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Preliminary communication

COENZYME B_{12} MODEL COMPOUNDS: A QUANTITATIVE ELECTROCHEMICAL COMPARISON

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Summary

A quantitative electrochemical comparative study is reported which demonstrates that Costa's B_{12} model is a closer electrochemical mimic of B_{12} than is the widely used cobaloxime model. Also reported are conditions allowing chemically reversible cyclic voltammetry of cobalt-alkyls of Costa's B_{12} model and the surprising effect of axial base concentration upon the apparent cobalt—carbon bond stability subsequent to electrochemical reduction.

The incompletely understood mechanism of adenosylcobalamin dependent rearrangement reactions continues to attract considerable interest [1,2]. Bis(dimethylglyoximato)cobalt or cobaloximes are widely accepted as coenzyme B_{12} models and are extensively utilized [3] in the search of chemical precedent for these enzyme catalyzed reactions. The wide acceptance of the cobaloxime model is, however, surprising in view of the lack of quantitative data comparing B_{12} to cobaloxime and other models. Our interest in the quantitative electrochemical comparison reported herein was heightened by reports suggesting that cobaloximes have greater cobalt—carbon bond strengths than alkyl cobalamins [4], that cobaloximes bind at least some of their axial bases ~10^2 more tightly than do their cobinamide counterparts [5], and by the fact that cobaloximes do not have the correct cobalt-localized, cationic charge found, for example, in Co^{III} alkylcobalamins.

Previous studies [6] have shown that the two closest B_{12} models that do not contain corrins or porphyrins [7a,b] are, by the electrochemical criterion*,

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*Our electrochemical criterion for a good B_{12} model is the close reproduction of the kinetic, thermodynamic, and follow-up electrochemistry of the Co^{III}/Co^{II}, Co^{II}/Co^{I}, and RCo^{III}/RCo^{II} couples.

Costa's B_{12} model [8] shown in Fig. 1 and the cobaloxime model shown in Fig. 2. It was heretofore not possible, however, to choose between these two models due to three obstacles: (1) the lack of definitive electrochemistry on B_{12} ; (2) the lack of models with the correct axial ligation; and (3) the incomplete and chemically irreversible electrochemistry in previous studies of the alkylcobalt complexes of Costa's model [9a,b,c] and the cobalxime model [9d,e,f,g]. Savéant and Lexa's recent thorough investigations [10] and other work [11] have removed the first obstacle and we have overcome the remaining ones with the results presented below.

The necessary complexes with the appropriate axial ligation for comparison to B_{12} * were prepared and isolated by literature [12] or analogous methods and have been characterized by 100 mHz ^{1}H NMR and elemental analysis**. The electrochemical results are summarized in Fig. 1—4. All potentials are referenced to SCE and are at ambient temperature unless otherwise noted. Experimental conditions are given with the figures or in the text. The data is summarized, when possible, using the format (ΔE_p ($\equiv E_{pc} - E_{pa}$); n; i_{pc}/i_{pa}) and where reversible potentials, $E_{1/2}$, were unavailable, cyclic voltammetric peak potentials, E_p, at 0.1 V/sec scan rates are reported.

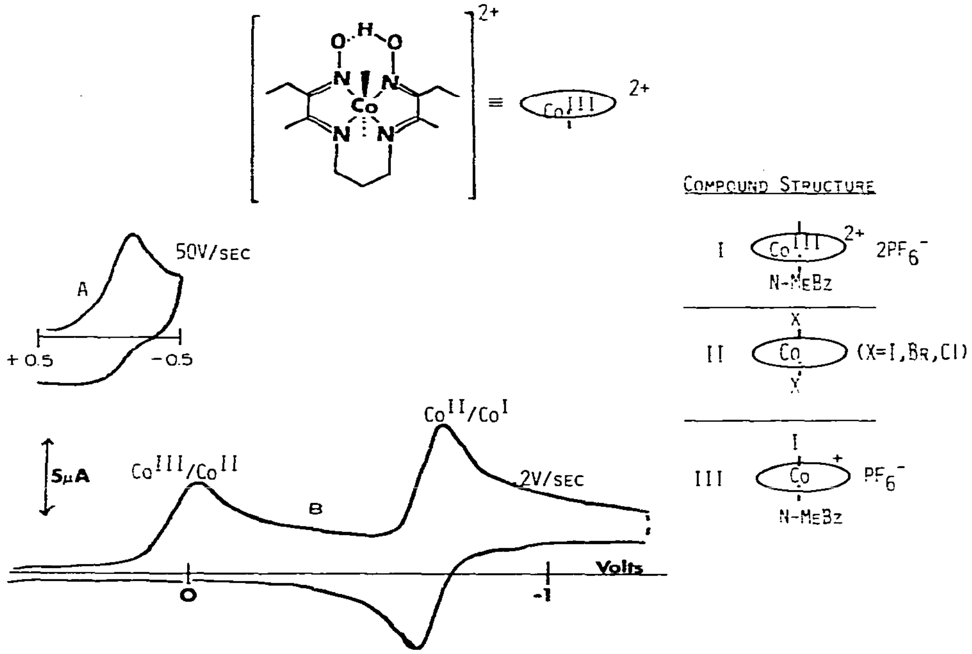

Fig. 1. Cyclic voltammogram of I, (A) 3.5 × 10^{-4} M, (B) 6.6 × 10^{-4} M, in CH_3CN, Pt vs. SCE, 0.1 M TBA^+ PF_6^-, 25°C. The —0.71 V wave is also the Co^{II}/Co^{I} couple observed for II and III. N-MeBz is 1,5,6-trimethylbenzimidazole. The Co^{III}/Co^{II} $E_{1/2}$ = —0.04 V was obtained from the rapid, 50 V/sec, scan rate experiment shown in A.

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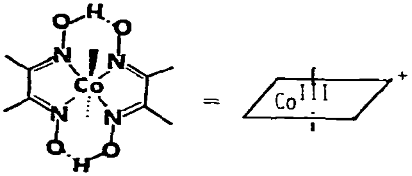
*It should be noted that B_{12} shows an extensive, pH sensitive electrochemistry. The B_{12} species utilized herein were chosen because they best allow a comparison to B_{12} of preparable Co^{III}, Co^{II}, and RCo^{III} model complexes.

**Copies of the elemental analysis and NMR data were supplied to the referees.



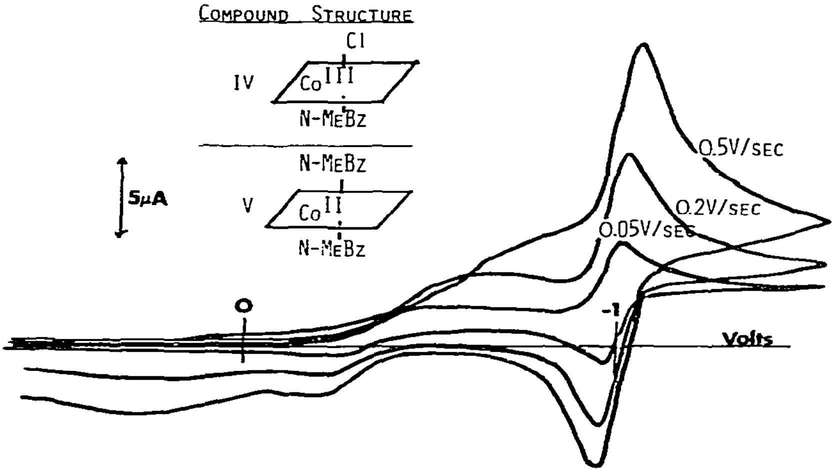


Fig. 2. Cyclic voltammogram of IV, 9.5 X 10^{-4} *M*, in CH_3CN, Pt vs. SCE, 0.1 *M* TBA^+ PF_6^-, 25°C. The —1.11 V wave is also the Co^{II}/Co^{I} couple observed for V. N-MeBz is 1,5,6-trimethylbenzimidazole. In the presence of excess N-methylimidazole bases, the Co^{III}/Co^{II} couple sharpens to a $E_{1/2}$ = —0.70 V, ΔE_p = 230 mV, wave.

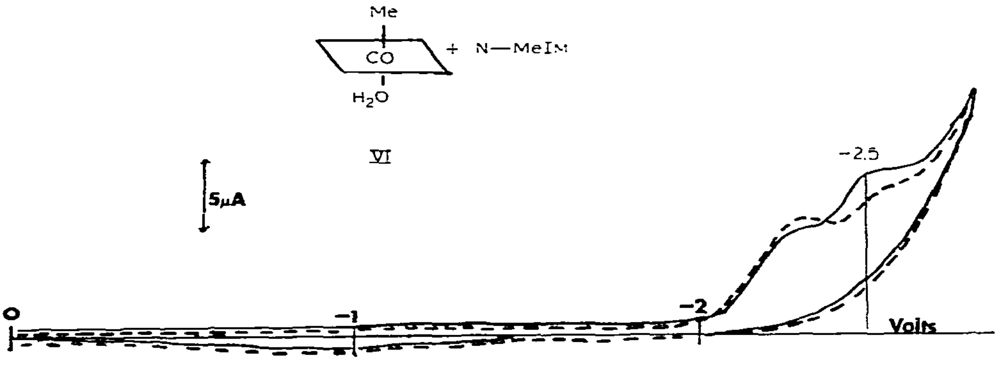


Fig. 3. Cyclic voltammogram of VI, 1.1 X 10^{-3} *M*, in CH_3CN, Pt vs. SCE, 0.1 *M* TBA^+ PF_6^-, —26°C, scan rate = 200 mV/sec, (——) is for 10% v/v *N*-methylimidazole/solvent, (- - - -) is for 5% v/v *N*-methylimidazole/solvent.

In Co^{III} aquocobalamin, de Tacconi, Lexa, and Savéant find [10a,b] a one electron, slow electron transfer reduction to base-on Co^{II} at a standard potential of —0.042 V (>450 mV; 1; —) in aq. pH = 1 to 3 Britton—Robinson buffer with 0.05 *M* $NaClO_4$ on a gold or a vitreous carbon electrode. We find that both models qualitatively reproduce the wave shape observed for the $B_{12(a)}/B_{12(r)}$ couple, but that only Costa's model closely reproduces the potential, $E_{1/2}$ = —0.04 V (—; 1; —), Fig. 1. The cobaloxime model, IV, gives

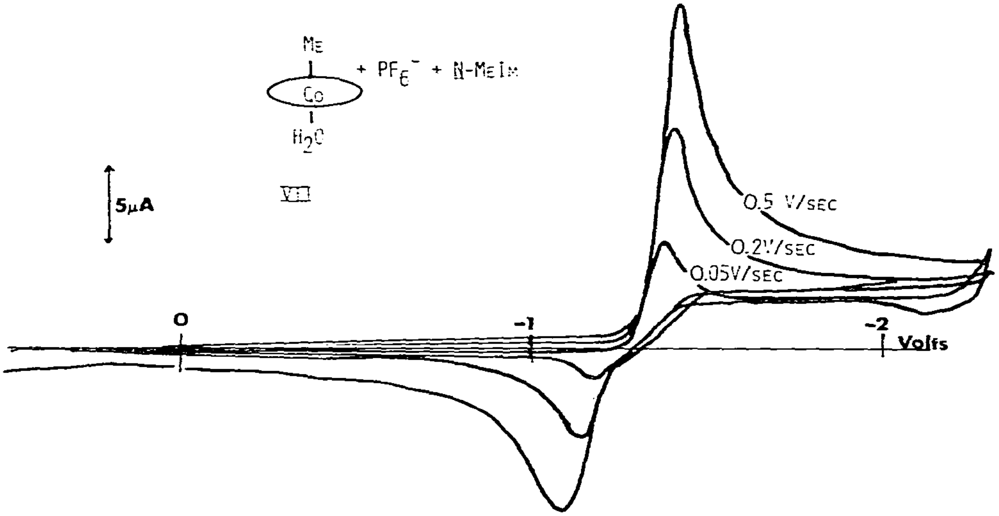


Fig. 4. Cyclic voltammogram of VII, 7.75×10^{-4} M, in CH_3CN, Pt vs. SCE, 0.1 M TBA^+ PF_6^-, −26°C, 10% v/v N-methylimidazole/solvent.

the cyclic voltammogram shown in Fig. 2. With added 1,5,6-trimethylbenzimidazole or N-methylimidazole the Co^{III}/Co^{II} wave sharpens into a chemically reversible but slow electron transfer couple, $E_{1/2} = -0.70$ V. Conductivity measurements demonstrate that IV exists in CH_3CN in the Cl^- ionized form, so that the $E_{1/2} = -0.70$ V couple is plausible assigned to $[(CH_3CN)Co(DMG)_2(N\text{-}MeBz)]^+$.

The further, Co^{II}/Co^{I}, reduction of base-off aquocobalamin is completely reversible and shows $E_{1/2} = -0.74$ V (ca. 59; 1; ca. 1). Again Costa's model is remarkably close, $E_{1/2} = -0.71$ V (71 mV; 1; 1) Fig. 1, second wave, and is in agreement with the $E_{1/2} = -0.79$ V previously reported [9a]. Each of the complexes I, II, and III, Fig. 1, shows the same couple at $E_{1/2} = -0.71$ V. The cobaloxime analogs IV and V both show a Co^{II}/Co^{I} couple at $E_{1/2} = -1.11$ V (75 mV; 1; 1), Fig. 2. Complex V is known to dissociate one of its axial bases in solution [13]. A compilation of Co^{II}/Co^{I} potentials of similar macrocycles found that this couple is relatively insensitive to potential axial ligands or to solvents and concluded, therefore, that this couple measures primarily the electronic influence of the equatorial tetradentate ligand [9g].

The electrochemistry of all the alkylcobalt complexes is more complicated due to chemical irreversibility as a result of axial base ejection and Co—carbon bond cleavage upon reduction. We have studied in detail the electrochemistry of both the methyl and n-butyl model alkylcobalts in both DMF/n-propanol and CH_3CN as a function of axial base concentration, temperature, and scan rate. Only the salient features of our studies necessary for the comparison of the models is given herein as full details will be reported elsewhere [14].

The most recent electrochemical study of methylcobalamin reveals Co—C bond cleavage to Co^I and R· and/or [7b] R^- following reduction at 25°C in DMF/n-propanol [10e]. At low temperatures and high scan rates the Co—C cleavage is suppressed although very high, 3 500 V/sec, scan rates were necessary to compete with axial base loss ($E_{1/2}$ est. −1.6 V at −30°C; others report [11c] −1.4 V at 25°C although these latter data may be affected by adsorption on Hg). Since cobaloxime potentials observed to this point have been ca. 0.4 to 0.7 V too negative, one would predict methyl(*N*-methylimidazole)cobaloxime to be reduced in the range −1.8 to 2.3 V, quite close to the potential observed for VI with or without N-MeIm (Fig. 3), E_p ca. −1.9 (25°C) to −2.3 V (−25°C). The reduction is, unlike methylcobalamin, chemically completely irreversible under all conditions of axial base, temperature, solvents, and high scan rates which we have examined.

The cyclic voltammetry of alkylcobalts of Costa's model is a sensitive and surprising function of the amount of added axial base. In the poorly coordinating solvent mixture DMF/n-propanol at 25°C, a single, diffusion controlled, chemically irreversible reduction at platinum is observed, E_p = −0.94 V, with a single oxidation appearing on the reverse scan, E_p = −0.57 V. The oxidation wave is assigned to the 4-coordinate, Co^I complex formed by the known disproportionation of two $MeCo^{II}$ to yield Me_2Co^{III} and Co^I [9a]. The serial addition of excess N-MeIm in either DMF/n-propanol or CH_3CN shifts the reduction E_p to a limiting, E_p = −1.26 V, at very large, 5—10% v/v N-MeIm/solvent, Fig. 4, and this potential is assigned to the base on form. There is an unexpected concomitant decrease in the extent of Co—C bond cleavage with added base at the expense of the Co^I oxidation. This greater apparent* Co—C bond stability in the presence of excess axial base in the model is due to axial base inhibition of the $R—Co^{II}$ disproportionation or other decomposition** pathways. The above results emphasize that, in the absence of complete mechanistic information, caution must be exercised in the interpretation of such apparent bond stabilities.

These results demonstrate that the readily available [8] B_{12} model pioneered by Costa is, by the electrochemical criterion, a considerably closer B_{12} mimic than is the much more widely used cobaloxime model, a conclusion fortified by the results of a ^{59}Co NMR study [15]. The lack of an appended axial benzimidazole, the different apparent Co—R bond stability, the 0.2 to 0.4 V too positive $E_{1/2}$ of the alkylcobalts, and the inability of any simple model to reproduce possible "conformational" [16] changes and steric effects in the more complicated coenzyme are, however, limitations of the Costa model which should be noted.

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*The apparent stability will depend upon the concentration of the RCo^{II} product of the one electron reduction if the disproportionation mechanism obtains.

**A second possibility that has been previously suggested [9a] is $RCo^{III+} + 2e \rightarrow RCo^{I-}$, then $RCo^{I-} + RCo^{III+} \rightarrow Co^I + R_2Co^{III}$. In this mechanism, the apparent stability is RCo^{III+} concentration dependent.

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