The Unusual, Slow Redox Properties of Cu, Ni, and Rh Cobalamins

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Summary The rates of the redox processes for several metal cobalamin complexes are virtually zero which suggests that the use of other complexes to model the redox properties of vitamin B_{12} compounds is questionable.

RECENTLY many studies of the electrochemistry of vitamin B_{12} {cyano[Co^{III}]cobalamin} and related cobalamins and cobinamides have been carried out in order to delineate the redox characteristics of the three cobalt oxidation states, Co^{III}, Co^{II}, and Co^{I}, found for these complexes.[1] In addition, investigations of the electrochemistry of diverse compounds suggested as models have also been published (see Table). The ultimate aim of these studies is to aid the interpretation of the detailed mechanism involved in the various coenzyme B_{12} catalysed reactions.

One of the most unusual features of vitamin B_{12} complexes is that the reduction of the Co^{III} complexes to Co^{II} {with the exception of aquo[Co^{III}] cobalamin} is slow compared to other cobalt(III) complexes.[2] No reduction wave is observed either in polarographic experiments or slow voltammetry studies (1 mV/s scan rates). The electrode reduction for these Co^{III}–Co^{II} couples was only recently demonstrated in a spectroelectrochemical study[2] which used a stepwise potentiostatic (and therefore equilibrium) scan of applied potential. In order to understand the reason for this extremely slow electrochemical reaction, a study of the redox characteristics of other metal–corrin complexes was undertaken.

Metals other than cobalt can be inserted into naturally occurring hydrogeno-cobalamin. This can be done for copper,[3] nickel, and rhodium[4] and these metal–corrin complexes have been examined by thin-layer spectroelectrochemistry. The u.v.-visible spectra are expected to be sensitive to the oxidation state of the central metal ion as in the cobalt case. Thus, for these strongly absorbing compounds, this method would yield the least ambiguous results without complications such as adsorption on the electrode, diffusion kinetics, and impurity oxidation and reduction.

We find that the copper, nickel, and dicyanorhodium cobalamin complexes are totally inert with respect to oxidation and reduction in the potential range $-0{\cdot}96$ to $+1{\cdot}25$ V *vs.* the NHE (normal hydrogen electrode); no changes in the spectra of all three are observed even when held at the extreme potentials for 1 h. In order to determine if electrode blockage by adsorption of the cobalamin complexes or some other poisoning of the surface caused the failure of electron transfer, bisbipyridylbisimidazoleruthenium(III) and methylviologen ($E^{\circ\prime}$ values of $+0{\cdot}96$ and $-0{\cdot}449$ V, respectively, *vs.* NHE) were added as electron transfer mediators to cover both the positive and negative potential regions. The spectroelectrochemical results were unchanged. Cyclic voltammetric studies using the same electrode material as in the spectroelectrochemical studies showed that the redox properties of the mediator in the presence of the Cu–cobalamin behaved reversibly indicating that the electrode was unaffected by the presence of the metal corrin complex.

Comparing Co^{III}–Co^{II} corrin redox potentials with those of other cobalt(III) complexes (Table) and expecting similar shifts for Ni and Cu complexes,[5] we expect oxidation–reduction potentials of the cobalamins to be about 0·5 V more negative than the 'usual' chelate and macrocycle complexes (see Table) which means that these compounds should have redox reactions well within the potential region investigated, *i.e.* the activation energies for the redox reactions of these metal-corrin complexes are extremely high even in comparison with the already slow Co^{III}–Co^{II} cobalamin couple.

It is known that the copper cobalamin complex binds only the ring nitrogens with no axial ligation,[5] and the nickel corrin complex is also thought to be only four-coordinate.[6] The results then suggest that there is no path for electron transfer through the ring system as is found in porphyrins,[7] and that the pathway for the cobalamin electron transfer involves the axial ligands only.

This conclusion can be rationalized further by recognizing that the periphery of the cobinamide ring is completely

TABLE Representative potentials of various metal complexes in aqueous media (*mediators used in these cases to determine $E^{o\prime}$)†

Central metal	System	Redox Reaction	$E^{o\prime}$ or $E_{\frac{1}{2}}$ (V *vs* NHE)	Central metal	System	Redox reaction	$E^{o\prime}$ or $E_{\frac{1}{2}}$ V *vs* NHE
Cu	$Cu(NH_3)_2^+$	1 → 2	−0 01[a]	Co	$Co(NH_3)_6^{3+}$	3 → 2	−0 01[a]
	$Cu(NH_3)_2^+$	1 → 0	−0 30[a]		$Co(NH_3)_6^{3+}$	2 → 0	−0 99[a]
	$Cu(en)_2^{2+}$	2 → 1	−0 38[d]		$Co(en)_3^{3+}$	3 → 2	−0 21[a]
	$Cu(edta)^{2-}$	2 → 0	−0 078[a]		Co(haematoporphyrin)	3 → 2	−0 19, −0 05[i]
	Cytochrome *c* oxidase*	2 → 1	0 340[b]		$Co(phen)_3^{3+}$	3 → 2	+0 42[j]
	Cytochrome *c* oxidase*	2 → 1	0 190[b]		$Co(OH_2)_4phen^{3+}$	3 → 2	+0 84[j]
	Stallacyanin*	2 → 1	0 184[c]		$Co(phen)_3^{2+}$	2 → 3	+0 34[j]
					Co^{III}tmpyp	3 → 2	−0·42[e]
	Plastocyanin*	2 → 1	0 347[c]		Cyano[Co^{III}]cobalamin(B_{12})	3 → 2	−0 426[k]
	Azurin*	2 → 1	0 330[c]		[Co^{III}]cobalamin(B_{12r})	2 → 1	−0 634[k,l]
	Laccase	2 → 1	0 415[d]		Dicyano[Co^{III}]cobalamin	3 → 2	−0 283[k,l]
	$Cu(phen)_2^{2+}$	2 → 1	0 174[d]		Methyl[Co^{III}]cobalamin	3 → 1	−1 11[l]
	Galactose oxidase	2 → 3	0 44[f]				
	$Cu(dgen)^+$	3 → 2	0 77[g]				
	$Cu(aen)_2^+$	3 → 2	1 15[g]				
	Cu-peptide complexes	3 → 2	1 02—0 45[h]				
Ni	$Ni(NH_3)_6^{2+}$	2 → 0	−0 85[a]	Rh	$Rh(NH_3)_5Cl^{2+}$	3 → 1	−0 72[a]
	$Ni(dmg)_2^{2+}$	4 → 2	−0 05[m]		$Rh(SCN)_6^{3-}$	3 → 1	> −1 3[q]
	$Ni(en)_3^{2+}$	2 → 0	−1 38[l], −1 5[n]		$Rh(CN)_6^{3-}$	3 → 1	> −1 3[q]
	$Ni(py)_6^{2+}$	2 → 0	−1 0[o]				
	$Ni(opda)_x^{2+}$	2 → 0	−0 98[p]				

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saturated, and thus presents only a hydrocarbon face to any approach in the plane of the ring [8] In addition, the 'bottom' (benzimidazole side) is blocked by three propionamide side chains and several methyl groups Similarly, the 'top' approach is hindered by three acetamide side chains, the effect of which may be overcome with a projecting axial ligand bound to the metal

The lack of a redox process for the dicyanorhodo(III)-cobalamin complex, having cyanides in both axial positions, seems to contradict this conclusion since it would be expected to be similar to dicyano[Co^{III}]cobalamin ($E^{o\prime}$ determined spectroelectrochemically is −0 283 V) However, electrochemical studies of Rh^{III} complexes show that the Rh^{II} valence state is virtually unknown and that the reduction potentials for the Rh^{III}–Rh^{I} couple shift to more negative potentials for stronger σ-donor ligands [9] The corrin system, especially with CN^- in the axial positions, would be expected to be overall a strong σ-donor system Since $Rh(SCN)_6^{3-}$ and $Rh(CN)_6^{3-}$ complexes do not exhibit reduction waves at potentials less negative than −1·3 V, it is reasonable that no reduction wave is observed in the Rh^{III} complex

Many of the compounds listed in the Table have been suggested as models for the vitamin and coenzyme B_{12} complexes Since redox reactions are considered to be involved in the coenzyme mechanism, the validity of using such complexes as models could be questionable

The Cu and Rh cobalamins were prepared and purified as in the literature [3,4] Nickel was inserted using absolute ethanol as solvent and the complex purified in the same way as the copper complex The supporting electrolyte was 0·1 M Na_2SO_4 + 10mM pH 6 8 phosphate buffer The rhodium solution was also 0 1N in NaCN.

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† Ligand abbreviations used en = ethylenediamine, H_4edta = ethylenediaminetetra-acetic acid, phen = 1,10 phenanthroline, H_2dgen = diglycylethylenediamine, Haen = *N*-acetylethylenediamine, H_2dmg = dimethylglyoxime, py = pyridine, opda = *o*-phenylenediamine, tmpyp = tetrakis-(4-*N*-methylpyridyl)porphine

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