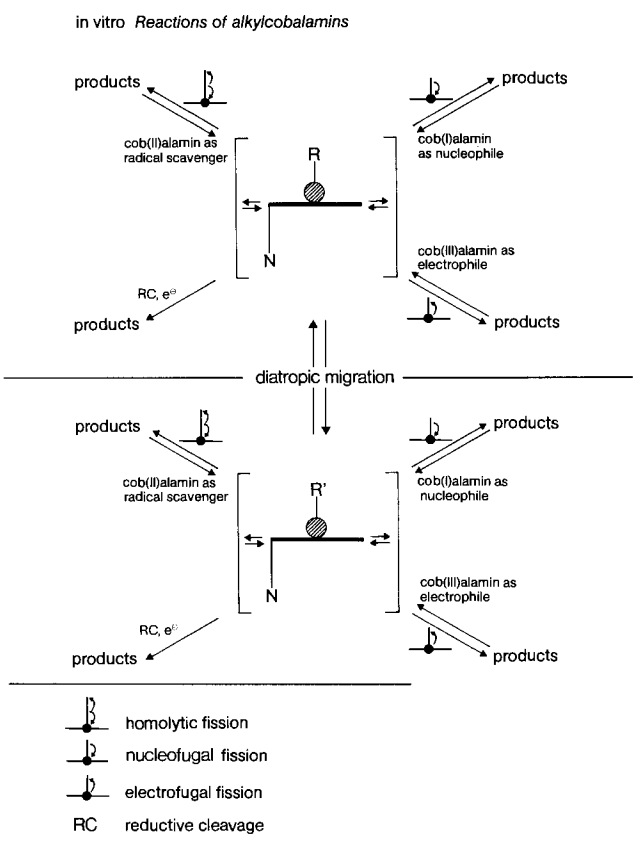


A similar short formula with a vertical double-arrow is used to describe the equilibrium between the octahedral and tetragonal-pyramidal complexes of alkylcobyrinates:



[3]) Catalytic amounts of Co(I)-corrinoid **1(I)** or **2(I)**; excess of metallic zinc as electron source; glacial acetic acid or aqueous solution of acetic acid; argon atmosphere; stirring in the dark.

Scheme 2[2])



The nucleofugal fission leading to cob(I)alamin and corresponding products[4]) as well as the adequate *retro*-reaction have been observed and will be discussed in more detail in a subsequent publication[5]).

The reductive cleavage of the Co, C-bond, initiated by the electron attack on the planar Co-corrin-π system (s. [12]), leads to the parent hydrocarbon[6]) under protic conditions (*cf.* [10] [11] [13–15]). In the presence of an electrophilic C-atom, the reductive cleavage of the Co, C-bond induces the formation of a new C, C-bond [16]. Under protic conditions, the reductive cleavage leads to the replacement of the Co, C-bond by an H, C-bond and the reaction has been shown to proceed with retention of configuration (s. [11] [15]).

Results have been published of investigations looking for rearrangements of simple alkylcobalamins paralleling the transformational patterns of the coenzyme

[4]) Olefins, *e.g.*; *cf.* [10] [11].
[5]) 10th Communication in this series (in preparation).
[6]) Obtained after formal replacement of the Co, C-bond by a H, C-bond.

B_{12}-dependent enzymatic reactions[7]). Up to now, no rearrangements have been detected starting from intermediate alkylcobalamins formed after an attack of catalytic amounts of cob(I)alamin **1**(**I**) on olefins under acidic conditions[8]). Following such a rearrangement, a new alkylcobalamin would be produced from which an identical set of reactions[9]) would open an access to corresponding products *(cf. Scheme 2)*.

An example of the remaining fission mode of the Co, C-bond which has not yet been mentioned, that is electrofugal fission, will be discussed in more detail in the next chapter. From the literature several ways to induce electrofugal fission of the Co, C-bond are known [42–62].

2. Reduction of epoxides and olefins using catalytic amounts of cob(I)alamin derivatives. – The 10,11-epoxyundecyl acetate **3** was reduced using 0.1 mol-equiv. of cyanocob(III)alamin (**1**), 6.0 mol-equiv. of activated zinc[10]) and glacial acetic acid[11]) as solvent. Stirring in the dark for 52 h under an argon atmosphere produced the mixture of compounds **3**–**12** shown in *Scheme 3* (experiment A1). A corresponding blank experiment revealed that the derivatives **8**–**12** are due to the action of zinc, to the solvent acetic acid or to both. As anticipated, a nucleophilic attack by the solvent opens the epoxide ring leading to both possible isomers **10** and **11**. Four products are generated by the action of cob(I)alamin (**1**(**I**)) only: the alkenyl acetate **4** and the parent alkyl acetate **5** are produced in 14 and 16.5% yield, respectively, and the two remaining derivatives **6**[12]) and **7** are formed in traces only. It seems reasonable to suggest that in a first step the epoxy acetate **3** is reduced to the alkenyl acetate **4** and that a subsequent saturation leads to undecyl acetate (**5**).

A parallel experiment[13]) using catalytic amounts of heptamethyl cob(I)yrinate (**2**(**I**)) and a larger excess of metallic zinc led to similar results. The two main products generated by the action of heptamethyl cob(I)yrinate (**2**(**I**)) are again the alkenyl acetate **4** (22.3%) and the saturated acetate **5** (51.5%, s. *Scheme 4*).

As **4** might be an intermediate in the reduction of **3** to **5**, the saturation of the potential intermediate **4** using **1**(**I**) and **2**(**I**) was studied. *Scheme 5* shows that under the conditions of experiment A2 (s. *Scheme 4*) complete saturation of the terminal double bond is observed, and that this reduction can clearly be ascribed to the action of the catalysts **1**(**I**) and **2**(**I**)[14]). To prove the hypothesis that **4** is an

---

[7]) Parallel to the enzymatic transformation methylmalonyl-SCoA ⇄ succinyl-SCoA ([17–20]) see *e.g.* [21–26]; in analogy to the enzymatic transformation methyl itaconate ⇄ α-methylideneglutarate ([27–29]) *cf. e.g.* [30]; for specific cobaloxime rearrangements see [31–33]; parallel to the reactivity of propandioldehydrase ([34–36]) *cf. e.g.* [37–41].

[8]) For appropriate conditions see footnote 3.

[9]) Compare the transformational possibilities of the alkylcobalamins shown in *Scheme 2*.

[10]) See *Exper. Part.*

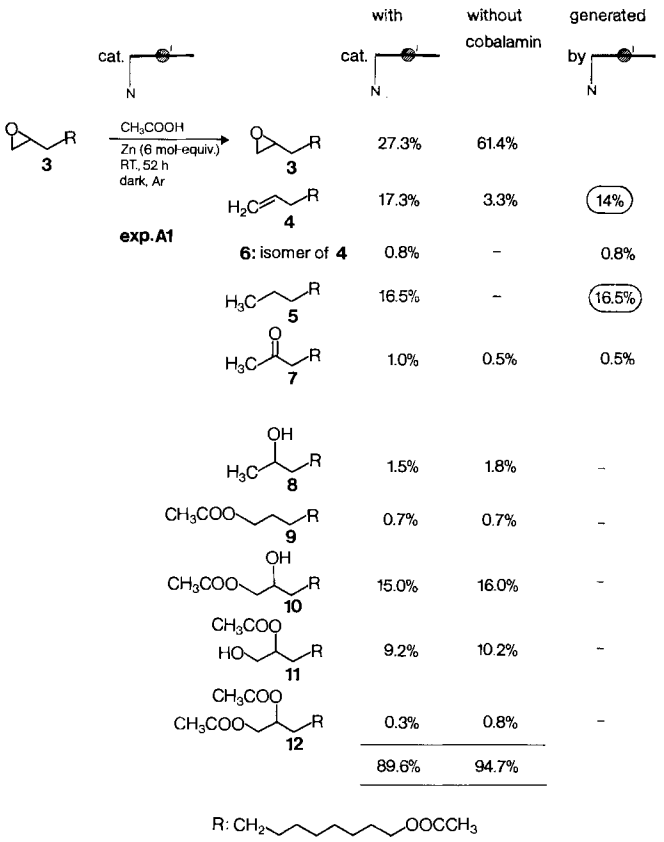
[11]) Similar reductions were possible using CH_3COOH/H_2O 4:1 solvent.

[12]) In the GLC./MS. **6** showed the same mass as **4**. In the ^{1}H-NMR. of the mixture **4**–**6** a signal at 5.3–5.45 ppm (*m*, –CH=CH–) was detected.

[13]) Experiment A2: with the exception of a larger excess of the electron source (metallic zinc, 20 mol-equiv.) the experiment was carried out under identical conditions to those of the transformation shown in *Scheme 3*.

[14]) Experiments A3 and A4. In the blank experiment, no saturation of **4** was observed.

Scheme 3

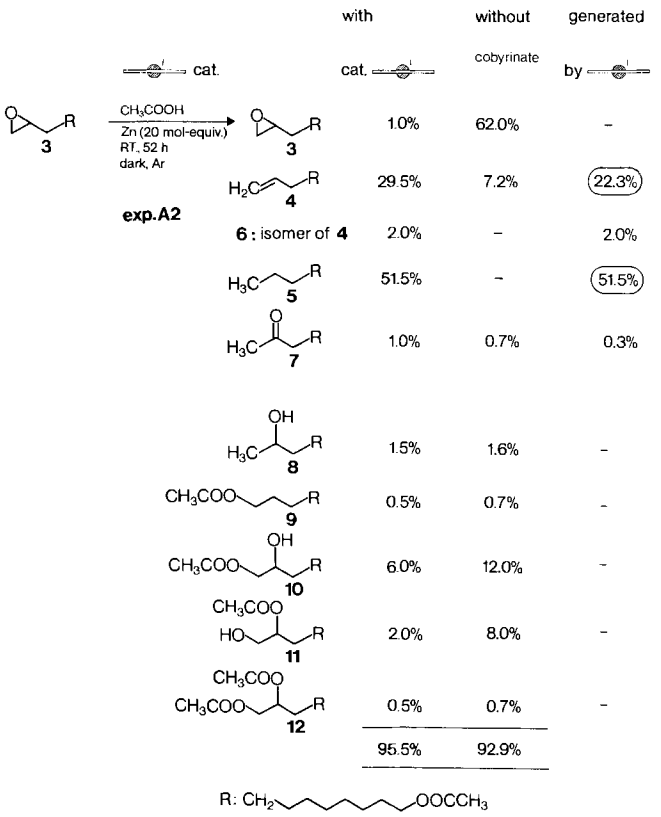


intermediate in the pathway leading from **3** to **5**, and to learn more about the mechanisms of the reactions involved, the time dependence of the formation of the two main products **4** and **5** and of the disappearance of the starting material **3** was examined (s. *Schemes 6–9*, experiments B1, B2, B3 and B4[15])).

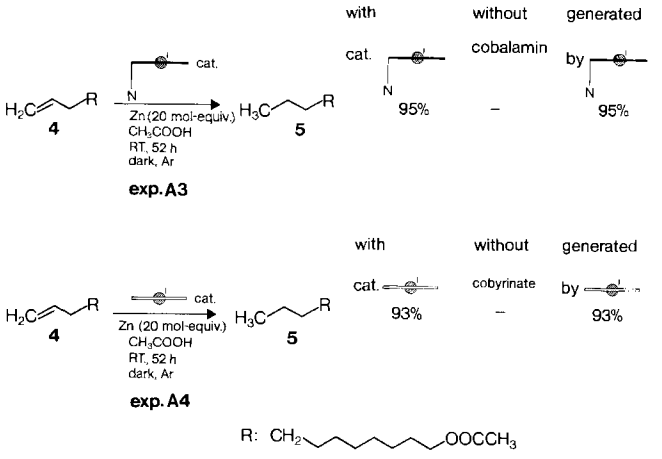
The results of the reduction of **3** using catalytic amounts of cob(I)alamin (**1(I)**) are shown in *Scheme 6* (experiment B1). The epoxy acetate **3** disappeared with a half-life of 11.2 h, and low concentrations of **4** were detected. The final product **5** was accumulated during the reaction and reached the level of about 78% after 40 h. *Scheme 7* shows the saturation of the alkenyl acetate **4** using **1(I)** as catalyst (experiment B2). With a half-life of 2.5 h, **4** was quickly reduced. Transient low concentrations of the isomer **6**[12]) were observed. After 15 h, saturation was complete, and the product **5** was present in 90% yield. This was, however, not the case with the reduction of **3** using catalytic amounts of heptamethyl cob(I)yrinate (**2(I)**). With a short half-life of 1.1 h, **3** disappeared, and the alkenyl acetate **4** was accu-

[15]) The four kinetic experiments B1–B4 were carried out under identical conditions using a special method for the preparation of the catalysts **1(I)** and **2(I)** (s. *Exper. Part*).

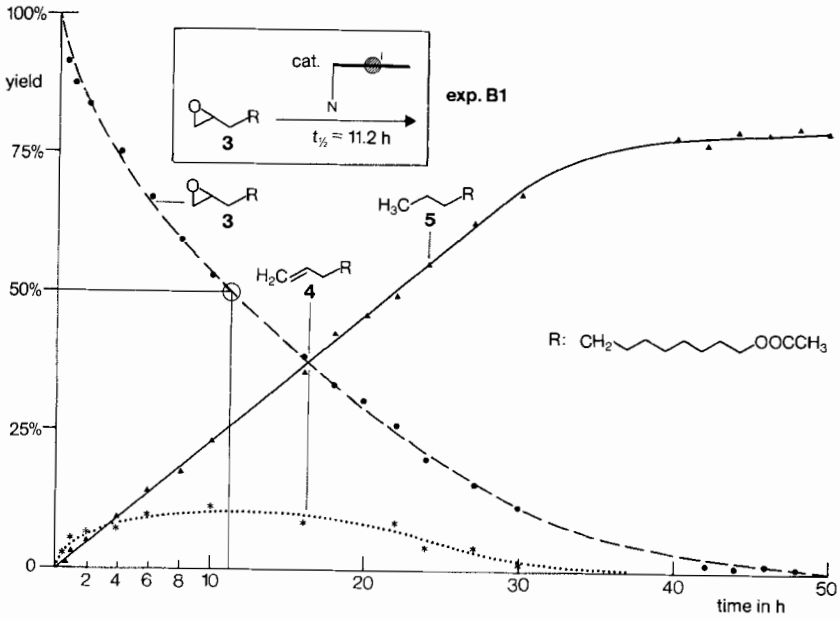
Scheme 4



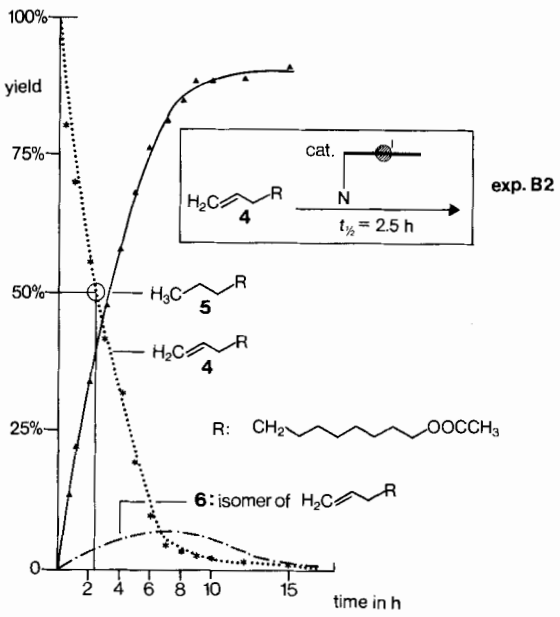
Scheme 5



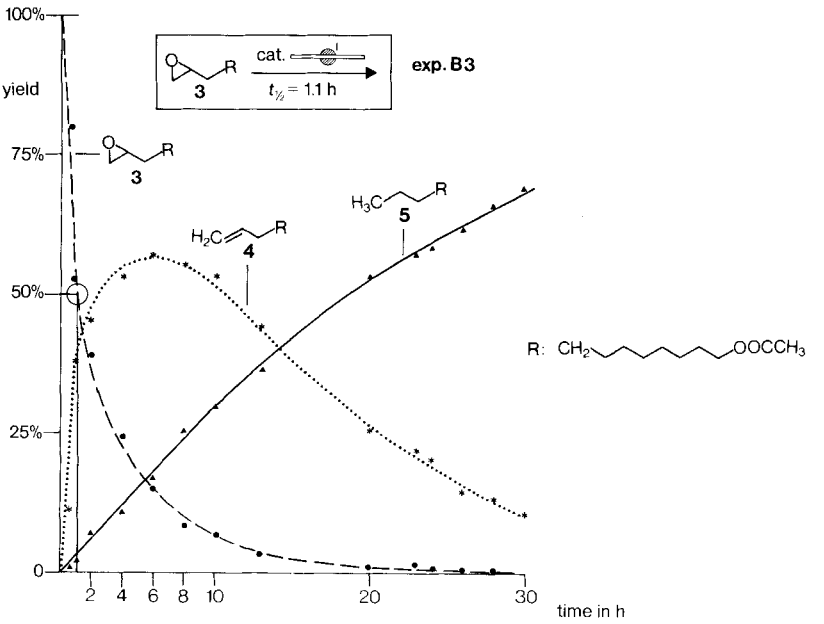
Scheme 6



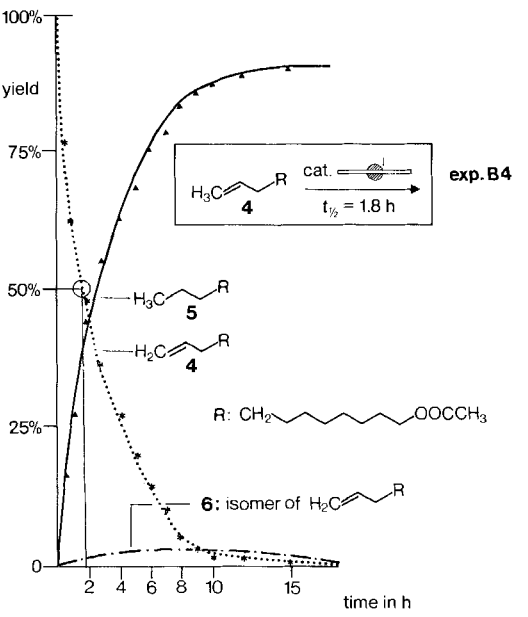
Scheme 7



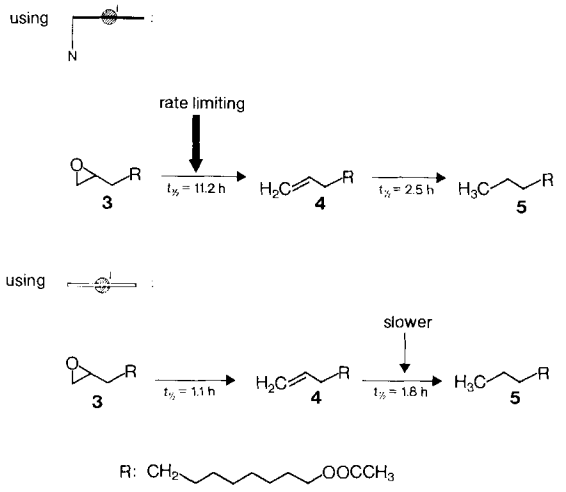
Scheme 8



Scheme 9



Scheme 10



mulated up to 57% reaching the maximum after 6 h (experiment B3). After 30 h, no starting material was observed, and the alkenyl acetate **4** was present to 12.4% and the final product **5** to 70% (s. *Scheme 8*). *Scheme 9* shows the saturation of **4** using catalytic amounts of **2(I)** (experiment B4); the half-life of **4** was 1.8 h. Transient low concentration of the isomer **6**[11]) were detected. After 15 h saturation was complete, and **5** was present in 91% yield.

Scheme 10 summarizes the results from the kinetic experiments displayed in *Schemes 6–9*. If **4** is an intermediate in the reduction of **3**, with cob(I)alamin (**1(I)**) as catalyst, **4** should only be present in low concentrations during the reaction (s. half-lives of **3** and **4**). *Scheme 6* shows that, in the kinetic experiment, **4** never exceeds 11.6%. If **4** is a true intermediate in the transformation with heptamethyl cob(I)yrinate (**2(I)**) as catalysts, **4** should be accumulated during the experiment (s. half-lives of **3** and **4**). This is confirmed by the kinetic studies showing peak concentration of **4** (57%) after 6 h. It is therefore reasonable to assume that the reductions of **3** catalyzed by **1(I)** or **2(I)** lead in a first step to the deoxygenated intermediate **4** which is subsequently saturated to the final hydrocarbon **5**. It is interesting to note that, using **1(I)**, the transformation **3** → **4** is rate-limiting, whereas, with **2(I)**, the slowest transformation in the overall reaction is the saturation of the intermediate **4**. The half-lives of the transformation **3** → **4** with **2(I)** and of **4** → **5** with **2(I)** show rather similar figures, and the value for the saturation **4** → **5** with **1(I)** is not very different. In contrast, the **1(I)** dependent transformation of **3** to the olefin **4** is distinctly slower.

3. Experiments with increasing amounts of zinc. – Earlier electrochemical studies have provided indications of the number, height and potential location of the polarographic [63] [65] and cyclic voltammetry waves of methylcobalamin [63–65] and methylcobinamide [63–64]. The reductive cleavage of the Co, C-bond in methylcobalamin has been shown to be induced by an electron attack requiring a standard

potential of -1.60 V (*vs.* aqueous SCE)[16]) at $-30°$ [12]. In this last publication, studies of the cyclic voltammetry of methylcobinamide are described, showing a single irreversible cathodic wave at low sweep rates corresponding to the fast reductive cleavage of the Co, C-bond. During this process, an overall exchange of two faradays per mol was observed. At high sweep rates[17]), the cathodic wave became progressively reversible, clearly showing the existence of a one-electron intermediate. This intermediate showed fast[18]) cleavage of the Co, C-bond. In another series of experiments [67], cob(I)alamin (**1**(**I**)) was generated electrochemically from aquocob(III)alamin at potentials of -1.5 V (*vs.* Ag/0.01 N $AgNO_3$). The 'supernucleophile' attacked appropriate electrophiles, producing (β-acyloxyethyl)cobalamins[19]) which proved to be stable at this potential. At a cathodic potential of -1.9 to -2.0 V (*vs.* Ag/0.01 N $AgNO_3$), a reductive fragmentation was induced revealing an absorption of two electrons and leading to the corresponding carboxylic acid, ethylene and cob(I)alamin (**1**(**I**)). It has been shown that the electron source, metallic zinc, can also be used to produce the same overall transformation during which **1**(**I**) is generated, and, subsequent to an electron attack on an alkylcobalamin, electrofugal fragmentation is initiated [67].

From the above electrochemical data, the following characteristics can be deduced: alkylcobalamins can be attacked by electrons. They are reduced to an intermediate which shows fast fission of the Co, C-bond, the overall process requiring the absorption of two electrons. As the transformation **3**→**4** proved to be rate-limiting[20]), and as it is mechanistically reasonable to accept that the opening of the epoxide **3** by cob(I)alamin (**1**(**I**)) leads to the two corresponding alkylcobalamins[21]), postulation was justified that a subsequent electrofugal fragmentation generating the intermediate alkenyl acetate **4** could be initiated by an electron attack on the intermediate alkylcobalamins. This process would lead to **4** which is subsequently saturated under the reaction conditions. If this assumption is correct, it should be possible to demonstrate an influence of the electron source on the half-life of **3**. To confirm or deny this, a series of experiments with increasing amounts of zinc was started.

Using the catalyst prepared from 0.1 mol-equiv. of cyanocob(III)alamin (**1**), **3** was reduced in glacial acetic acid at room temperature in the dark under an atmosphere of argon during 52 h. The electron source was used in an excess of 6, 20 and 60 mol-equiv. With the lowest excess of zinc, 27.3% of starting material, 16.5% of product **5**, 17.3% of the intermediate **4** and 24.5% of the acetates **10**–**12**, obtained after nucleophilic opening of the epoxide ring by the solvent, were isolated (s. *Scheme 11*). In *Scheme 11*, an additional column indicates the amounts of reduced products (31.5%) derived from cob(I)alamin only, *i.e.* the amount of **5** plus the

---

[16]) The potential difference between the Ag/Ag^+ electrode in acetonitrile *vs.* SCE is -0.29 V, see [66]. In DMF a difference of -0.36 V was measured, see [16].

[17]) Complete reversibility was reached at 200 V s^{-1} [12].

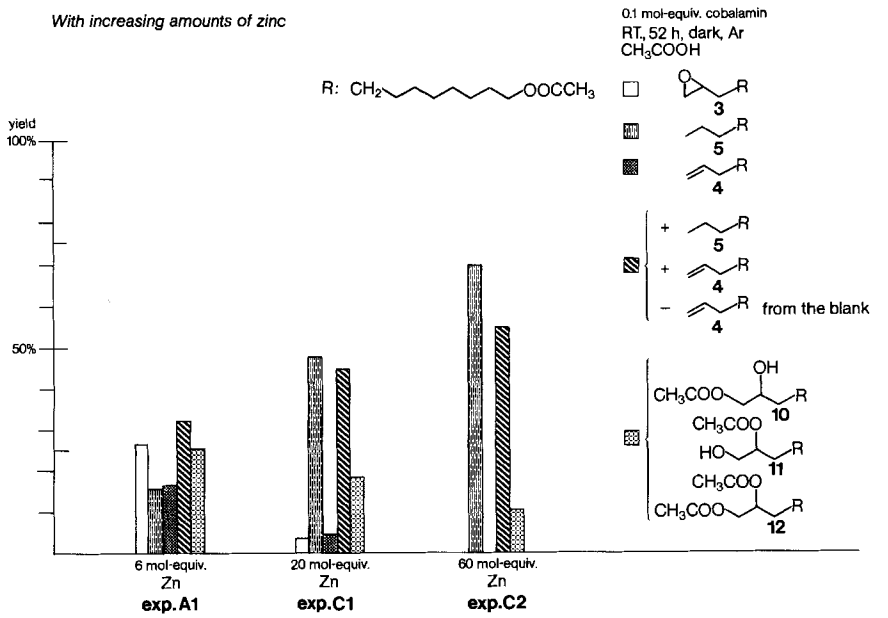
[18]) Rate constant: 2500 s^{-1} at 19°, activation energy 19 kcal/mol.

[19]) Compare the structural resemblance between the (β-acyloxy-ethyl)cobalamins mentioned here and the alkylcobalamins **13** and **14** in *Scheme 12*.

[20]) See *Scheme 10*, *6* and *7*.

[21]) See below, *Scheme 12* (**13** and **14**).

Scheme 11. *Experiments with increasing amounts of zinc*



yield of the olefins **4** and **6** observed in the experiment, minus the amount of **4** detected in the corresponding blank experiment[22]).

Working with 20 mol-equiv. of the electron source, 3.5% of **3**, 47% of **5**, 5.2% of **4** and 18.3% of **10–12** were isolated. The relevant figure indicating the amount of deoxygenated derivatives produced exclusively by the action of cob(I)alamin was distinctly higher (45.9%).

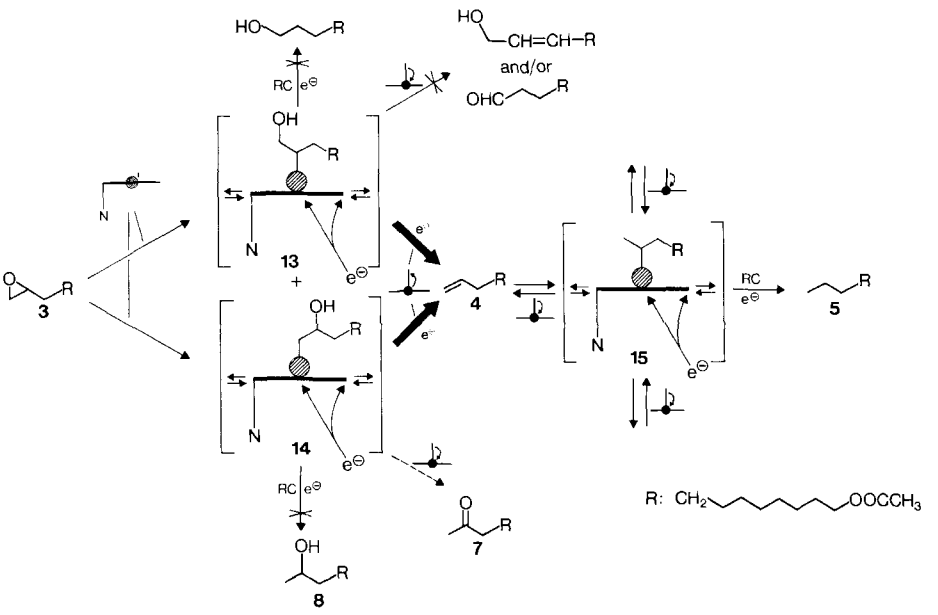
With 60 mol-equiv. of Zn no starting material was found and **4** was detected in only 1.9%. Product **5** was isolated in 71% yield, and the three solvolysis products **10–12** were present in 10.4% yield. The deoxygenated products derived from cob(I)alamin only were calculated to be present in 53.9% yield.

The series of experiments show that, by enhancing the excess of the electron source in the system, the amount of deoxygenation products generated by cob(I)-alamin (**1(I)**) only is increased. Taking into consideration the electrochemical experiments mentioned above and bearing in mind that, in the cob(I)alamin-catalyzed reduction of **3** to **5**, the transformation **3**→**4** has been shown to be rate-limiting (s. *Scheme 10*), it is reasonable to accept an electron attack on a corresponding alkylcobalamin in the rate-limiting step.

4. Mechanistic view of the transformation 3→5. – The starting material **3** is attacked by the 'supernucleophile' cob(I)alamin (**1(I)**) leading to the two theoretically accessible alkylcobalamins **13** and **14** (s. *Scheme 12*). Owing to the steric demand of the nucleophile, it is reasonable to assume that the primary alkylcobal-

[22]) *Schemes 3* and *4* reveal that minor amounts of **4** are formed by a reduction of **3** with zinc only.

Scheme 12[2])



amin **14** is formed as the major product. The presence of this intermediate is disclosed by the product of its nucleofugal fragmentation (s. also *Scheme 2*), which leads to the methyl ketone derivative **7** identified in low yield. The minor isomer is therefore the alkylcobalamin **13** which has not yielded any detectable products following nucleofugal fragmentation[23]). The opening of the oxirane system by cob(I)alamin (**1**(**I**)) is certainly a fast process. Indeed, the reaction of ethylene oxide with **1**(**I**) was shown to be concluded after three minutes[24]). As the deoxygenation **3**→**4** was found to be rate-limiting[25]), and the generation of the intermediate alkylcobalamins **13** and **14** was shown to be a fast process, the rate-limiting transformation must be the electrofugal fragmentation leading to **4**. In view of the electrochemical experiment discussed in *Chapter 3*, it is reasonable to accept that an electron attack on the alkylcobalamins **13** and **14** represents the rate-limiting step in the transformation **3**→**4** under the conditions applied. It is interesting to note that the reduced species obtained after an electronic attack on the alkylcobalamins **13** and **14** does not show a protolytic cleavage of the Co, C-bond, well known in other cases (*cf.* [10]), but leads exclusively to the product of the electrofugal fragmentation. The *β*-hydroxy group in **13** and **14** might have an easy access to the optimal antiperiplanar[26]) conformation required for the electrofugal fragmenta-

---

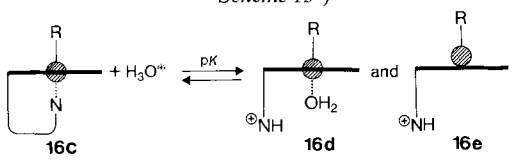
[23]) *I.e.*: the corresponding aldehyde and/or the allylic alcohol (s. *Scheme 12*).

[24]) Yield 74% [68]. Experimental details from other authors show the same reaction to be completed after 30 minutes [54].

[25]) See *Scheme 10*, transformation **3**→**4** using **1**(**I**), $t_{1/2}$ = 11.2 h.

[26]) As the electrofugal fragmentation has been shown to follow *trans*-stereochemistry (s. *Chap. 5*), it is the C,(OH)- and Co,C-bond that have to be arranged in an antiperiplanar situation.

Scheme 13[2])



base-on form — protonated base-off forms

R	p*K*	R	p*K*
OH_2	−2.4 [69]	CH_2CH_2OH	3.15 [47]
CN	+0.1 [69] [70]	CH_2CH_3	3.87 [47]
CH_3	2.7 [69] [71]	$CH(CH_3)_2$	≧5 probably [72]

tion to **4**. This optimal arrangement is automatically produced after the nucleophilic opening of the oxirane system by cob(I)alamin (**1**(**I**)).

The alkenyl acetate **4** itself is also attacked by **1**(**I**) present in the system, with formation of the secondary alkylcobalamin **15**. From this intermediate, three different electrophilic fragmentations are possible leading back to **4**, and to (*E*)- and (*Z*)-9-undecenyl acetate. The experiments show the transient presence of a position isomer of **4** in traces only. The slow[27]) electron attack on the Co-corrin-π system **15** inducing the reductive cleavage leads under the protic conditions applied, to the final product **5**.

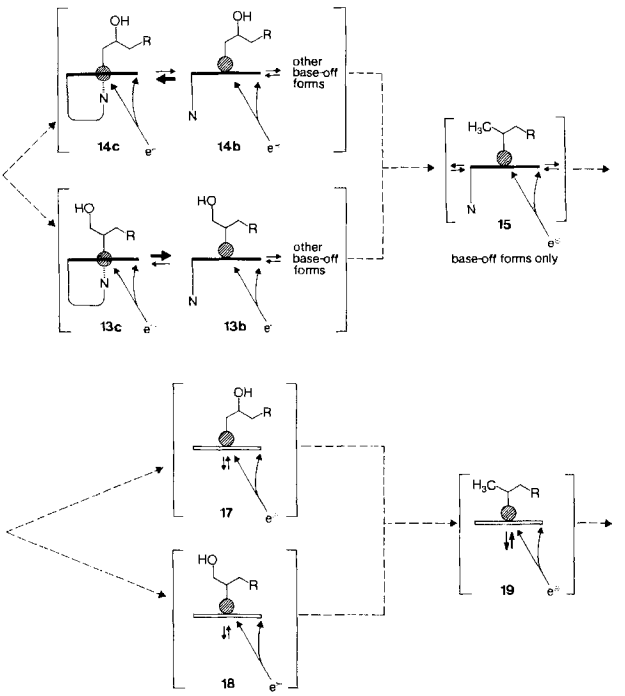
Before discussing the rate differences shown in *Scheme 10*, it is necessary to consider studies dealing with equilibria between base-on and base-off forms in cobalamin derivatives (see *Scheme 13*). The p*K* of the normally existing base-on form of aquocob(III)alamin (**16c**, R = OH_2) has been calculated to be −2.4 [69]. Measurements in sulfuric acid showed that a very strong acid would be needed to open the ribonucleotide loop in aquocob(III)alamin [69]. In vitamin B_{12} itself (**16c**, R = CN), the corresponding p*K* was 0.1 [69] [70]. In methylcobalamin, a 1:1 relation between the base-on form **16c** (R = CH_3) and the two protonated base-off forms **16d** (R = CH_3) and **16e** (R = CH_3) was produced after regulation of the pH at 2.7 [69] [71]. There is a good estimate of the pK_A [73] of the uncoordinated ribonucleotide loop based upon the pK_A (4.7) of the β-anomer of the nucleoside present in the elongated side-chain of vitamin B_{12}.

The p*K* of the equilibrium between the base-on and the base-off forms of methylcobalamin, therefore, leads mainly to the generation of protonated base-off forms (**16d**, **16e**; R = CH_3), and unprotonated derivatives showing a free ribonucleotide loop can be present in traces only (*cf.* [73]). (β-Hydroxyethyl)cobalamin (**16c**; R = CH_2CH_2OH) and ethylcobalamin (**16c**; R = CH_2CH_3) showed p*K*'s of 3.15 and 3.87, respectively [47]. Isopropylcobalamin (**16c**; R = $CH(CH_3)_2$) displayed a p*K* of ≧5 [72] indicating the presence of the base-off forms only, regardless of the pH of the solution[28]). At a higher pH, therefore, unprotonated base-off forms become accessible, and these apparently do not form a macroring by coordination

[27]) For a publication dealing with the rapid equilibrium cob(I)alamin, olefin and $H^{\oplus}$ ⇄ alkylcobalamin as well as for the slow reductive cleavage of the Co,C-bond see [10].

[28]) Compare the $pK_A = 4.7$ of the β-anomer of the nucleoside present in vitamin B_{12} [73].

Scheme 14[2])



of the dimethylbenzimidazole terminus to the central Co-atom. The *trans*-effect revealed by the examples shown in *Scheme 13* has been ascribed to the donation of electrons from the coordinating atom of the ligand on the β-face[29]) to the central Co-atom [74]. In explanation of this phenomenon, it is postulated that the isopropyl residue in **16c** ($R = CH(CH_3)_2$) enhances the electron density on the Co-atom to such an extent that a rupture of the bond between the benzimidazole terminus and the Co-atom is produced. With a lower donation of electrons, as for example in **16c** ($R = CH_3$), the base-on form becomes accessible, and a further decrease of e^--donation from the β-face leads to a strong Co, N-linkage on the α-face which can only be opened protolytically by a very strong acid[30]).

Taking these equilibria into account, the mechanism of the transformations **3**→**5** (s. *Schemes 10* and *12*) using cob(I)alamin (**1**(**I**)) and heptamethyl cob(I)yrinate (**2**(**I**)) as catalysts can be discussed in more detail. The mechanistic pathway disclosed in *Scheme 12* is presented again and in condensed form at the top of *Scheme 14*. The synopsis only shows the different forms of the intermediate alkylcobalamins obtained by varying the ligands on the α-face of the molecule. As it is reasonable to assume that the electron attack on an alkylcobalamin is the rate-

[29]) The face substituted by the three acetic acid side-chains is called β-face.

[30]) Compare **16c** ($R = OH_2$, *Scheme 13*). For the discussion of the equilibria between the octahedral base-off forms and the corresponding protonated or unprotonated tetragonal-pyramidal base-off forms see [2a].

limiting step leading to a fast fission of the Co, C-bond, it is worthwhile discussing the electronic and steric features of the different alkylcobalamins involved. The alkylcobalamins formed during the transformation **3**→**4**→**5** using cob(I)alamin (**1**(**I**)) are shown at the top, and the alkylcobyrinate intermediates produced by an interaction of heptamethyl cob(I)yrinate (**2**(**I**)) are presented at the bottom of *Scheme 14*. After the nucleophilic attack by **1**(**I**) on the oxirane ring of **3**, the primary alkylcobalamin **14** (s. *Scheme 12*) is probably produced in larger amounts. The secondary alkylcobalamin **13** would therefore be the minor isomer. According to the equilibria of alkylcobalamins shown in *Scheme 13*, the intermediate **14** should be present mainly in the base-on form **14c**[31]) under the conditions applied[32]). The secondary alkylcobalamin **13** should clearly prefer the base-off forms as it has to be compared with isopropylcobalamin (**16c**; $R = CH(CH_3)_2$). For the same reasons, the alkylcobalamin **15** should be present in the base-off forms only. For metallic zinc approaching the system, the intermediates **13b** and **15** existing in the base-off forms are easier to attack than **14c** in which the coordinated base inhibits an easy approach of the electron source to the Co-corrin-π system. The rate-limiting electron transfer should therefore be slowest for **14c**. This deduction is in agreement with the experimental data (s. *Scheme 10*).

In the three alkylcobyrinates **17**–**19**, formed from **3** and **2** (**I**), there is sterically an equivalent situation as in **13b** and **15** for the transfer of an electron from an attacking zinc particle to the Co-corrin-π system. Therefore, the production and the saturation of **4** should proceed at a similar rate. The experimental data indicate a slightly higher half-life for the saturation of the intermediate **4** (s. *Scheme 10*).

The regulation of the electron density on the central Co-atom by a ligand on the β-face of the molecule by way of electron donation has been used as an argument to explain the effects shown in *Scheme 13* (*cf.* [74]). Estimating the relative electron density on the central Co-atom in the intermediate alkylcobyrinates **17**–**19** and taking into account the data displayed in *Scheme 13*, the highest electron density on the central Co-atom[33]) should be present in **19**. A medium electron donation from the alkyl residue should be operating in **18**, and the derivative **17**, the (β-hydroxyalkyl)cobyrinate formed in majority, should display the lowest electron density. The overall electron density in the Co-corrin-π system is, certainly, of thermodynamic relevance and should also display kinetic effects as the three possible alkylcobyrinates are *a priori* placed under identical reaction conditions and the steric factors influencing the approach of the electron source can be assumed to be very similar. The reduction of **18** and especially of **17** should be somewhat faster than the electron transfer to **19**, which is in agreement with the experimental data (s. *Scheme 10*).

In the reduction experiments using cob(I)alamin (**1**(**I**)) the same considerations apply to the electron density on the central Co-atom of **13**–**15**. As mentioned above, the major intermediate **14** is present mainly in the base-on form **14c**, the minor intermediate **13** essentially in the base-off forms, and the alkylcobalamin **15**

---

[31]) Compare the $pK = 3.15$ of **16c** ($R = CH_2CH_2OH$).

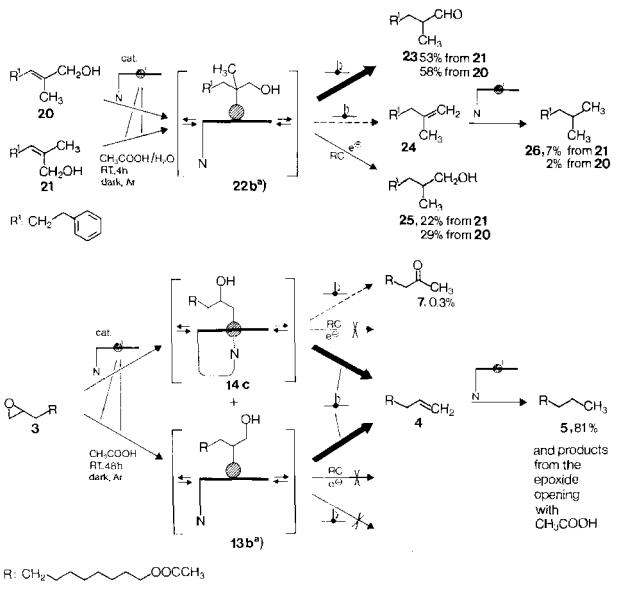
[32]) Aqueous solutions of acetic acid or glacial acetic acid.

[33]) And therefore also in the Co-corrin-π system.

exclusively in the base-off forms. Therefore, the electron density can be estimated to be highest in **14c**, medium in **15** and somewhat lower in **13b**. The medium electron density in **15**, as compared to the higher charge concentration in **14c**, might lead to a faster saturation of the intermediate **4**. This agrees with the experimental data (s. *Scheme 10*). The argument is based on the discussion of electronic effects only and is therefore just one of the factors influencing the rate of the electron transfer from metallic zinc to the Co-corrin-π system. The steric argument has been discussed *(vide supra)* and shown to be in agreement with the experimental data as well.

5. Comments on the stereochemistry of the electrofugal fragmentation of (β-hydroxyalkyl)cobalamins. – The transformation of the allylic alcohols **20** and **21** using catalytic amounts of cob(I)alamin (**1(I)**) has been published [10]. The reaction was shown to produce first the tertiary alkylcobalamin **22** (s. *Scheme 15*) which should exist in the protonated or unprotonated (**22b** (analogous to **16b**)) tetragonal-pyramidal form, according to the data in *Scheme 13* which is discussed in the previous chapter, and according to the studies dealing with the equilibria between octahedral base-off forms and corresponding tetragonal-pyramidal complexes [2b] [72]. The aldehyde **23**, produced by a nucleofugal fragmentation from **22**, was shown to be the major product. Taking into account the conclusions of the experiments **3** → **4** → **5**, it is reasonable to assume that an absorption of electrons by the Co-corrin-π system leads to the alcohol **25** by a protolytic pathway. From the same reduced intermediate, the olefin **24** is formed following an electrofugal fragmentation; the intermediate olefin is subsequently saturated to the isolated hydrocarbon **26**. It has been shown that the aldehyde **23** is stable under the reaction conditions and is therefore not the precursor of the alcohol **25**. It is interesting to note that the tertiary alkylcobalamin is obviously prone to fragment by an nucleofugal pathway. This might be the consequence of the degree of electron density on the central Co-atom of a tetragonal-pyramidal complex, which is relatively low compared with the higher electron density in the octahedral primary

Scheme 15[2])



[a]) The preferred form of the equilibrium given in footnote 2 is reproduced.

alkylcobalamins[34]) which are more stable under the reaction conditions. In addition, it is notable that the electron attack on the Co-corrin-π system does not lead exclusively to the product of an electrofugal fragmentation (*i.e.* **24**) as is the case in the transformation **3**→**4**→**5** shown at the bottom of *Scheme 15*. The olefin **24** is only a minor product[35]), and the protolytic cleavage of the Co,C-bond leads to the alcohol **25** in 22% (from **21**) and 29% yield (from **20**), respectively. As the electrofugal fragmentation of alkylcobalamins triggered by an electron attack on the Co-corrin-π system has been shown [75] to follow *trans*-stereochemistry, we explain the relative amounts of **24** and **25** as the consequence of difficult access to the optimal fragmentation geometry displaying the C,OH- and the Co,C-bond of the alkylcobalamin **22** in antiperiplanar conformation.

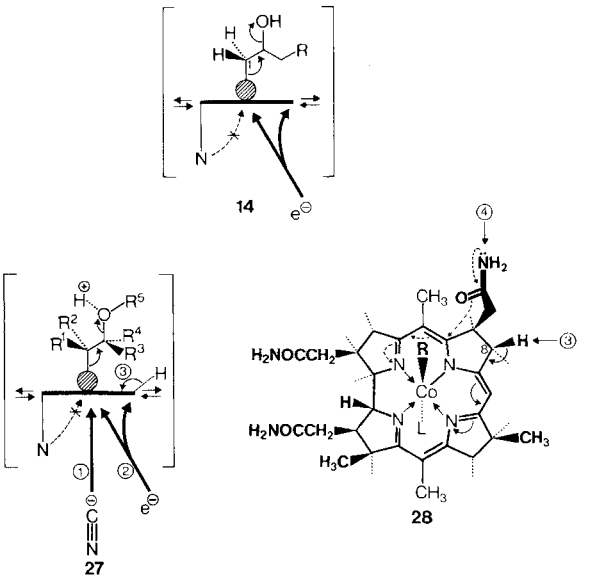
On the other hand, the epoxide **3** is mainly opened by cob(I)alamin (**1**(**I**)) at the terminal position leading to a primary alkylcobalamin which exists, as discussed above, primarily in the base-on form **14c**. The experiment shows that **14c** is not disposed to induce nucleofugal fragmentation as displayed by the methyl ketone **7** which is isolated in traces only (0.3%). The stability of the primary alkylcobalamin **14c** could be due to a somewhat enhanced electron density on the central Co-atom generated by the coordination of the benzimidazole terminus to the Co-atom. The electron attack on the Co-corrin-π system of **14c** leads in this case exclusively to the product of the electrofugal fragmentation **4**. No traces of the product from a protolytic cleavage of the Co,C-bond were detected. To explain this behavior, we postulate that there is an easy access to the optimal antiperiplanar fragmentation geometry. It might be of some significance that this conformation is obtained just after opening of the oxirane ring.

6. Final comment. – Under the conditions applied, electrofugal fragmentation is initiated by an enhancement of electron density on the central Co-atom produced after electron attack on the Co-corrin-π system (s. **14** and **27** (reaction ②, *Scheme 16*). In the primary alkylcobalamin **14** the ribonucleotide is mainly coordinated to the Co-atom, as discussed in the previous chapter, thereby enhancing the electron density in the Co-corrin chromophore. This electronic effect is obviously not great enough to initiate an electrofugal fragmentation. In the base-on form **14c** (s. *Scheme 15*) an alkylcobalamin seems to be sterically and electronically protected to some degree from an interaction which would lead to a strong increase of electron density in the Co-corrin-π system. The attack by cyanide on the α-face of coenzyme B_{12} (*cf.* [49] and *Scheme 16*, **27** (reaction ①)) might serve as an example illustrating that an appropriate electron density in the Co-corrin chromophore induces electrofugal fragmentation. In coenzyme B_{12} the ribonucleotide loop might also have the function of protecting the system and guaranteeing the structural integrity of the coenzyme. Up to now, examples only of electrofugal fragmentations initiated by a high electron density on the Co-atom have been discussed. There is naturally the question of whether electrofugal fragmentations of corresponding alkylcobalamins are possible without an increased electron density on the central Co-atom, in spite of the fact that alkylcobalamins show only 6 d-electrons and a total of 16 electrons around the Co-atom in the base-off form. The fragmentation of (β-hydroxyethyl)cobalamin (*cf.* [46] [47]) in aqueous hydrochloric acid leading to cob(III)alamin, ethylene and water might serve as an example of

[34]) *Cf. Scheme 15* at the bottom and *vide infra*.

[35]) *Ca.* 7% from **21** and *ca.* 2% from **20**.

Scheme 16[2])



fragmentation initiated by an electron-poor Co-corrin-π system. An examination of the publications in the field shows that, even under these conditions, an enhancement of the electron density in the Co-corrin-π system cannot be excluded. In this case, peripheral deprotonation of the corrinoid system, studied and described as preferential loss of the proton in position 8 (*cf.* **28** (reaction ③ [76])), might be possible. It is at this position that oxidation under acidic conditions[36]), similar to the acidic milieu in the electrofugal fragmentation mentioned above, has been achieved. The oxidation mechanism has been formulated to lead primarily to a deprotonated system possessing an sp^2-C-atom at position 8 and, therefore, having an extended chromophore. Such a deprotonated species shows an enhanced electron density in the π-system as a result of the delocalization of the negative charge produced after proton expulsion.

Another theoretical possibility of enhancing electron density on the central Co-atom might be a nucleophilic attack by, for instance, the acetic acid side-chain in ring B on the C-atom in position 6 leading to an interrupted corrin chromophore and to an increased electron density on the central Co-atom (s. *Scheme 16*, **28** (reaction ④)). Such a reactivity would lead to intermediate structures showing some resemblance to the stable yellow corrinoids [81] [82] formed, for example, after treatment with ascorbic acid in the presence of oxygen [83–85]. There is no information in the literature to indicate that such a participation of a side chain would trigger an electrofugal fragmentation of an appropriate alkylcobalamin.

---

[36]) The c-lactone is formed by cyclization of the acetic acid side-chain in ring B to the C-atom at position 8. For an oxidation in aqueous hydrochloric acid using chloramine-T and starting from a) cyanocob(III)alamin, see [77]; b) methylcob(III)alamin, see [78–80]; and c) coenzyme B_{12}, see [78] [79].

The author would like to express his gratitude to his colleagues from the Central Research Units, and in particular to Dr. *A. Dirscherl* (microanalysis), Dr. *M. Vecchi* (GC.), *G. Oesterheld* (GC./MS.), Dr. *L. Chopard* (IR.), Dr. *G. Englert* (NMR.), Dr. *W. Arnold* (NMR.) and *W. Meister* (MS.) for the analytical and spectroscopic data.

Experimental Part

General remarks. – S. [10] [14] [86]. The procedure followed during a usual or normal extraction is described in [14]. Except in the kinetic experiments, the catalysts were prepared following the prescriptions published in [9]. The preparation of the catalysts used in the kinetic experiments is given below. Abbreviations: r.t. = room temperature.

A. Reductions of the epoxy acetate 3 and the alkenyl acetate 4. – A-1. *Reduction of* **3** *to 10-undecenyl acetate* (**4**), *undecyl acetate* (**5**) *and by-products* **6–12** *using cob(I)alamin* (**1**(**I**)) *as catalyst.* Following the procedure described earlier [9], 600 mg (0.1 mol-equiv.) of cyanocob(III)alamin (**1**) was transformed into the catalyst. Prior to the complete elimination of acetic acid, the metallic zinc was removed by filtration, and the red filtrate was evaporated to dryness at 50°. The residue was dissolved in 30 ml of glacial acetic acid, and 1.7 g (6 mol-equiv.) of activated[37]) metallic zinc were added to the red solution. The suspension was stirred at r.t. under Ar until[38]) a dark green colour revealed the presence of cob(I)alamin (**1**(**I**)). To the suspension of the soluble catalyst and the electron source was added 1.0 g of **3** in 10 ml of glacial acetic acid[39]). The mixture was stirred in the dark at r.t. for 52 h under Ar. Following the usual extraction procedure, the crude product was separated by chromatography (SiO_2, ether/hexane 1:10, ether): 273 mg (27.3%) of **3**, 161 mg (17.3%) of **4**, 155 mg (16.5%) of **5**, 7.5 mg (0.8%) of **6**, 10 mg (1.0%) of **7**, 15 mg (1.5%) of **8**, 8.4 mg (0.7%) of **9**, 190 mg (15.0%) of **10**, 116 mg (9.2%) of **11**, and 4.4 mg (0.3%) of **12**.

Data of **3**. Rf 0.31 (ether/hexane 1:2), t_R (GC., 100→280°) 15.0 min. – IR. (liq.): 3080 (CH, epoxide); 1747 (C=O, ester); 1245, 1140 (ester); 840 (epoxide). – ^{1}H-NMR.: 1.2–1.85 (*m*, 16 H, 8 CH_2); 2.03 (*s*, 3 H, CH_3COO); 2.4–3.2 (*m*, 3 H, H–C(10) and 2 H–C(11)); 4.08 (*t*, *J* = 6, 2 H, 2 H–C(1)). – MS. (CI.): 246 (55, $[M+NH_4]^+$), 229 (100, $[M+H]^+$), 169 (18, $M^+ - CH_3COO$), 157 (62), 109 (11), 95 (36), 35 (20).

Data of **4**. Rf 0.5 (ether/hexane 1:2); t_R (GC., 200→280°) 9.56 min. – IR. (liq.): 3105 (CH_2, olefine); 1752 (C=O, ester); 1245 (ester); 911 (vinyl). – ^{1}H-NMR.: 1.1–2.3 (*m*, 16 H, 8 CH_2); 2.04 (*s*, 3 H, CH_3COO); 4.09 (*t*, *J* = 6, 2 H, 2 H–C(1)); 4.94 (br. *d*, *J* = 11, 1 H, 1 H–C(11)); 4.97 (br. *d*, *J* = 17, 1 H, 1 H–C(11)); 5.5–6.2 (*m*, 1 H, H–C(10)). – MS.: 152 (7, $M^+ - CH_3COOH$), 124 (9), 110 (20), 95 (36), 82 (60), 68 (65), 55 (72), 43 (100, CH_3CO^+).

Data of **5**. Rf 0.5 (ether/hexane 1:2); t_R (GC., 100→280°) 9.83 min. – IR. (liq.): 1754 (C=O, ester); 1242 (ester). – ^{1}H-NMR.: 0.9 (br. *t*, *J* = 6, 3 H, 3 H–C(11)); 1.15–1.85 (*m*, 18 H, 9 CH_2); 2.05 (*s*, 3 H, CH_3COO); 4.08 (*t*, *J* = 6, 2 H, 2 H–C(1)). – MS.: 154 (2.5, $M^+ - CH_3COOH$), 125 (10), 111 (8), 97 (24), 83 (32), 69 (40), 61 (22, $CH_3COOH_2^+$), 55 (51), 43 (100, CH_3CO^+).

Data of **6** *(undecenyl acetate).* Rf 0.5 (ether/hexane 1:2); t_R (GC., 100→280°) 10.1 min. – GC./MS.: 152 (11, $M^+ - CH_3COOH$), 123 (3), 109 (12), 95 (18), 81 (32), 68 (81), 67 (41), 55 (81), 43 (100, CH_3CO^+), 29 (26). – The ^{1}H-NMR. of a mixture of **4**–**6** shows a signal at 5.3–5.45 (*m*, CH=CH).

Data of **7** *(10-oxoundecyl acetate).* Rf 0.30 (ether/hexane 1:2); t_R (GC., 100→280°) 14.6 min. – IR. (liq.): 1730 (C=O, ester, ketone); 1248 (ester). – ^{1}H-NMR.: 1.1–2.4 (*m*, 16 H, 8 CH_2); 2.04 (*s*, 3 H, CH_3COO); 2.11 (*s*, 3 H, 3 H–C(11)); 4.06 (*t*, *J* = 6, 2 H, 2 H–C(1)). – MS.: 185 (1, $M^+ - CH_3CO$), 171 (2), 153 (1), 111 (53), 97 (4), 81 (10), 69 (73), 67 (13), 58 (63, $CH_3COCH_3^+$), 55 (59), 43 (100, CH_3CO^+), 41 (29).

Data of **8** *(10-hydroxyundecyl acetate).* Rf 0.1 (ether/hexane 1:2); t_R (GC., 100→280°) 22.4 min. – IR. (liq.): 3485 (OH); 1742 (C=O, ester); 1242 (ester); 1049 (alcohol-II band). – ^{1}H-NMR.: 1.2 (*d*, *J* = 6.5, 3 H, 3 H–C(11)); 1.15–1.85 (*m*, 17 H, 8 CH_2 and HO); 2.04 (*s*, 3 H, CH_3COO); 3.78–3.9 (*m*, 1 H, H–C(10)); 4.05 (*t*, *J* = 6, 2 H, 2 H–C(1)). – GC./MS. (after trimethylsilylation): 287 (1,

---

[37]) For the procedure used to activate zinc, see [9].

[38]) For the development of the green color, a period of 5–10 min was usually required.

[39]) Owing to the access of air after opening the flask, the color turned again back to red.

$[M+(CH_3)_3Si]^+ - CH_3$), 133 (11), 117 (100, $(CH_3)_3SiOCHCH_2^+$), 73 (39), 69 (4), 55 (7), 43 (19, CH_3CO^+), 41 (3), 28 (5).

Data of **9** *(undecamethylene diacetate).* Rf 0.31 (ether/hexane 1:2); t_R (GC., 100→280°) 14.2 min. – IR. (liq.): 1743 (C=O, ester); 1247 (ester). – ^{1}H-NMR.: 1.2–1.8 (*m*, 18 H, 9 CH_2); 2.03 (*s*, 6 H, 2 CH_3COO); 4.06 (*t*, *J* = 6, 4 H, 2 H–C(1), 2 H–C(11)).

Data of **10** *(2-hydroxyundecamethylene diacetate).* Rf 0.53 (ether); t_R (GC., 100→280°) 23.3 min. – IR. (liq.): 3490 (OH); 1744 (C=O, ester); 1243 (ester); 1046 (alcohol-II band). – ^{1}H-NMR.: 1.1–1.8 (*m*, 16 H, 8 CH_2); 1.85–2.0 (*m*, 1 H, HO); 2.03 (*s*, 3 H, CH_3COO); 2.09 (*s*, 3 H, CH_3COO); 3.75–3.9 (*m*, 1 H, H–C(2)); 3.95 (*A*-part of *ABC*-system, $J_{AB} = 11$, $J_{AC} = 7.5$, 1 H, 1 H–C(1)); 4.04 (*t*, *J* = 6.5, 2 H, 2 H–C(11)); 4.15 (*B*-part of *ABC*-system, $J_{AB} = 11$, $J_{BC} = 3$, 1 H, 1 H–C(1)). – MS.: 215 (18, $M^+ - CH_3COOCH_2$); 155 (3, $M^+ - CH_3COOCH_2 - CH_3COOH$), 137 (11, $M^+ - CH_3COOCH_2 - CH_3COOH - H_2O$), 95 (27), 81 (27), 69 (24), 55 (25), 43 (100, CH_3CO^+).

Data of **11** *(11-hydroxy-1,10-undecanediyl diacetate).* Rf 0.67 (ether); t_R (GC., 100→280°) 22.8 min. – IR. (liq.): 3485 (OH); 1742 (C=O, ester); 1241 (ester); 1041 (alcohol-II band). – ^{1}H-NMR.: 1.1–1.9 (*m*, 17 H, 8 CH_2 and HO); 2.02 (*s*, 3 H, CH_3COO); 2.08 (*s*, 3 H, CH_3COO); 3.62 (*A*-part of *ABC*-system, $J_{AB} = 12.5$, $J_{AC} = 6.5$, 1 H, 1 H–C(11)); 3.72 (*B*-part of *ABC*-system, $J_{AB} = 12.5$, $J_{BC} = 3.5$, 1 H, 1 H–C(11)); 4.04 (*t*, *J* = 6.5, 2 H, 2 H–C(1)); 4.85–4.95 (*m*, 1 H, H–C(10)). – MS.: 215 (13, $M^+ - CH_3COOCH_2$), 155 (1, $M^+ - CH_3COOCH_2 - CH_3COOH$), 137 (20, $M^+ - CH_3COOCH_2 - CH_3COOH - H_2O$), 95 (29), 81 (68), 69 (13), 55 (19), 43 (100, CH_3CO^+).

Data of **12** *(1,2,11-undecanetriyl triacetate).* Rf 0.11 (ether/hexane 1:2); t_R (GC., 100→280°) 21.0 min. – IR. (liq.): 1745 (C=O, ester); 1247 (ester). – ^{1}H-NMR.: 1.1–1.6 (*m*, 16 H, 8 CH_2); 2.03 (*s*, 3 H, CH_3COO); 2.04 (*s*, 3 H, CH_3COO); 2.1 (*s*, 3 H, CH_3COO); 3.98 (*A*-part of *ABC*-system, $J_{AB} = 12$, $J_{AC} = 6$, 1 H, 1 H–C(1)); 4.03 (*t*, *J* = 6.5, 2 H, 2 H–C(11)); 4.17 (*B*-part of *ABC*-system, $J_{AB} = 12$, $J_{BC} = 4$, 1 H, 1 H–C(1)); 4.85–5.0 (*m*, 1 H, H–C(2)). – MS.: 257 (2, $M^+ - CH_3COOCH_2$), 227 (3), 215 (41, $M^+ - CH_3COOCH_2 - CH_2CO$), 137 (10), 95 (21), 81 (23), 67 (18), 55 (20), 43 (100, CH_3CO^+), 41 (17), 28 (9).

Blank experiment parallel to the transformation A-1. Similarly to procedure A-1 1.7 g (6 mol-equiv.) of activated[37]) metallic zinc suspended in a solution of 1.0 g of **3** in 40 ml of glacial acetic acid was stirred for 52 h in the dark under Ar. After a usual extraction and a chromatographic separation as described in A-1, 614 mg (61.4%) of **3**, 30.5 mg (3.3%) of **4**, 5 mg (0.5%) of **7**, 18 mg (1.8%) of **8**, 8.4 mg (0.7%) of **9**, 200 mg (16%) of **10**. 129 mg (10.2%) of **11**, and 11.6 mg (0.8%) of **12** were isolated[40]).

A-2. *Reduction of* **3** *to* **4**, **5** *and by-products* **6**–**12** *using heptamethyl cob(I)yrinate* (**2**(**I**))[41]) *as catalyst.* Parallel to the preparation of the catalyst as described in A-1, 477 mg (0.1 mol-equiv.) of heptamethyl dicyano-cob(III)yrinate (**2**) were transformed into **2**(**I**). The red residue was dissolved in 30 ml of glacial acetic acid, and 5.7 g (20 mol-equiv.) of activated[37]) metallic zinc were added. The suspension was stirred at r.t. under Ar until[38]) a dark green color revealed the presence of **2**(**I**). A solution of 1.0 g of **3** in 10 ml of glacial acetic acid was added to the suspension. The mixture was stirred in the dark at r.t. for 52 h under Ar. Following the usual extraction, the crude product was separated by chromatography (SiO_2, ether/hexane 1:10; ether): 10 mg (1.0%) of **3**, 274 mg (29.5%) of **4**, 484 mg (51.5%) of **5**, 18.6 mg (2.0%) of **6**, 10 mg (1.0%) of **7**, 15.1 mg (1.5%) of **8**, 6.0 mg (0.5%) of **9**, 75.5 mg (6.0%) of **10**, 25.3 mg (2.0%) of **11**, and 6.3 mg (0.5%) of **12**[40]).

The blank experiment parallel[42]) *to the transformation A-2* led to 620 mg (62%) of **3**, 67 mg (7.2%) of **4**, 7 mg (0.7%) of **7**, 16.1 mg (1.6%) of **8**, 8.3 mg (0.7%) of **9**, 151.5 mg (12.0%) of **10**, 101 mg (8.0%) of **11** and 10 mg (0.7%) of **12**[40]).

A-3. *Reduction of* **4** *to* **5** *using* **1**(**I**) *as catalyst.* As described in A-1, 650 mg (0.1 mol-equiv.) of **1** and 6.15 g (20 mol-equiv.) of activated[37]) zinc were used to transform 1.0 g of **4** into **5**. As solvent, 40 ml of glacial acetic acid were used, and the suspension was stirred at r.t. for 52 h in the dark under Ar. After the usual extraction and chromatographic purification, 890 mg (95%) of **5**[40]) were isolated. No by-products were observed.

A-4. *Reduction of* **4** *to* **5** *using* **2**(**I**) *as catalyst.* As in A-3, 500 mg of **4** were saturated using **2**(**I**) (prepared from 256.5 mg of **2**), 3.1 g (20 mol-equiv.) of activated[37]) metallic zinc, and 20 ml of

---

[40]) For the data of **3**–**12** see A-1.

[41]) For the preparation of **2** see [87].

[42]) With 1.0 g of **3**, 5.7 g (20 mol-equiv.) of activated[37]) zinc, 40 ml of glacial acetic acid, at r.t., 53 h in the dark, under Ar.

glacial acetic acid. The suspension was stirred for 52 h at r.t. in the dark under Ar. After the usual extraction and chromatographic purification, 438 mg (93%) of **5**[40]) were isolated. No by-product was observed.

After the blank experiment parallel to the reductions A-3 and A-4, unchanged starting material **4** was isolated. The saturated product **5** could not be detected.

B. Kinetic experiments. – B-1. *Reduction of* **3** *using* **1(I)** *as catalyst.* For the kinetic experiments, the catalyst was prepared as follows: 17.2 g (20 mol-equiv.) of activated[37]) zinc were added to a solution[43]) of 1.8 g (0.1 mol-equiv.) of **1** in 60 ml of glacial acetic acid. The suspension was stirred at 70° under Ar for 20 min. The solution was concentrated under reduced pressure[44]) at r.t. to about 60% of the volume. After elimination of the metallic zinc by filtration, the solvent was removed at 50° using a rotatory evaporator. The red residue was dissolved in 90 ml of glacial acetic acid, 17.2 g (10 mol-equiv.) of activated[37]) zinc were added, and the suspension was stirred under Ar until[38]) a green color revealed the presence of **1(I)**.

A solution of **3** (3.0 g) in 30 ml of glacial acetic acid was added, and the mixture was stirred at r.t. in the dark under Ar. From this suspension, samples of 1 ml were taken using a syringe, and, after usual extraction, the product distribution in the samples was analyzed by GC. comparing the products formed with authentic **3**–**5**[40]). The results obtained are given in the *Table B-1.*

B-2. *Saturation of* **4** *using* **1(I)** *as catalyst.* Using exactly the same procedure as in B-1, 1.95 g (0.1 mol-equiv.) of **1** were transformed into **1(I)** using 18.6 g (20 mol-equiv.) of activated[37]) zinc. Dissolved in 30 ml of glacial acetic acid, 3.0 g of **4** were added to the suspension of 18.6 g of activated[37]) zinc in 90 ml of a solution of **1(I)** in glacial acetic acid. The mixture was stirred at r.t. in the dark under Ar. The samples taken using a syringe yielded the results[40]) given in the *Table B-2.*

Table B-1.

Time [h]	**3**[a]) [%]	**4**[%]	**5** [%]	Time [h]	**3**[a]) [%]	**4** [%]	**5** [%]
1/2	92.3	2.5	0.9	22	28.9	7.2	49.8
1	87.3	5.3	3.0	24	20.1	5.1	56.0
2	83.1	6.9	5.3	27	16.2	5.3	62.1
4	75.5	6.0	9.4	30	12.3	3.1	68.2
6	66.2	8.0	13.8	40	3.7	–	78.0
8	59.2	9.5	17.2	42	2.2	–	77.7
10	53.7	11.6	22.1	44	1.5	–	78.3
16	39.8	9.4	35.0	46	1.4	–	78.2
18	34.9	9.2	42.3	48	0.6	–	80.0
20	32.2	8.7	46.7	50	–	–	79.3

[a]) $t_{1/2}$ (**3**) = 11.2 h (see *Schemes 6* and *10*).

Table B-2.

Time [h]	**4**[a]) [%]	**5** [%]	**6** [%]	Time [h]	**4**[a]) [%]	**5** [%]	**6** [%]
1/2	80.3	14.8	1.1	7	4.2	82.2	7.3
1	70.7	23.1	1.9	8	2.9	85.1	7.0
2	56.1	34.0	3.1	9	2.1	88.9	5.1
3	41.9	47.7	4.6	10	1.7	90.0	3.2
4	31.0	58.2	5.7	12	1.1	89.6	1.6
5	19.5	68.1	6.5	15	0.8	90.3	1.1
6	10.0	76.3	7.1				

[a]) $t_{1/2}$ (**4**) = 2.5 h (see *Schemes 7* and *10*).

[43]) Gentle warming was needed to dissolve the crystals of vitamin B_{12} completely.

[44]) Evaporation for 6 min at 17 Torr.

Table B-3.

Time [h]	3[a]) [%]	4 [%]	5 [%]	Time [h]	3[a]) [%]	4 [%]	5 [%]
1/2	79.8	14.2	0.6	13	4.3	45.1	48.0
1	51.5	37.6	1.9	20	1.5	26.8	52.3
2	39.9	46.0	7.1	23	1.5	22.3	58.0
4	25.2	52.5	12.2	24	1.1	21.7	58.2
6	16.6	57.5	16.8	26	1.3	17.1	61.8
8	9.8	55.0	25.7	28	0.8	15.3	67.4
10	7.2	53.2	31.9	30	-	12.4	70.0

[a]) $t_{1/2}$ (**3**) = 1.1 h (see *Schemes 8* and *10*).

Table B-4.

Time [h]	4[a]) [%]	5 [%]	6 [%]	Time [h]	4[a]) [%]	5 [%]	6 [%]
1/2	77.0	16.7	0.5	7	11.0	78.2	3.0
1	63.5	28.0	0.8	8	5.1	84.9	2.9
2	47.9	46.1	1.7	9	4.2	87.5	2.8
3	36.8	55.7	2.0	10	3.1	87.9	2.8
4	27.1	64.7	2.3	12	2.0	89.1	2.8
5	20.8	59.8	2.8	15	0.6	91.0	2.0
6	15.9	75.3	2.9				

[a]) $t_{1/2}$ (**4**) = 1.8 h (see *Schemes 9* and *10*).

B-3. *Reduction of* **3** *using* **2(I)** *as catalyst.* Using exactly the same procedure as in B-1, 1.43 g (0.1 mol-equiv.) of **2** were transformed into **2(I)** with 17.2 g (20 mol-equiv.) of activated[37]) zinc. Dissolved in 30 ml of glacial acetic acid, 3.0 g of **3** were added to the suspension of 17.2 g of activated[37]) zinc in 90 ml of a solution of **2(I)** in glacial acetic acid. The mixture was stirred at r.t. in the dark under Ar. The samples taken using a syringe as in B-1 showed the distribution of products[40]) given in the *Table B-3.*

B-4. Reduction of **4** *using* **2(I)** *as catalyst.* Following the same procedure as in B-1, 1.54 g (0.1 mol-equiv.) of **2** were transformed into **2(I)** using 18.6 g (20 mol-equiv.) of activated[37]) metallic zinc. Dissolved in 30 ml of glacial acetic acid, 3.0 g of **4** were added to the suspension of 18.6 g of activated[37]) zinc in 90 ml of a solution of **2(I)** in glacial acetic acid. The mixture was stirred at r.t. in the dark under Ar. The samples taken using a syringe yielded the distribution of products in the GC. analysis[40]) given in the *Table B-4.*

C. Experiments with increasing amounts of zinc. – C-1. *Reduction of* **3** *with* **1(I)** *using 20 mol-equiv. of zinc.* Following the procedure described in A-1, 600 mg (0.1 mol-equiv.) of **1** were transformed into **1(I)**. Dissolved in 10 ml of glacial acetic acid, 1.0 g of **3** were added to a suspension of 5.7 g (20 mol-equiv.) of activated zinc[37]) in 30 ml of a solution of **1(I)** in glacial acetic acid. The mixture was stirred for 52 h at r.t. in the dark under Ar. After the usual extraction and chromatographic separation (SiO_2, ether/hexane 1:10, ether) the following products[40]) were isolated: 35 mg (3.5%) of **3**, 48.5 mg (5.2%) of **4**, 441 mg (47%) of **5**, 8.4 mg (0.9%) of **6**, 12 mg (1.2%) of **7**, 10 mg (1.0%) of **8**, 6 mg (0.5%) of **9**, 164 mg (13%) of **10**, 63.2 mg (5.0%) of **11**, and 4.3 mg (0.3%) of **12**.

The corresponding blank experiment is described *(vide supra)* as control experiment of the transformation A-2.

C-2. *Reduction of* **3** *with* **1(I)** *using 60 mol-equiv. of zinc.* Following exactly the procedure described in C-1, but using 17 g (60 mol-equiv.) of activated[37]) zinc, the following products[40]) were isolated: 1.9 mg (0.2%) of **4**, 667 mg (71%) of **5**, 13 mg (1.3%) of **7**, 9 mg (0.9%) of **8**, 8.3 mg (0.7%) of **9**, 78.5 mg (6.2%) of **10**, 51.8 mg (4.1%) of **11**, and 2.9 mg (0.2%) of **12**.

The blank experiment parallel to C-2 produced 360 mg (36%) of **3**, 177 mg (19%) of **4**, 10 mg (1.0%) of **7**, 23.1 mg (2.3%) of **8**, 10.7 mg (0.9%) of **9**, 202 mg (16%) of **10**, 126 mg (10%) of **11**, and 14.5 mg (1.0%) of **12**[40]).

REFERENCES

[1] *A. Fischli & J.J. Daly*, Helv. Chim. Acta *63*, 1628 (1980).
[2] *J.M. Pratt*, 'Inorganic Chemistry of Vitamin B_{12}', Academic Press, New York 1972; a) p. 124ff.; b) p. 130ff.; c) p. 236ff., 266ff.
[3] *G. Costa, G. Mestroni, G. Tauzher & L. Stefani*, J. Organomet. Chem. *6*, 181 (1966); *G. Costa & G. Mestroni*, ibid. *11*, 325 (1968); *S. Brückner, M. Calligaris, G. Nardin & L. Randaccio*, Inorg. Chim. Acta *3*, 308 (1969); *G. Costa, G. Mestroni & L. Stefani*, J. Organomet. Chem. *7*, 493 (1967); *H.A.O. Hill, J.M. Pratt & R.J.P. Williams*, Chem. Ind. *1964*, 197; *R.A. Firth, H.A.O. Hill, B.E. Mann, J.M. Pratt, R.G. Thorp & R.J.P. Williams*, J. Chem. Soc. (A) *1968*, 2419.
[4] *W. Friedrich & R. Messerschmidt*, Z. Naturforsch. *24B*, 465 (1969).
[5] *G.N. Schrauzer, J.W. Sibert & R.J. Windgassen*, J. Am. Chem. Soc. *90*, 6681 (1968).
[6] *W. Friedrich & J.P. Nordmeyer*, Z. Naturforsch. *23B*, 1119 (1968).
[7] *J.M. Pratt*, J. Chem. Soc. *1964*, 5154.
[8] *D.H. Dolphin, A.W. Johnson & R. Rodrigo*, J. Chem. Soc. *1964*, 3136.
[9] *A. Fischli & D. Süss*, Helv. Cim. Acta *62*, 48 (1979).
[10] *A. Fischli & P.M. Müller*, Helv. Chim. Acta *63*, 529 (1980).
[11] *A. Fischli & P.M. Müller*, Helv. Chim. Acta *63*, 1619 (1980).
[12] *D. Lexa & J.-M. Savéant*, J. Am. Chem. Soc. *100*, 3220 (1978).
[13] *A.I. Scott, J. Kang, D. Dalton & S.K. Chung*, J. Am. Chem. Soc. *100*, 3603 (1978).
[14] *A. Fischli*, Helv. Chim. Acta *61*, 2560 (1978).
[15] *L. Walder, G. Rytz, K. Meier & R. Scheffold*, Helv. Chim. Acta *61*, 3013 (1978).
[16] *R. Scheffold, M. Dike, S. Dike, T. Herold & L. Walder*, J. Am. Chem. Soc. *102*, 6342 (1980).
[17] *M. Flavin & S. Ochoa*, J. Biol. Chem. *229*, 965 (1957).
[18] *E.R. Stadtman, P. Overath, H. Eggerer & F. Lynen*, Biochem. Biophys. Res. Commun. *2*, 1 (1960).
[19] *H. Eggerer, P. Overath, F. Lynen & E.R. Stadtman*, J. Am. Chem. Soc. *82*, 2643 (1960).
[20] *R. Stjernholm & H.G. Wood*, Proc. Natl. Acad. Sci. U.S.A. *47*, 303 (1961).
[21] *J.N. Lowe & L.L. Ingraham*, J. Am. Chem. Soc. *93*, 3801 (1971).
[22] *G. Bidlingmaier, H. Flohr, U.M. Kempe, T. Krebs & J. Rétey*, Angew. Chem. *87*, 877 (1975).
[23] *P. Dowd & M. Shapiro*, J. Am. Chem. Soc. *98*, 3724 (1976).
[24] *A.I. Scott & K. Kang*, J. Am. Chem. Soc. *99*, 1997 (1977).
[25] *H. Flohr, W. Pannhorst & J. Rétey*, Helv. Chim. Acta *61*, 1565 (1978).
[26] *A.I. Scott, J. Kang, D. Dalton & S.K. Chung*, J. Am. Chem. Soc. *100*, 3603 (1978).
[27] *L. Tsai, I. Pastan & E.R. Stadtman*, J. Biol. Chem. *241*, 1807 (1966).
[28] *H.F. Kung, S. Cederbaum, L. Tsai & T.C. Stadtman*, Proc. Natl. Acad. Sci. U.S.A. *65*, 978 (1970).
[29] *H.F. Kung & T.C. Stadtman*, J. Biol. Chem. *246*, 3378 (1971).
[30] *P. Dowd, B.K. Trivedi, M. Shapiro & L.K. Marwaha*, J. Am. Chem. Soc. *98*, 7875 (1976).
[31] *A. Bury, M.R. Ashcroft & M.D. Johnson*, J. Am. Chem. Soc. *100*, 3217 (1978).
[32] *M.P. Atkins, B.T. Golding & P.J. Sellers*, J. Chem. Soc., Chem. Commun. *1978*, 954.
[33] *M.P. Atkins, B.T. Golding, A. Bury, M.D. Johnson & P.J. Sellars*, J. Am. Chem. Soc. *102*, 3630 (1980).
[34] *T.C. Stadtman*, Science *171*, 859 (1971).
[35] *T.H. Finlay, J. Valensky, A.S. Mildvan & R.H. Abeles*, J. Biol. Chem. *248*, 1285 (1973).
[36] *J. Halpern*, Ann. N.Y. Acad. Sci. *239*, 2 (1974).
[37] *B.T. Golding, T.J. Kemp, E. Nocchi & W.P. Watson*, Angew. Chem. *87*, 841 (1975).
[38] *B.T. Golding & L. Radom*, J. Chem. Soc., Chem. Commun. *1973*, 939.
[39] *B.T. Golding & L. Radom*, J. Am. Chem. Soc. *98*, 6331 (1976).
[40] *I.P. Rudakova, T.E. Ershova, A.B. Belikov & A.M. Yurkevich*, J. Chem. Soc., Chem. Commun. *1978*, 592.
[41] *A.J. Hartshorn, A.W. Johnson, S.M. Kennedy, M.F. Lappert & J.J. Mac Quitty*, J. Chem. Soc., Chem. Commun. *1978*, 643.
[42] *K. Bernhauer & E. Irion*, Biochem. Z. *339*, 521 (1964).
[43] *H.A.O. Hill, J.M. Pratt, S. Ridsdale, F.R. Williams & R.J.P. Williams*, J. Chem. Soc., Chem. Commun. *1970*, 341.
[44] *J.H. Bayston, F.D. Looney, J.R. Pilbrow & M.E. Winfield*, Biochemistry *10*, 2164 (1970).
[45] *F. Wagner & K. Bernhauer*, Ann. N.Y. Acad. Sci. *112*, 580 (1964).

[46] *H. P. C. Hogenkamp*, Fed. Proc., Fed. Am. Soc. Exp. Biol. *25*, 1623 (1966).
[47] *H. P. C. Hogenkamp, J. E. Rush & C. A. Swenson*, J. Biol. Chem. *240*, 3641 (1965).
[48] *H. P. C. Hogenkamp*, Biochemistry *5*, 417 (1966).
[49] *J. I. Toohey, D. Perlman & H. A. Barker*, J. Biol. Chem. *236*, 2119 (1961).
[50] *K. Bernhauer, P. Gaiser, O. Müller & O. Wagner*, Biochem. Z. *333*, 106 (1960).
[51] *A. W. Johnson & N. Shaw*, J. Chem. Soc. *1962*, 4608.
[52] *O. Müller & G. Müller*, Biochem. Z. *335*, 340 (1962).
[53] *O. Müller & G. Müller*, Biochem. Z. *336*, 299 (1962).
[54] *A. W. Johnson, L. Mervyn, N. Shaw & E. L. Smith*, J. Chem. Soc. *1963*, 4146.
[55] *H. P. C. Hogenkamp & T. G. Oikawa*, J. Biol. Chem. *239*, 1911 (1964).
[56] *B. Zagalak & J. Pawelkiewicz*, Acta Biochim. Pol. *12*, 103 (1965).
[57] *H. A. Barker, H. Weissbach & R. D. Smyth*, Proc. Natl. Acad. Sci. U.S.A. *44*, 1093 (1958).
[58] *H. Weissbach, J. Toohey & H. A. Barker*, Proc. Natl. Acad. Sci. U.S.A. *45*, 521 (1959).
[59] *C. G. D. Morley, R. L. Blakley & H. P. C. Hogenkamp*, Biochemistry *7*, 1231 (1968).
[60] *H. A. Barker, R. D. Smyth, H. Weissbach, A. Munch-Petersen, J. I. Toohey, J. N. Ladd, B. E. Voleani & R. M. Wilson*, J. Biol. Chem. *235*, 181 (1960).
[61] *H. P. C. Hogenkamp & H. A. Barker*, J. Biol. Chem. *236*, 3097 (1961).
[62] *J. N. Ladd, H. P. C. Hogenkamp & H. A. Barker*, Biochem. Biophys. Res. Commun. *2*, 143 (1960).
[63] *H. P. C. Hogenkamp & S. Holmes*, Biochemistry *9*, 1886 (1970).
[64] *P. G. Swetik & D. G. Brown*, J. Electroanalyt. Chem. *51*, 433 (1974).
[65] *I. Y. Levitin, I. P. Rudakova, A. L. Sigan, T. A. Pospelova, A. M. Yurkevich & M. E. Volpin*, Zh. Obshch. Khim. *45*, 1879 (1975).
[66] *R. C. Larson, R. T. Iwamoto & R. N. Adams*, Anal. Chim. Acta *25*, 371 (1961).
[67] *R. Scheffold & E. Amble*, Angew. Chem. *92*, 643 (1980).
[68] *O. Müller & G. Müller*, Biochem. Z. *337*, 179 (1963).
[69] *G. C. Hayward, H. A. O. Hill, J. M. Pratt, N. J. Vanston & R. J. P. Williams*, J. Chem. Soc. *1965*, 6485.
[70] *G. H. Beaven, E. R. Holiday, E. A. Johnson, B. Ellis & V. Petrow*, J. Pharm. Pharmacol. *2*, 944 (1950).
[71] *D. H. Dolphin, A. W. Johnson, R. Rodrigo & N. Shaw*, Pure Appl. Chem. *7*, 539 (1963).
[72] *R. A. Firth, H. A. O. Hill, B. E. Mann, J. M. Pratt, R. G. Thorp & R. J. P. Williams*, J. Chem. Soc. (A) *1968*, 2419.
[73] *M. T. Davies, P. Mamalis, V. Petrow & B. Sturgeon*, J. Pharm. Pharmacol. *3*, 420 (1951).
[74] *R. A. Firth, H. A. O. Hill, J. M. Pratt, R. G. Thorp & R. J. P. Williams*, J. Chem. Soc. (A) *1968*, 2428.
[75] *R. Scheffold*, unpublished results.
[76] *D. Bormann, A. Fischli, R. Keese & A. Eschenmoser*, Angew. Chem. *79*, 867 (1967); ibid. Int. Ed. *6*, 868 (1967).
[77] *R. Bonnett, J. R. Cannon, V. M. Clark, A. W. Johnson, L. F. J. Parker, E. L. Smith & A. Todd*, J. Chem. Soc. *1957*, 1158.
[78] *F. Wagner & P. Renz*, Tetrahedron Lett. *1963*, 259.
[79] *F. Wagner & K. Bernhauer*, Ann. N.Y. Acad. Sci. *112*, 580 (1964).
[80] *D. H. Dolphin, A. W. Johnson & R. Rodrigo*, Ann. N.Y. Acad. Sci. *112*, 590 (1964).
[81] *A. Gossauer, B. Grünig, L. Ernst, W. Becker & W. S. Sheldrick*, Angew. Chem. *89*, 486 (1977); ibid. Int. Ed. *16*, 481 (1977).
[82] *B. Grünig & A. Gossauer*, in 'Vitamin B_{12}', Proceedings of the Third European Symposium on Vitamin B_{12} and Intrinsic Factor, editors B. Zagalak and W. Friedrich, W. de Gruyter, Berlin and New York 1979, p. 141.
[83] *N. R. Trenner, R. P. Buhs, F. A. Bacher & W. G. Gakenheimer*, J. Am. Pharm. Assoc. Sci. Ed. *39*, 361 (1950).
[84] *E. M. Stapert, E. B. Ferrer & L. Stubberfield*, J. Am. Pharm. Assoc. Sci. Ed. *43*, 87 (1954).
[85] *A. J. Rosenberg*, J. Biol. Chem. *219*, 951 (1956).
[86] *A. Fischli*, Helv. Chim. Acta *61*, 3028 (1978).
[87] *L. Werthemann*, Diss. ETHZ Nr. 4097, Zürich 1968.