206. Influence of the Axial Alkyl Ligand on the Reduction Potential of Alkylcob(III)alamins and Alkylcob(III)yrinates

by **De-Ling Zhou, Olivier Tinembart, Rolf Scheffold,** and **Lorenz Walder***

Institut für Organische Chemie, Universität Bern, Freiestrasse 3, CH-3012 Bern

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The irreversible-reduction potentials of 26 alkylcob(III)alamins ($RCbl^{III}$; **1a–z**) and 26 alkylcob(III)yrinates (R'Cby'^{III}; **2a–z**) (E_p **1a–z** and E_p **2a–z**, resp.) have been measured *in situ* by single-scan voltammetry of hydroxocob(III)alamin hydrochloride (vitamin B_{12b} · HCl; **1**) or heptamethyl cob(II)yrinate perchlorate (ClO_4'Cby'^{II}; **2**) in presence of the corresponding alkyl halides (RX; **3a–z**) in DMF. The reduction potentials of alkylcobalt complexes exhibiting half-life times as short as a few seconds become measurable by this technique. Thermodynamic cycles prove that the observed reduction potentials are closely related to the standard reduction potentials $E°(R{-}Co^{III} + e^- \leftrightarrows R^{\cdot} + Co^{I})$. Electron-withdrawing groups and/or an increased degree of substitution at the Co-bound C-atom in $RCbl^{III}$ and R'Cby'^{III} shift E_p(**1a–z**) and E_p(**2a–z**) towards positive potentials. Linear correlations have been found between E_p(**1a–z**) (E_p(**2a–z**)) of $RCbl^{III}$ (R'Cby'^{III}) and the pK_a of RH (or the *Taft* σ^*- or the *Hammett* σ_p^--values of R) within each class of R, *i.e.* $MeCbl^{III}$ (Me'Cby'^{III}), primary $RCbl^{III}$ (R'Cby'^{III}) and secondary $RCbl^{III}$ (R'Cby'^{III}). The correlations allow to distinguish between electronic effects of the Co-bound alkyl residues and their steric interactions with the corrin side chains. The correlations have further been used to visualize the light-induced formal insertion of an olefin into the Co,C-bond of an alkylcobalamin (*Scheme 2*, **1a**→**1u**), a key step in the vitamin-B_{12}-catalized C,C-bond formation.

1. Introduction. – The mechanism of adenosylcobalamin-dependent enzymatic rearrangement reactions continues to attract considerable interest [1]. Some of the current questions are directly related to the nature of the Co,C-bond present in organocobalamins. One specific problem deals with the extent of participation of Co^{II}, *e.g.* if Co^{II} forms a bond with the methylmalonyl-CoA radical or the succinyl-CoA radical in the corresponding rearrangement reaction [1b]. In order to detect such intermediate organocobalamins, a fast analytical technique is required that can distinguish between alkylcobalamins with different alkyl residues, *e.g.* different degree of substitution and/or electron-withdrawing and electron-releasing groups at the Co-bound C-atom. Another question is concerned with the fact that homolysis in adenosylcob(III)alamin ($AdoCbl^{III}$; coenzyme B_{12})[1]) proceeds 10 orders of magnitude faster in the enzymatic reaction than in an enzyme-free environment [2a–c]. Conformational changes of the coenzyme induced by interactions within the protein-substrate complex that lower the bond-dissociation energy have been invoked to rationalize the rate enhancement. This hypothesis is supported by increased homolysis rates observed for organocobalamins under nonenzymatic conditions but exhibiting steric hindrance between the organic residue and the corrin macrocycle [3–5]. Another possibility to activate an alkyl(III)cobalamin ($RCbl^{III}$)[1]) towards radical-type bond cleavage would be an electron transfer [6]. The rate enhancement of

[1]) Cbl = cobalamin (see [2e]); for convenience, we use 'Cby' for heptamethyl cobyrinate (*cf.* Cby = cobyric acid [2e]).

Co,C-bond homolysis in methylcob(III)alamin ($MeCbl^{III}$)[1]) achieved by one-electron reduction *in vitro* [7] is even of the same order of magnitude as the acceleration of bond homolysis introduced by the enzyme in case of $AdoCbl^{III}$. A reductively triggered Co,C-bond homolysis in an enzymatic reaction seemed so far unrealistic because the reduction potentials of isolated $MeCbl^{III}$ and most other $RCbl^{III}$ including $AdoCbl^{III}$ [7–13] are generally too negative to be accessible to biological reductants. However, nothing is known on the influence of interactions between the enzyme and the alkyl ligand of an $RCbl^{III}$ on its reduction potential. If conformational restrictions in the coenzyme-substrate-enzyme complex could shift the reduction potential positively enough, the generation of an adenosyl radical by reduction of the Co,C-bond could become biochemically feasible.

The few studies on the electrochemical reduction of $RCbl^{III}$ include polarography [8–11] and cyclic voltammetry [7] [11–13] in H_2O [8] [9] [11–13], DMF [10], DMF/PrOH [7], and DMSO [14]. The standard reduction potential E° for the formal Co^{III}/Co^{II} couple of base-on $MeCbl^{III}$ has been determined as −1.6 V (*vs.* SCE) by fast cyclic voltammetry in DMF/PrOH at −30° [7]. More positive reduction potentials [12] and unexpected high reversibilities [11] have been reported for MeCbl, but these results are probably due to absorption phenomena. Using slower electrochemical techniques, the compound exhibits a chemically irreversible reduction due to the fast cleavage of the organometallic bond following electron transfer. The EC mechanism shifts the reduction potentials in the range of −1.37 to −1.51 V *vs.* SCE as measured under very different conditions[2]). Much related to this work is an early report on the reduction potentials of a series of 10 $RCbl^{III}$ by *Hogenkamp* and *Holmes* [8]. The authors observed that primary unactivated $RCbl^{III}$'s undergo polarographic reduction at −1.37 to −1.39 V but that two $RCbl^{III}$'s with $R = CH_2COOH$ or CH_2COOMe are reduced surprisingly at −0.84 and −1.14 V (*vs.* SCE). It was explained by the electron-withdrawing effect of the carbonyl group. Recently, we could confirm the extraordinary reduction potential of $MeOOCCH_2Cbl^{III}$ (−0.955 V *vs.* SCE in DMSO) and establish a detailed reduction mechanism [14].

Much more electrochemical studies have been done on organometallic derivatives of bis-bidentate or tetradentate azacobalt complexes [17–27] that play an important role as model compounds for organocobalamins [16]. A strong influence of the alkyl group on the reduction potential has been found and substantiated by different authors as correlations between the pK_a of RH or the *Taft* constant σ^* and the reduction potential of [CoR(chel)] for chel = (DO)(DOH)pn [17–22], salen [17–20] [23], bae [18] [23], $(DH)_2$ [21] [22] [24] [25], $(DBF_2)_2$ [21] [22], and $DOBF_2$ [21] [22][2]) for a limited range of compounds corresponding to relatively weak acids on the MSAD scale (see below, [33]). *Brockway et al.* have extended these studies to the more activated perfluoroalkylorganometallics with chel = salen [26]. *Le Hoang et al.* reported on the reduction of alkylcobaloximes at very positive potentials including some highly activated compounds, but no correlation was included in this paper [27]. *Costa* found that *steric hindrance* between the alkyl residue and the macrocyclic systems shows up in the reduction and oxidation potentials of

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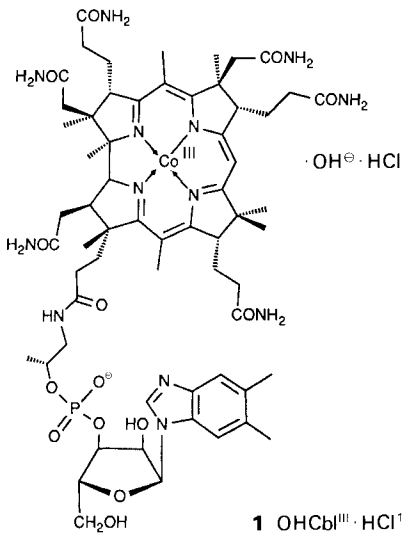
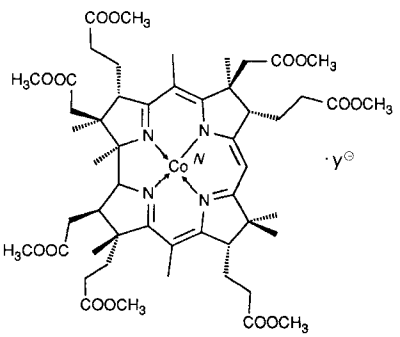
[2]) EC mechanism: E (heterogeneous electron transfer) followed by C (chemical reaction) [15]. Abbreviations used for the planar ligands (chel) of the B_{12} models are: $(DH)_2$=$(DMG)_2$: bis(dimethylglyoxymato) (*Fig. 6*); $(DBF_2)_2$: O–H···O in $(DH)_2$ replaced by O–BF_2···O; (DO)(DOH): 2,3,9,10-tetramethyl-1,4,8,11-tetraazaundeca-1,3,8,10-tetraene-11-ol-1-olato (*Fig. 6*); $DOBF_2$; O–H···O in (DO)(DOH) replaced by O–BF_2···O; bae: *N,N'*-ethylenebis(acetylacetoneiminato); salen: *N,N'*-ethylenebis(salicylideneiminato).

organocobaloximes and organocobalt chelates with bisiminooxime-based ligand systems. Steric hindrance tends to shift the reduction potentials to more positive values [24], probably *via* a lengthening of the Co,C-bond that also translates into a ^{59}Co-NMR chemical shift [22].

We became interested in the question: *Do the parent alkylcobalamins exhibit similar* pK_a vs. $E_{1/2}$ *and steric hindrance* vs. $E_{1/2}$ *dependences as their model systems?* The scarce $RCbl^{III}$ electrochemistry discussed above indicates that such correlations may exist, but much more data were needed to confirm this guess. A problem related with this task was the synthesis of $RCbl^{III}$ that usually precedes their measurement. Sterically hindered $RCbl^{III}$ [3–5] and those bearing electron-withdrawing groups at the Co-bound C-atom [14] are very labile compounds, and this is probably one reason they have not been studied by electrochemistry so far. We avoided the troublesome synthetic work and used an *in-situ* technique allowing us to measure the reduction potential of 26 alkylcob(III)-alamins($RCbl^{III}$)**1a–z** and alkylcob(III)yrinates (R'Cby'^{III})**2a–z** within seconds after their



1 $OHCbl^{III} \cdot HCl^{1})$



2 $N = II$, $y^- = ClO_4^-$; ClO_4'Cby'^{III})
2' $N = III$, $y^- = 2\,I^-$; I_2'Cby'^{III})

generation[1]). Preliminary results concerning reduction-potential correlations have been presented elsewhere [28]. This publication includes detailed information on the *in-situ* technique, further experimental results, and correlations of pK_a or σ^* of RH with the reduction potential of $RCbl^{III}$ and R'Cby'^{III} that allow for the first time to discriminate between electronic and steric effects in organocobalamins and organocobyrinates. Finally, a preliminary application of these correlations is presented, *i.e.* the detection of a so far unknown organometallic vitamin-B_{12} derivative resulting from the visible-light-induced formal insertion of an activated olefin into the Co,C-bond of $MeCbl^{III}$ (**1a**), a key step in the vitamin-B_{12}-catalyzed C,C-bond formation [28].

2. Results and Discussion. – 2.1. *Electrochemistry of Alkylcobalamins* (RCbl) *and Alkylcobyrinates* (R'Cby'). In cyclic voltammetry (CV), hydroxocob(III)alamin (vitamin B_{12b}; $OHCbl^{III}$ **1**) undergoes two successive metal-centered one-electron reductions

which are attributed to the Co^{III}/Co^{II} and Co^{II}/Co^{I} couple according to *Eqns. 1* and *2*.

$$OHCbl^{III} + e^- \rightleftarrows Cbl^{II} \quad E^\circ_1 \approx 0\ V \tag{1}$$

$$Cbl^{II} + e^- \rightleftarrows Cbl^{I} \quad E^\circ_2 = -0.7\ V \tag{2}$$

Cob(I)alamin (vitamin B_{12s}; Cbl^I) exhibits high nucleophilic reactivity towards alkylating agents leading to relatively stable organocob(III)alamins ($RCbl^{III}$; *Eqn. 3*). The rate of

$$Cbl^I + RX \xrightarrow{k_3} RCbl^{III} + X^- \tag{3}$$

this reaction depends on the structure of RX, but it is generally high enough for the reaction to be completed within a second under pseudo-first-order conditions, even at RX concentrations in the mmol range [30]. Generally, the $RCbl^{III}$'s are irreversibly reduced at a potential E_p(Co–R) that is more negative than E°_2 (*Eqn. 4*) [7–14]. In the course of a CV

$$RCbl^{III} + e^- \begin{cases} \xrightarrow{a)} R^\cdot + Cbl^I \\ \xrightarrow{b)} R^- + Cbl^{II} \end{cases} \qquad E_p(Co{-}R) \tag{4}$$

using **1** and an appropriate amount of RX, $RCbl^{III}$ is formed in a reaction layer at the electrode surface once Cbl^I is generated. All three reduction processes corresponding to *Eqns. 1, 2,* and *4* are then observed as three waves in a single CV. Actually, an electrocatalytic situation exists for electrode potentials $\leqslant E_p$(Co–R) because Cbl^I is regenerated according to the sequence of *Reactions 4 → 3 → 4* or *4 → 2 → 3 → 4* [31]. However, a catalytic current is only expected for the third wave if the rate of reaction *3* is fast as compared to the potential scan rate. For a situation where a diffusion layer of $RCbl^{III}$ develops during the time necessary for the potential to increase from E°_2 to E_p(Co–R) but where electrocatalysis at E_p(Co–R) is negligible, the third peak potential is identical with that of a solution of $RCbl^{III}$. An obvious condition for the appearance of E_p(Co–R) is related to the thermal stability of $RCbl^{III}$ towards any of the formal Co,C-bond cleavages shown in *Eqn. 5*. The rates of these reactions should be slow as compared to the scan rate.

$$RCbl^{III} \begin{cases} \xrightarrow{a)} Cbl^{III} + R^- \\ \xrightarrow{b)} Cbl^{II} + R^\cdot \\ \xrightarrow{c)} Cbl^{I} + R^+ \end{cases} \tag{5}$$

From these considerations, we expected that the reduction potentials of so-far unknown $RCbl^{III}$'s exhibiting half-life times as short as a few seconds should become accessible to CV using **1** and the corresponding alkylating agent.

The CV of vitamin B_{12b} (**1**) in DMF in the potential range from 0.4 to −1.8 V revealed two chemically reversible redox processes centered around 0 and −0.7 V (*vs.* SCE) for the redox processes of *Eqns. 1* and *2*. At a scan rate of 100 mV/s the Co^{III}/Co^{II} couple exhibited large peak separation, but an almost *Nernst*ian behaviour was observed for Co^{II}/Co^{I}. Thus, the electrochemical behaviour of **1** in DMF is very similar to that reported in DMSO [29]. Single-scan voltammograms of vitamin B_{12b} in presence of the

different alkylating agents RX = $R^1R^2R^3CX$ (**3**) are shown in *Fig. 1*. The reduction processes (*Eqns. 1* and *2*) are easily identified and essentially unaffected by the presence of the alkylating agents. The expected additional wave is observed and definitely related to the presence of **3**[3][4]). Its height has been adjusted to the size of the Co^{II}/Co^{I} reduction process by variation of the concentration of **3**. The peak potential of the third wave (E_p(**1a–z**)) is strongly influenced by the activating groups present in $R^1R^2R^3CX$ (**3**). When the electron-withdrawing abilities of R^1 increase according to the series H (**3a**) < CH_2=CH (**3g**) < Ph (**3h**) < CN (**3o**) < COOMe (**3p**) < COMe (**3q**) with

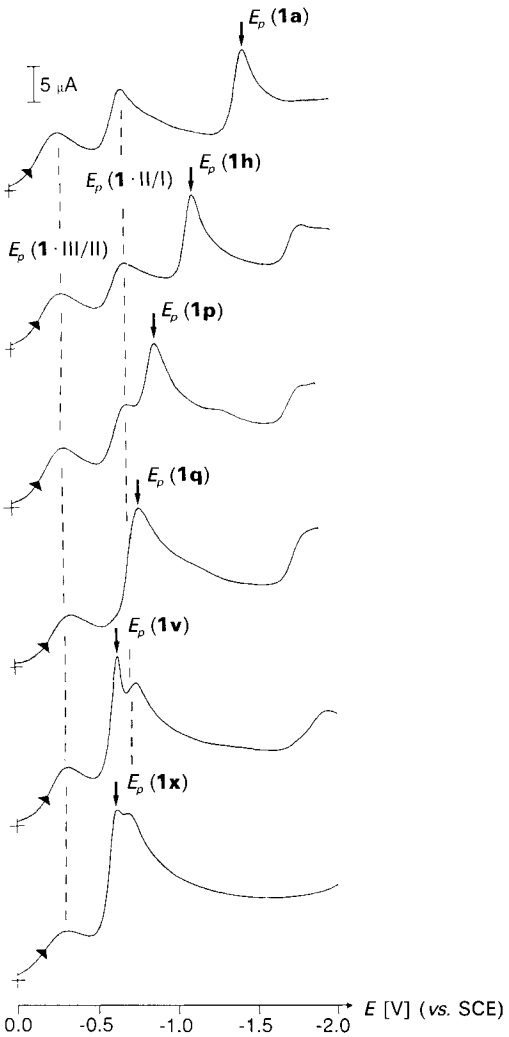


Fig. 1. *Single-scan voltammograms of vitamin* B_{12b} (**1**) *in the presence of the alkylating agents RX* **3a**, **h**, **p**, **q**, **v**, *and* **x** *in 0.1* M Bu_4NClO_4/*DMF at* v = *100 mV/s*. For **3**, see *Table*. The arrows indicate the reduction potentials of the corresponding $RCbl^{III}$. Conditions, see *Exper. Part*.

[3]) The *direct* reduction of **3** at the electrode is ruled out as noticed from its reduction potential measured in the absence of **1**, **2**, or **2′** (E_p(**3a–z**), *Table*).

[4]) A fourth wave appeared sometimes at –1.7 to –2 V. Its origin is not clear.

Table. *Reduction Potentials of the Alkyl Halides* (E_p(**3a–z**)), *the Corresponding Alkylcobalamins* (E_p(**1a–z**)), *and Alkylcobyrinates* (E_p(**2a–z**)). *Selected Acidities and σ-Values of the Alkanes* **4a–z**

	Alkyl halides $R^1R^2R^3CX$ (RX; **3a–z**)				Reduction potentials [V][a]			Acidity of $R^1R^2R^3CH$ (**4a–z**)		σ_p^{0}[d]
	R^1	R^2	R^3	X	E_p(**3a–z**)	E_p(**1a–z**)	E_p(**2a–z**)	[b]	[c]	
a	H	H	H	I	< –2.0	–1.45, –1.46[e]	–1.33	40	56	
b	F	F	F	Br	–1.70	–1.00	–0.88	28		
c	Me	H	H	I	< –2.0	–1.39	–1.26	42		
d	Et	H	H	Br	< –2.0	–1.40	–1.23			
e	Pr	H	H	I	< –2.0	–1.41	–1.26			
f	*t*-Bu	H	H	I	< –2.0	–1.49	–1.35	44		
g	CH_2=CH	H	H	Br	–1.78[f]	–1.12	–1.07	35.5	44	
h	Ph	H	H	Br	–1.81	–1.1	–1.07	35	43	0
i	*p*-$MeOC_6H_4$	H	H	Cl	< –2.0	–1.15	–1.11			–0.12
j	*p*-MeC_6H_4	H	H	Br	–1.84	–1.13	–1.08			–0.14
k	*p*-FC_6H_4	H	H	Br	–1.74	–1.13	–1.09			0.15
l	*p*-$CF_3C_6H_4$	H	H	Br	–1.56	–1.02	–0.98			0.53
m	*p*-NCC_6H_4	H	H	Br	–1.31	–0.94	–0.88		30.8	0.71
n	C_6F_5	H	H	Br	–1.22	–0.86	–0.83			1.13[i]
o	CN	H	H	Cl	–2.00	–0.92	–0.90		31.3	
p	COOMe	H	H	Br	–1.68	–0.89, –0.90[e]	–0.85		30–31	
q	COMe	H	H	Cl	–1.91	–0.78	–0.69		26.5	
r	Me	Me	H	I	< –2.0	–1.3	–1.17	44		
s	Et	Me	H	I	< –2.0	–1.3	–1.16			
t	$-(CH_2)_5-$		H	I	< –2.0	–1.33	–1.22	45		
u	CN	Et	H	Br	–1.58	–0.87	–0.82			
v	Ph	COOMe	H	Br	–1.28[g]	–0.63	–0.47		22.6[h]	
w	COOMe	Me	H	Br	–1.67	–0.82	–0.77			
x	COOMe	COOMe	H	Br	–1.17	–0.62	–0.42		16.4[h]	
y	COMe	COMe	H	Cl	–1.63	–0.68	–0.48		13.3	
z	Me	Me	Me	I	–1.93	–0.8 to –1.0	–0.7 to –1.0			

[a]) From single-scan voltammograms (*vs.* SCE). Conditions, see *Fig. 1* and *Exper. Part.*
[b]) MSAD scale [33].
[c]) *Bordwell*'s pK_a scale (DMSO) [34] [35].
[d]) *Hammett* substituent constants [36].
[e]) Voltammograms of solutions of isolated **1a** and **1p**, respectively.
[f]) Measured in 0.1M Bu_4NClO_4/MeCN [37].
[g]) Estimated from the corresponding ethyl ester, measured in 0.1M Et_4NClO_4/DMF at 200 mV/s [38].
[h]) Value for the corresponding ethyl esters.
[i]) $\sigma^0 = 3^*\sigma_p^0 + 2^*\sigma_m$ [39].

$R^2 = R^3 = H$, the third-peak potential moves from −1.45 to −0.78 V. When two electron-withdrawing groups are present (**3v, 3x, 3y**), the additional peak occurs even on the positive side of the Cbl^{II}/Cbl^{I} reduction (*Fig. 1, Table*). This is surprising because – according to *Eqn. 3* – the presence of Cbl^{I} is a prerequisite for the formation of the hypothetical $RCbl^{III}$ [5]). However, even traces of Cbl^{I} that are produced at the foot of the Cbl^{II}/Cbl^{I} reduction wave as far as 120 mV before the peak may suffice to be consumed by

[5]) Indeed, Cbl^{II} may undergo oxidative addition with alkylating agents, but the rates are generally orders of magnitude smaller than those typically observed for Cbl^{I} [32]. Alkylation of Cbl^{II} is, therefore, very unlikely to contribute to the formation of $RCbl^{III}$ under our experimental conditions.

alkylation and to give rise to a current due to the reduction of an easily reducible $RCbl^{III}$. In such a case, the reduction potential of $RCbl^{III}$ is strongly influenced by the kinetics of the alkylation reaction and by the position of the Cbl^{II}/Cbl^{I} wave.

The hypothetical organometallic derivatives obtained with vitamin B_{12b} and MeI (**3a**), EtI (**3c**), i-PrI (**3r**), and *t*-BuI (**3z**) reveal another trend: For increasing branching at the Co-bound C-atom, a positive shift of the reduction potential is observed (in spite of the electron-releasing character of these substituents). In case of *t*-BuI (**3z**), the reduction peak is ill-defined, probably because *Reaction 5* proceeds at a rate comparable to the potential scan.

Using heptamethyl cob(II)yrinate perchlorate (**2**) or heptamethyl cob(III)yrinate diiodide (**2'**), the same trends are observed: electron-withdrawing groups and/or a high degree of substitution at the halogen-bound C-atom render the additional reduction wave (E_p(**2a–z**)) more positive (*Table*).

The electrochemical behaviour of two *isolated* $RCbl^{III}$'s, **1a** and **1p**, has been studied under otherwise identical experimental conditions. The reduction of $MeCbl^{III}$ (**1a**) and base-off $MeOOCCH_2Cbl^{III}$ (**1p**) occurred at the same potential (±0.01 V) as the third wave obtained by the *in-situ* technique (*Table*). It seems, therefore, justified to generalize our observations and to interpret the reduction potentials E_p(**1a–u, w, z**) and E_p(**2a–u, w, z**) reported in the *Table* as those of the corresponding $RCbl^{III}$ and R'Cby'^{III}.

2.2. *Correlations.* Inspection of the *Table* indicates that the reduction potentials of the organocobalt species are related to the stability of the coordinated alkyl anion $R^1R^2R^3C^-$ towards protonation. Such dependences have been described for organomercury compounds [40], for $[Fe(R)Cp(CO)_2]$ (Cp = cyclopentadienyl) [41] and for organometallic

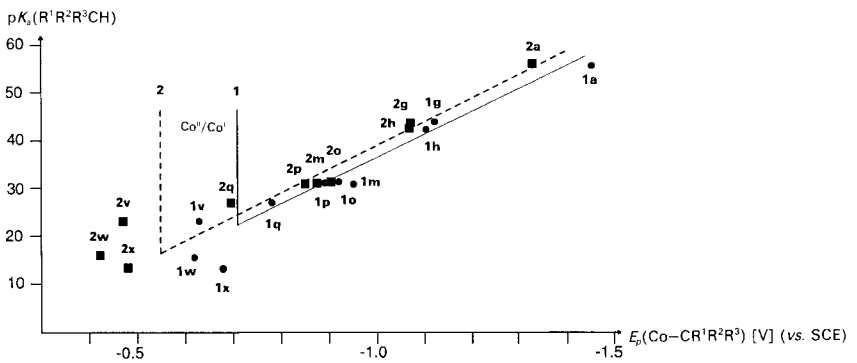


Fig. 2. Bordwell's pK_a *values of selected alkanes* $R^1R^2R^3CH$ (**4**) vs. *the reduction potential of the corresponding alkylcobalamins* $R^1R^2R^3CCbl^{III}$ (●, —) *and alkylcobyrinates* $R^1R^2R^3C'Cby'^{III}$ (■, ---). Values from *Table*.

derivatives of vitamin-B_{12} model systems [17–25] and have been substantiated by linear-free-energy relationships of $E_{1/2}$ of the organometallics MR and the pK_a of the corresponding alkanes RH. Ten pK_a values in DMSO are available for the 26 alkanes **4a–z** from recent compilations [34] [35] (*Table*). A plot containing E_p values *vs.* the corresponding pK_a's is shown in *Fig. 2*. When the linear-regression analysis is restricted to the substrates **3a, g, h, m, o–q,** *i.e.* to those with reduction potentials more negative than the

Co^{II}/Co^{I} reduction peak, the two sets of data correlate over a potential range of 650 mV and a pK_a range of *ca.* 25 units according to *Eqns. 6* and *7*.

Cbl correlation: $pK_a = -47.2\,[V^{-1}] \cdot E_p(\mathbf{1})\,[V] - 11.1$ (corr.coeff., 0.985) (6)

'Cby' correlation: $pK_a = -50.2\,[V^{-1}] \cdot E_p(\mathbf{2})\,[V] - 11.2$ (corr.coeff., 0.981) (7)

For pK_a values less than 25, *i.e.* those with corresponding E_p values in the range of the Co^{II}/Co^{I} redox couple, the data scatter, probably because the kinetics of the formation of the organometallic species interfere. Caution, with respect to the further interpretation, is also recommended because only three values with $pK_a > 40$ can be used including a rough estimate for methane.

The 2 sets of 7 benzylcobalt complexes **1h–n** and **2h–n** are interesting because they span a large potential range that is mainly due to *electronic effects* as steric hindrance is

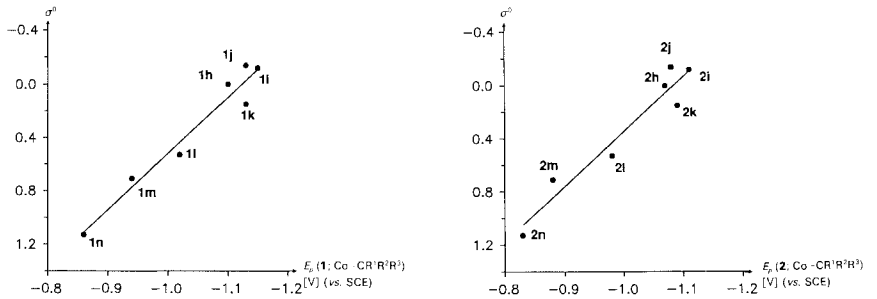


Fig. 3. Hammett *substituent constants* σ_p^- vs. *the reduction potentials of substituted benzylcob(III)alamins* (left) *and benzylcob(III)yrinates* (right). Values from *Table*.

supposed to be constant. Using the substituent constants σ^0 in stead of the pK_a values, two *Hammett* plots with linear correlations are observed (*Fig. 3, Eqns. 8* and *9*)[6]).

Cbl correlation: $\sigma^0 = 4.22\,[V^{-1}] \cdot E_p(\mathbf{1})\,[V] + 4.73$ (corr.coeff., 0.976) (8)

'Cby' correlation: $\sigma^0 = 4.16\,[V^{-1}] \cdot E_p(\mathbf{2})\,[V] + 4.50$ (corr. coeff., 0.966) (9)

For historical reasons, and also because it contains estimates for some very weak C–H acids, most correlations reported for the organometallic derivatives of the vitamin-B_{12} models are based on the MSAD scale [33]. *Costa* found linearity for a limited series of [CoR(salen)DMF] and [CoR(DO)(DOH)(pn)] complexes with increasing $E_{1/2}$ for R = Et, Me, Ph, and $PhCH_2$ according to the decreasing pK_a of RH [18] [19]. In order to compare the pK_a *vs.* E_p slopes of the models with those of $RCbl^{III}$, we used the MSAD acidity constants, too. As seen from *Fig. 4*, the representation does not lead to a simple linear correlation of our data. A closer look reveals that the reduction potential of, *e.g.*, $MeCbl^{III}$ is more negative than that of $EtCbl^{III}$ in contrast to *Costa*'s complexes and to the sequence pK_a (MeH) < pK_a (EtH). The reversed trend continues for i-$PrCbl^{III}$ being easier reduced than $EtCbl^{III}$, but pK_a (EtH) < pK_a (i-PrH)[7]). This additional influence on the

[6]) Only the pK_a values of **4h** and **4m** are available from *Bordwell*'s compilation.

[7]) This phenomenon has recently also been observed for organometallic derivatives of the model compounds and has been interpreted as steric hindrance [22] [24].

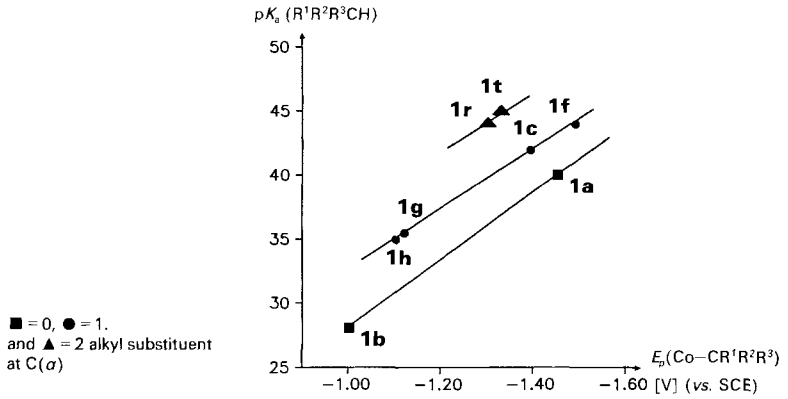


Fig. 4. *MSAD-p*K$_a$ *values of some selected alkanes* vs. *the reduction potentials of the corresponding* $R^1R^2R^3CCbl^{III}$*'s.* Values from *Table.* The $R^1R^2R^3C'Cby'^{III}$ exhibit a similar dependence.

reduction potential becomes clear, when the alkyl residues in the pK_a *vs.* E_p plot are classified according to their degree of substitution, *i.e.* MeCbl^{III} (**1a**) (and its derivative **1b**), primary RCbl^{III} (**1h, 1g, 1c, 1f**) and *sec*-RCbl^{III} (**1r, 1t**). Thus, parallel dependences on pK_a within each of the three non-pK_a-related classes (exhibiting a constant degree of substitution at the Co-bound C-atom) are observed. Furthermore, *Fig. 4* indicates that substitution at C(β) influences the reduction potential mainly through the pK_a as EtCbl^{III} (**1c**), PhCH$_2$Cbl^{III} (**1h**), and *t*-BuCH$_2$Cbl^{III} (**1f**) lie on a line.

In a *Taft* σ^* *vs.* E_p representation, no linear dependences but clear separation of the data clusters according to the classes of methyl, primary, secondary, and one tertiary alkyl derivatives is observed (*Fig. 5*). Some consistent positive shifts, related to the introduction of an alkyl group at the Co-bound C-atom, are directly read out from the

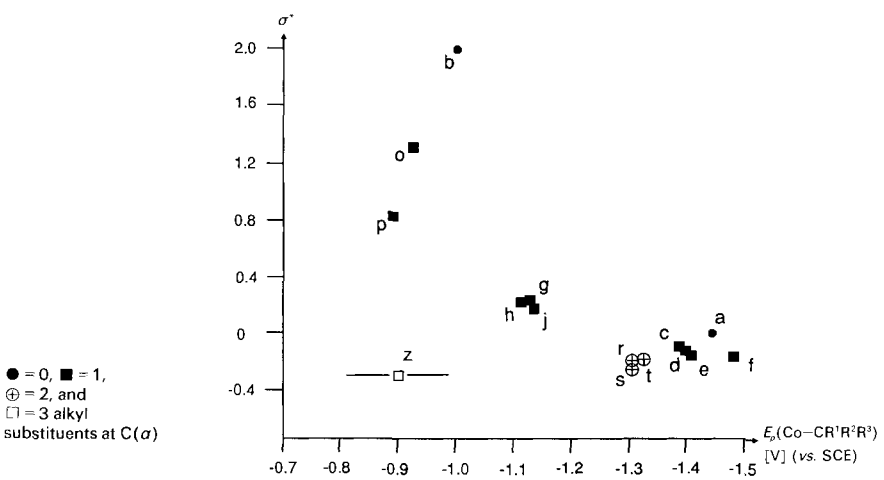


Fig. 5. Taft σ* *values* vs. *the reduction potentials of* $R^1R^2R^3CCbl^{III}$*'s.* Values from [42] and *Table.* The $R^1R^2R^3C'Cby'^{III}$ exhibit a similar dependence.

Table, i.e. +50 mV from **1o** (−0.92 V) to **1u** (−0.87 V), +70 mV from **1p** (−0.89 V) to **1w** (−0.82 V), and +100 mV from **1d** (−1.40 V) to **1s** (−1.30 V). Generally, the same trends are observed for the R'Cby'^{III}'s.

These results call for further interpretation and application. In *Chapt. 2.3*, we have tried to rationalize the reduction potentials of RCbl^{III} and R'Cby'. In *Chapt. 3*, we demonstrate the use of the pK_a *vs.* E_p correlation for the detection of so-far unknown organometallic derivatives of vitamin B_{12}.

2.3. *Theory and Interpretation.* The thermodynamic relation between the pK_a of RH (*Eqn. 10*) and the standard reduction potential of the organometallic compound M^NR (E°_{14}, *Eqn. 14*; N = oxidation number) is shown by the two thermodynamic cycles *Eqn. 10* = *Eqn. 11* + *Eqn. 12* + *Eqn. 13* and *Eqn. 14* = *Eqn. 15* + *Eqn. 16*, respectively.

$$\underline{RH \rightleftarrows H^+ + R^-} \quad pK_a \tag{10}$$

$$RH \rightleftarrows H^\cdot + R^\cdot \tag{11}$$

$$R^\cdot + e^- \rightleftarrows R^- \tag{12}$$

$$H^\cdot - e^- \rightleftarrows H^+ \tag{13}$$

$$\underline{M^NR + e^- \rightleftarrows M^{N-1} + R^-} \quad E^\circ_{14} \tag{14}$$

$$M^NR \rightleftarrows M^{N-1} + R^\cdot \tag{15}$$

$$R^\cdot + e^- \rightleftarrows R^- \tag{16}$$

With the reduction of the alkyl radical occurring in both cycles (*Eqns. 12* and *16*) and with *Eqn. 13* contributing a constant value for different R's, a correlation of E°_{14} and pK_a implies some restrictions for the respective homolysis reactions *Eqns. 11* and *15*. Either they contribute both a small value that may be non-correlated or one or both are large and correlated. If the reduction of the organometallic compound leads to an organic

$$\underline{M^NR + e^- \rightleftarrows M^{N-2} + R^\cdot} \quad E^\circ_{14} \tag{17}$$

$$M^NR \rightleftarrows M^{N-1} + R^\cdot \quad \Delta G_{18};\ \Delta G_{BD} \tag{18}$$

$$M^{N-1} + e^- \rightleftarrows M^{N-2} \tag{19}$$

radical (*Eqn. 17*), the thermodynamic cycle *Eqn. 17* = *Eqn. 18* + *Eqn. 19* indicates that E°_{17} is not expected to correlate with pK_a but obviously to do so with the free energy for radical-type bond dissociation (ΔG_{18}). The thermodynamic product distribution expected from the two types of M,C-bond cleavages (*Eqns. 14* and *17*) is given by the redox reaction *Eqn. 20* (from *Eqn. 17* and *Eqn. 14*), which is itself related to the two standard

$$\underline{M^{N-1} + R^- \rightleftarrows M^{N-2} + R^\cdot} \tag{20}$$

$$M^{N-1} + e^- \rightleftarrows M^{N-2} \tag{21}$$

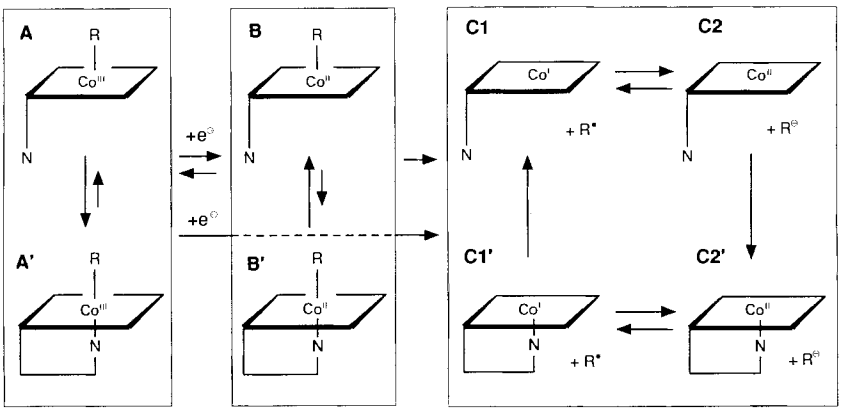
$$R^- - e^- \rightleftarrows R^\cdot \tag{22}$$

reduction potentials formulated in *Eqns. 21* and *22*. A positive reduction potential of the alkyl radical and a negative reduction potential for the unalkylated M^{N-1}/M^{N-2} couple favour the alkyl-anion cleavage and *vice versa*. Obviously, the pK_a of RH and/or the bond dissociation energy of MR may correlate with the standard reduction potential (E°) of an

organometallic compound, but unfortunately $E°$ values are not accessible to straightforward electrochemical measurements, because the organic product is generally too reactive to allow a measurement under equilibrium conditions. The observed reduction potential contains, therefore, information on both the standard reduction potential and the thermodynamics/kinetics of these coupled reactions.

The reduction mechanism of an $RCbl^{III}$ consists of a specific pathway out of a complicated set of possible reactions that are linked to the electron transfer (*Scheme 1*)[8]). These include the base-on/base-off equilibria **A⇆A′, B⇆B′, C⇆C′,** a dissociative electron transfer (**A,A′→C,C′**) or a pathway *via* a one-electron reduced intermediate (**A,A′⇆B,B′→C,C′**), and the two redox reactions **C1⇆C2** and **C1′⇆C2′**.

Scheme 1



The influence of the benzimidazole-coordination equilibrium **A′⇌A** is demonstrated by the consistent negative shift of the reduction potentials of $RCbl^{III}$ as compared to the corresponding R'Cby'^{III}. At 100 mV/s, the establishment of the equilibrium **A′⇄A** is fast as compared to the scan rate, and the reaction supplies the more easily reducible base-off form of $RCbl^{III}$ for the electron transfer by a CE mechanism. The differences in reduction potentials of the $RCbl^{III}$ **1c–w** and R'Cby'^{III} **2c–w** (20 to 170 mV) may, therefore, reflect the stabilization of $RCbl^{III}$ towards reduction by benzimidazole complexation as compared to solvent complexation (0.5 to 4 kcal) [14] [42a].

Recently, the standard reduction potentials of unactivated primary ($\leqslant -1.3$ and -1.57 to -1.6), secondary ($\leqslant -1.38$ and -1.68 to -1.72) and tertiary alkyl radicals ($\leqslant -1.48$ and -1.77 V *vs.* SCE) have been estimated [43a, b]. The product situation **C1,C1′** in *Scheme 1* is, therefore, thermodynamically favoured by 0.6 to 1 V over **C2, C2′** (*Eqns. 20–22*), and radical follow-up reactions are also experimentally observed upon the vitamin-B_{12}-catalyzed reduction of unactivated alkyl halides [44]. Thus, for these organocobalamins, the standard reduction potential $E°(Co^{III} - R)/(Co^{I} + R^{\cdot})$ is available from $E°(Co^{II}/Co^{I})$ and $\Delta G°_{BD}$ according to *Eqns. 17–19*. For $AdoCbl^{III}$ and $MeCbl^{III}$,

[8]) The *in-situ* generation and measurement technique is limited to 100 mV/s and is, therefore, unsuitable for a thorough elucidation of the reduction mechanism. However, based on the large set of reduction potentials reported here, some conclusions are still obtainable.

calculated $E°(Co - R)/(Co^I + R^·)$ is close to the observed reduction potential E_p[9]) indicating a surprisingly high electron-transfer rate. From the fact that the electrochemical reduction of an $RCbl^{III}$ does not involve a high activation barrier, we may conclude that the heterogeneous electron transfer is accelerated by a stepwise mechanism, *i.e.* that the electron is initially accepted by a rather delocalized orbital. $MeCbl^{III}$ [7] and other primary $RCbl^{III}$[11]) are reduced *via* a short lived intermediate (**A,A'⇆B,B'→C1**). Thus, the electron-accepting orbital has not much antibodingCo,C-σ* character and is delocalized, *e.g.* a corrin-localized π*-orbital. The decay of the intermediate is then due to an intramolecular dissociative redox reaction involving a thermal electronic transition from the corrin π* to the Co,C localized σ* orbital, and the phenomenon could be classified as intramolecular electron-transfer catalysis, *i.e.* a slow heterogeneous charge transfer to the relevant Co,C-localized orbital that is cut out by a fast electron transfer to an energetically higher but more delocalized empty orbital. The E_p *vs.* pK_a dependence for different electron-withdrawing groups could then be related to changes of the energy level of the Co,C σ* orbital that controls the rate of the intramolecular electron transfer from an unaffected corrin-localized orbital. On the other hand, the electron density at the Co-bound C-atom could exert a *cis* effect and could tune the corrin-localized orbital[11]). As the observed reduction potentials are close to the corresponding standard potentials, the energetic (horizontal) displacement between the Me derivatives and primary-alkyl derivatives (140 mV ≈ 3.2 kcal/mol) and between primary $RCbl^{III}$ and *sec*-$RCbl^{III}$ (200 mV ≈ 4.6 kcal/mol) in *Fig. 4* may be interpreted as the *bond-energy decrease due to steric hindrance increase* in the ground state[9])[12]). Approximately 300 to 500 mV (6.9 to 11.5 kcal/mol) is the energy difference between the cluster of *sec*-$RCbl^{III}$ and one *tert*-$RCbl^{III}$ (*Fig. 5*).

In *Fig. 6* the pK_a *vs.* E_p dependence of $RCbl^{III}$'s is compared with published pK_a *vs.* $E_{1/2}$ data for the vitamin-B_{12} models $[CoR(DH)_2]$ and [CoR(DO)(DOH)] [22][13]). Lacking further common data, a straight line has been used in all cases to connect R = $PhCH_2$ and R = Et (*Fig. 6*). Similar slopes, *i.e.* −31, −42, and −47 (pK_a units/V), have been obtained for the vitamin-B_{12} derivatives $RCbl^{III}$ $[CoR(DMG)H_2O]$, and $[CoR(DOH)H_2O]^2$), re-

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[9]) From $\Delta G_{BD} = \Delta H_{BD} - T\Delta S_{BD}$ with ΔH_{BD} = 31.5 kcal/mol ($AdoCbl^{III}$) [2a] and with a crude estimate for $\Delta S_{BD} \approx +40$ to +50 cal/mol · K (from the additional translational partition function for R · [45]), it is possible to bracket $16.5 < \Delta G°_{BD} < 19.8$ kcal/mol. This translates with $E°(Co^{II}/Co^I) = -0.7$ V (*vs.* SCE) to the potential range $-1.56 < E°(Co^{III} - R/Co^I + R^·) < -1.43$ and can be compared to the observed reduction potential of $AdoCbl^{III}$ $E_p = -1.2$ (*vs.* SCE; under our conditions)[10]). From $\Delta\Delta H_{BD} = \Delta H_{BD}$ ($MeCbl^{III}$) − ΔH_{BD} ($AdoCbl^{III}$) = 37 − 31.5 kcal/mol = 6.5 kcal/mol (see [2d] and [2a], resp.) the potential difference $E°(MeCbl^{III}) - E°(AdoCbl^{III}) = -0.24$ V follows. Experimentally, the peak-potential difference E_p ($MeCbl^{III}$) − E_p ($AdoCbl^{III}$) = −1.45 + 1.2 V = −0.25 V is observed.

[10]) A positive shift of E_p as compared to $E°$ is expected for a reversible electron transfer followed by an irreversible chemical reaction which is fast (k) as compared to the scan rate (v) according to $E_p = E° - 0.78\ RT/F + RT/2F \cdot \ln(k/v \cdot RT/F)$ [15]. E_p values of different alkylcobalt complexes may, therefore, be influenced by the individual reactivity of R·. In order to judge this influence, E_p values have been measured in presence of a radical trap at variable concentration. Positive potential shifts < 30 mV have been observed at small [radical trap] but no further shift at ten-fold higher concentrations.

[11]) We have recently found short-lived one-electron-reduced intermediates for **1b** and **1e** with a reversible-reduction potential different from $E°$ of **1a**.

[12]) This interpretation does not explain the position of t-$BuCH_2Cbl^{III}$ (**1f**) displaying no extra steric hindrance as compared to $EtCbl^{III}$ (**1c**).

[13]) The pK_a values in [22] have been replaced by the corresponding MSAD values.

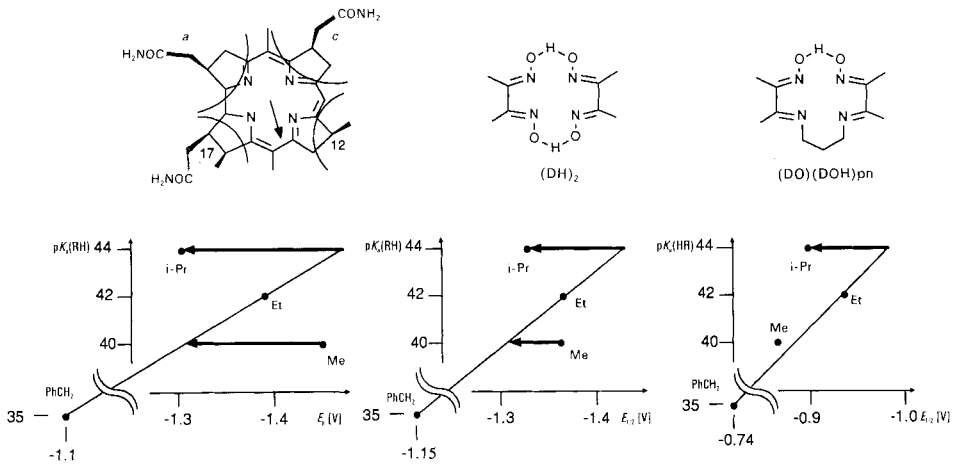


Fig. 6. *MSAD-p*K_a *values of selected alkanes* vs. *the reduction potentials of* $RCbl^{III}$*'s and alkyl derivatives of the vitamin-*B_{12} *models [*$Co(DH)_2$*] and [*$Co[(DO)(DOH)pn]$*]* from *Table* and from [22], resp. Only the β-side chains of the corrin ligand are shown. The steric hindrance is indicated by half-circles and the prefered conformation of the $C_{(\alpha)}$–$C_{(\beta)}$ axis of a Co-bound primary-alkyl ligand by an arrow.

spectively. Taking the higher electronic susceptibility of the E_p of $RCbl^{III}$ into account, it is still evident that the organometallic vitamine-B_{12} derivatives $RCbl^{III}$ respond more sensitively to the degree of substitution at the Co-bound C-atom than the two models. This is expected for the following structural reasons. $RCbl^{III}$'s exhibit – in contrast to their model compounds – nonbonding interactions between the alkyl residue and the methylene H-atoms of the corrin side chains *a* and *c* as well as the Me groups at C(12) and C(17) [1c]. From our results, we can conclude that steric hindrance starts to decrease the expected bond energy when going from the non-interfering $MeCbl^{III}$ (**1a**) or CF_3Cbl^{III} (**1b**) to the primary $RCbl^{III}$. As known from X-ray analyses of primary $RCbl^{III}$ in the solid state and from NMR studies in solution, the free rotation about the Co,C-bond is restricted, and C(β) of the alkyl residue points preferentially towards the flatest part of the corrin macrocycle, *i.e.* between ring C and D [46]. Remarkably, even a neopentyl-type (*t*-$BuCH_2$) organocob(III)yrinate finds still an appreciable conformational energy minimum in this sector [46c]. Introduction of a second alkyl substituent at the Co-bound C-atom complicates the energy minimum problem in *sec*-$RCbl^{III}$ as compared to the *sec*-alkylcobalt complexes of the flat models, because now two valleys, separated by an angle of 120°, are needed on the corrin periphery. Preliminary results from force-field calculations indicate that a low-energy solution exists for *sec*-$RCbl^{III}$ but not for *tert*-$RCbl^{III}$ [14]). We may, therefore, conclude that the pronounced positive shift observed for the reduction potentials of $RCbl^{III}$'s as compared to the model complexes is mainly due to unfavourable steric interactions of the alkyl residue with the corrin side chains.

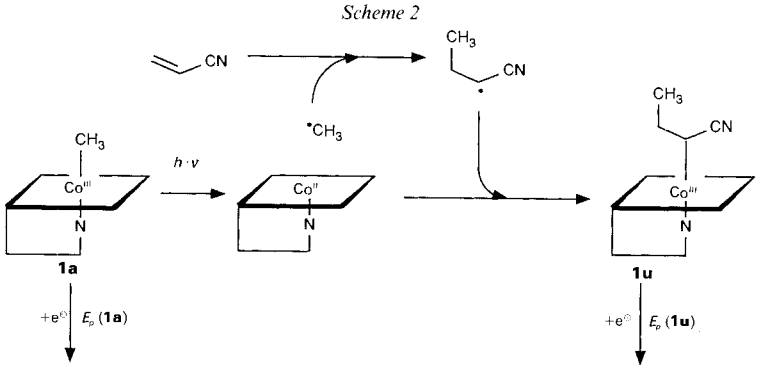
The standard reduction potentials of 4-substituted benzyl radicals measured in MeCN *vs.* SCE cover the range of −1.75 V (4-MeO) to −0.71 V (4-MeCO) [43c], and the reduction of the formylmethyl radical ($OCHCH_2^{\cdot}$) in aqueous solution has been reported

[14]) Using *Alchemy II*® (Molecular Modeling Software, *Tripos Associates, Inc.*, Missouri) and X-ray data from [46a].

as < -0.3 V (*vs.* SCE) [43d,e]. Thus, for the reduction of **1q** and possibly **1m, 1n,** and **1w,** an anionic cleavage is expected as the product situation **C2, C2′** is thermodynamically favoured over **C1,C1′.** The border line between radical-type and anionic Co^{II},C-bond cleavage may further depend on the availability of protons in the solvent as recently shown experimentally [14]. In this context, it is interesting to compare the electrochemistry of $CNCbl^{III}$ with that of the $RCbl^{III}$'s reported here. The formal carbanion CN^- is stabilized towards both, protonation and oxidation. The electrochemistry of $CNCbl^{III}$ is well known, *i.e.* the Co^{III}/Co^{II} and the Co^{II}/Co^{I} couples merge together, and electron transfer is coupled with the expulsion of CN^- [47]. $CNCbl^{III}$ is not considered as an $RCbl^{III}$ but rather as a coordination compound, however, its electrochemistry parallels that of $RCbl^{III}$'s with formal *C*-coordinated enolates, *e.g.* we could not find the one-electron reduced intermediate for **1p** under conditions where we see $\mathbf{1a}^{-\cdot}$ definitely and in presence of protons two-electron reductive protolysis occurs [14]. For stabilized carbanions coordinated to Co^{III}, the reduction may, therefore, be heterolytic, and according to *Eqns. 10–16* again a correlation of pK_a and E_p is expected.

3. Applications: the Detection of Organometallic Reaction Intermediates. – The data reported in the *Table* can be used as a reference for the analytical discrimination of different $RCbl^{III}$ or $R'Cby'^{III}$. The Co,C-bond of an $RCbl^{III}$, *e.g.* $MeCbl^{III}$ (**1a**), undergoes homolytic cleavage upon visible-light illumination. Under appropriate experimental conditions, the resulting nucleophilic Me radical can be trapped by an olefin such as acrylonitrile – rather than by Co^{II} – to yield an electrophilic stabilized radical which then

Scheme 2



recombines with vitamin B_{12r} (cob(II)alamin; Cbl^{II}; *Scheme 2*). This sequence of reactions which we have postulated some time ago [28] can now be visualized. Cyclic voltammograms recorded during the stepwise illumination of $MeCbl^{III}$ (**1a**) in the presence of an excess acrylonitrile are shown in *Fig. 7*. $MeCbl^{III}$ (**1a**) with $E_p = -1.45$ V is transformed *via* Cbl^{II} to a new $RCbl^{III}$ with $E_p = -0.87$ V. Using the *Table*, it is identified as **1u**. A further slower photodecomposition of **1u** leads to Cbl^{II} (shoulder at ≈ -0.75 V). Thus, upon visible-light illumination, a C,C-double bond has been shown to insert into a Co,C-bond of an $RCbl^{III}$ yielding a *sec*-$RCbl^{III}$ with an electron-withdrawing group at the Co-bound C-atom. It would probably be difficult to isolate this labile organometallic compound in

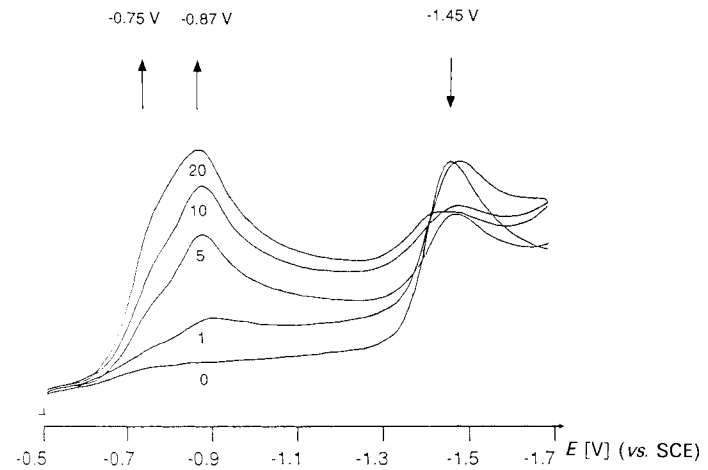


Fig. 7. *Cyclic voltammograms recorded during the photolysis of MeCbl^{III}* (**1a**) *in presence of acrylonitrile leading to the formation of the (EtCH(CN))Cbl^{III}* (**1u**). The numbers refer to illumination times in min. Conditions, see *Exper. Part.*

order to carry out a thorough structural analysis by NMR. Another transient spectroscopic technique, *i.e.* UV/VIS spectroscopy, can not distinguish different RCbl^{III} but rather their base-on and base-off isomers. However, the new electrochemical technique is fast and very sensitive to different alkyl residues in RCbl^{III}.

We are, therefore, convinced that the reduction potentials of RCbl^{III}'s and R'Cby'^{III}'s as well as their correlations reported in this paper will be extremely helpful for further mechanistic studies in the field of organometallic vitamin-B_{12} chemistry.

The authors thank the *Swiss National Foundation* for financial support.

Experimental Part

Chemicals. The alkyl halides **3c** (*Fluka, puriss.*), **3a**, **d**, **e**, **g**, **h**, **p**, **r**–**t** (*Fluka, purum*), and **3f**, **o**, **q**, **x**–**z** (*Fluka, pract.*) were distilled under normal pressure or *in vacuo* before use (**3f**, **r**–**t**, **z** were treated with aq. $Na_2S_2O_3$ soln. prior to distillation). The halides **3j**, **l**, **m**, **v**, **w** (*Fluka, purum*), **3k**, **n** (*Fluka, pract.*), **3b** (*Du Pont*), and **3i** (*Aldrich*, 98%) were used as received. Halide **3u** was prepared according to the method of *Stevens* and *Holland* [48]. Vitamin B_{12b} (**1**; hydroxocob(III)alamin hydrochloride, OHCbl^{III}·HCl; pyrogen-free *Fr. Ph. Bp;* 10,7% loss on drying; < 2% CNCbl^{III}) was purchased from *Roussel Uclaf;* heptamethyl cob(II)yrinate perchlorate (**2**; ClO_4'Cby'^{II}) and heptamethyl cob(III)yrinate diiodide (**2'**; Ie'Cby'^{III}) were prepared following the method of *Werthemann* [49]; MeCbl^{III} (**1a**) was from *Aldrich* (99%); $MeOOCCH_2Cbl^{III}$ (**1p**) was prepared as described [14]; 5'-deoxyadenosyl coenzyme B_{12} (*Fluka, BioChemika*) was used directly. *N,N*-Dimethylformamide (DMF; *Fluka, puriss.* and *Siegfried, purum*) was dried over 4 Å molecular sieves and then distilled under reduced pressure; acrylonitrile (*Fluka, puriss.*) was freshly distilled; Bu_4NClO_4 (*Fluka, purum*) was twice recrystallized from AcOEt and dried *in vacuo;* Bu_4NBF_4 (*Fluka, puriss.*) was used directly without further purification.

Electrochemical Measurements. All measurements were performed in *Metrohm* cells under Ar at 23 ± 2°. The solns. were deaerated by flushing with Ar before use. The working electrode was a *Metrohm* (*6.2802.000*) glassy C-electrode with an active diameter of 4.8 mm. The reference electrode was a *Metrohm* (*6.0724.100*) KCl-sat. (aq.) calomel electrode (SCE), separated from the soln. by a salt bridge containing the same solvent and electrolyte as the

soln. The counter electrode was a Pt wire placed directly in the soln. close to the working electrode. The electrochemical equipment was composed of an *EG & G P.A.R.* model *173* potentiostat/*175* function generator, both from *Princeton Applied Research*. A *Philips-PM-8041-X-Y* recorder or a digital data recorder [50] were used for slow and fast data aquisition, resp. Though the measurements were carried out with different scan rates, all data reported in this paper are based on the 100 mV/s scan.

Determination of the Reduction Potentials E_p (**1a–z**) *and* E_p (**2a–z**). Under dimmed-light conditions, $7.2 \cdot 10^{-4}$ M solns. of vitamin B_{12b} (**1**) or cobyrinate **2** or **2'** were used in 10 ml 0.1M Bu_4NClO_4/DMF or 0.1M Bu_4NBF_4/DMF. Appropriate amounts of the deaerated alkylating agents were added in order to obtain approximately equal peak heights for the Co^{II}/Co^{I} and the Co^{III}–R reduction peak at a scan rate of 100 mV/s. Using Bu_4NBF_4 instead of Bu_4NClO_4 as electrolyte did not influence the CV's.

Detection of the Acrylonitrile-Inserted Organocobalamin **1u** *from the Photolysis of MeCbl*^{III} (**1a**). The measurements were performed under dimmed red light conditions. Cyclic voltammograms (CV's) were recorded using a deaerated soln. of 9.7 mg (0.74 mmol) of **1a** in 10 ml of 0.1M Bu_4NClO_4/DMF. Then, acrylonitrile (48 µl, 72 mmol) was added, and CV's were recorded at regular intervals (5 min), but no changes were observed. The soln. was then exposed to white-light illumination (30-W halogen lamp, focused into the soln.), and CV's were recorded at regular intervals.

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