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Kinetic Studies of Dealkylation of Ethylcobalamin by Tetrachloroaurate

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In a recent paper,[1] we have described the reaction between methylcobalamin (CH_3-B_{12}) and AuX_4^- (X = Cl or Br). This reaction proceeds with a 2:1 stoichiometry ($AuX_4^-:CH_3-B_{12}$) under an atmosphere of Ar, yielding CH_3X, metallic gold, and $H_2O-B_{12}^+$ with an oxidized corrin ring. The stoichiometry and products are inconsistent with a mechanism involving a direct displacement of Co atom by attack at the α-carbon. Consequently, they are interpreted in terms of a one-electron transfer that generates a $CH_3-B_{12}^+$ and Au(II) radical pair, which then collapses to the final products. Since the reactions of CH_3-B_{12} with an electrophile such as Hg^{2+} [2] or $PdCl_4^{2-}$ [3] are widely discussed in terms of direct electrophilic attack, we seek further evidence to support the electron-transfer mechanism. A criterion that has been frequently used for the electrophilic attack mechanism is the very great difference in the dealkylation rates of CH_3-B_{12} and $C_2H_5-B_{12}$.[2a] Therefore, we extended the kinetic study to the dealkylation of ethylcobalamin by $AuCl_4^-$. Comparison of the dealkylation rate of $C_2H_5-B_{12}$ with that of CH_3-B_{12} indeed provides additional evidence for the electron-transfer mechanism.

Experimental Section

Materials. $C_2H_5-B_{12}$ was a generous gift from Dr. Hogenkamp.[4] $NaAuCl_4\cdot 2H_2O$ was purchased from Goldsmith Metal & Chemicals Inc. and was used as received. All other chemicals were reagent grade.

Stoichiometry and Kinetics. The stoichiometry was determined spectrophotometrically at 350 nm (γ band of $H_2O-B_{12}^+$) or at 315 nm (absorbance maximum of $AuCl_4^-$) under an atmosphere of N_2. B_{12} products were examined spectrophotometrically with a Cary 15 instrument. Dealkylation products were examined with a Becker gas chromatograph, Model 417.

Kinetic measurements were carried out with a McPherson/GCA spectrophotometer at 525 or 350 nm, as they provided the most convenient spectral changes during the course of reaction. The temperature was kept at 23 ± 0.3 °C with a circulating-water jacket. A large excess of $AuCl_4^-$ was used in all the rate measurements to provide the pseudo-first-order conditions in $C_2H_5-B_{12}$. The plots of log ($A_\infty - A_t$) vs. time gave straight lines for at least 80% of the reactions. pH was controlled in a range of 0–3 with HCl. At higher pH, both the quality and reproducibility of the kinetic measurements became poor, apparently because of the interference by buffer solution. Ionic strength was maintained at 1.0 M with NaCl and HCl.

Results and Discussion

In the demethylation of CH_3-B_{12} by $AuCl_4^-$,[1] we have demonstrated that the reaction occurs with a 2:1 stoichiometry
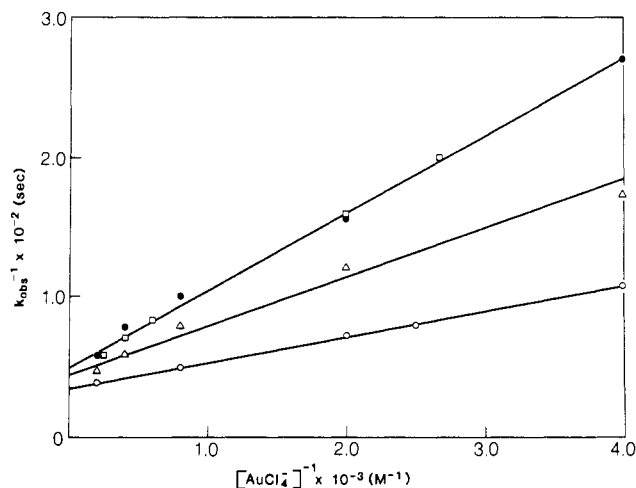
(1) Fanchiang, Y.-T. *Inorg. Chem.* **1982**, *21*, 2344.
(2) (a) De Simone, R. E.; Penley, M. W.; Charbonneau, L.; Smith, S. G.; Wood, J. M.; Hill, H. A. O.; Pratt, J. M.; Ridsdale, S.; Williams, R. J. P. *Biochim. Biophys. Acta* **1973**,. *304*, 851. (b) Chu, V. C. W.; Gruenwedel, D. W. *Bioinorg. Chem.* **1977**, *7*, 169. (c) Craig, P. J.; Morton, S. F. *J. Organomet. Chem.* **1978**, *145*, 79.
(3) Scovell, W. M. *J. Am. Chem. Soc.* **1974**, *96*, 3451.
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Figure 1. Kinetic measurements for the dealkylation of ethylcobalamin by $AuCl_4^-$ ([$C_2H_5-B_{12}$] = 6.0 × 10^{-5} M, μ = 1.0 M (HCl + NaCl); temperature 23 ± 0.3 °C): (O) pH 3.00; (△) pH 2.00; (□) pH 1.30; (●) pH 0.558.

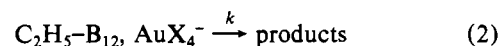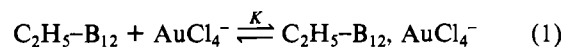**Table I.** Kinetic Parameters for the Dealkylation of Alkylcobalamins by $AuCl_4^-$ [a]

| | $C_2H_5-B_{12}$ | | CH_3-B_{12} | |
pH	10^3k, s^{-1}	$10^{-3}K$, M^{-1}	10^3k, s^{-1}	$10^{-3}K$, M^{-1}
0.558	20	0.91	8.6	2.3
1.30	20	0.91	9.3	4.4
2.00	23	1.21	10.3	6.6
3.00	29	1.46	13.0	9.2

[a] μ = 1.0 M (HCl + NaCl); 23 ± 0.3 °C.

under an atmosphere of Ar ($AuCl_4^-:CH_3-B_{12}$), yielding CH_3Cl, metallic gold, and $H_2O-B_{12}^+$ with an oxidized corrin ring. It should be stressed that the exclusion of oxygen from the reaction solution is crucial for the stoichiometric study. This is because Au(II) is an intermediate. Thus, in the absence of O_2, Au(II) would be reduced to Au(0) by the corrin ring, while in the presence of O_2, it would be reoxidized to $AuCl_4^-$ for further demethylation.

$C_2H_5-B_{12}$ (3.5 × 10^{-5} M) is quantitatively dealkylated to $H_2O-B_{12}^+$ by $AuCl_4^-$ (5.0 × 10^{-4} M) with isosbestic points at 480 and 370 nm (pH 2, 1.0 M NaCl). Although similar stoichiometry and products for the dealkylation of $C_2H_5-B_{12}$ by a high level of excessive $AuCl_4^-$ (under N_2) were observed, a complication should be noted: when $C_2H_5-B_{12}$ is dealkylated by a deficient amount of $AuCl_4^-$ under N_2, a stoichiometry of ~1:1 is observed. This implies that the $C_2H_5-B_{12}^+$ intermediate (vide infra) undergoes a different reaction when deficient amounts of $AuCl_4^-$ are used. The change of stoichiometry from 2:1 to 1:1 has also been observed for the reaction of $IrCl_6^{2-}$ with CH_3-B_{12} as the $IrCl_6^{2-}$ concentration is decreased.[5]

The dealkylation of $C_2H_5-B_{12}$ by $AuCl_4^-$ is first order in $C_2H_5-B_{12}$, as demonstrated by the straight-line plots of log ($A_\infty - A_t$) vs. time. Similar to that for CH_3-B_{12},[1] the reaction is first order in $AuCl_4^-$ at low [$AuCl_4^-$] but approaches zero order in gold as its concentration is increased. The hyperbolic dependence of k_{obsd} on [$AuCl_4^-$] is interpreted in terms of eq 1 and 2. Plots of k_{obsd}^{-1} vs. [$AuCl_4^-$]$^{-1}$ are various pHs are

$$C_2H_5-B_{12} + AuCl_4^- \overset{K}{\rightleftharpoons} C_2H_5-B_{12}, AuCl_4^- \quad (1)$$

$$C_2H_5-B_{12}, AuX_4^- \overset{k}{\longrightarrow} products \quad (2)$$

straight lines, as shown in Figure 1 These data can be de-

(5) Fanchiang, Y.-T. *Organometallics* **1983**, *2*, 121.

scribed by rate laws 3 and 4.

$$\frac{d[H_2O-B_{12}{}^+]}{dt} = k_{obsd}[C_2H_5-B_{12}] \qquad (3)$$

$$k_{obsd} = \frac{kK[AuCl_4{}^-]}{1 + K[AuCl_4{}^-]} \qquad (4)$$

The reciprocals of the intercepts of $k_{obsd}{}^{-1}$ vs. $[AuCl_4{}^-]^{-1}$ plots give values of k, and the slopes give values of $1/kK$. These values, together with those for the demethylation of CH_3-B_{12}, are documented in Table I.

We have previously pointed out[1] that, for the demethylation of CH_3-B_{12} by $AuCl_4{}^-$, the values of k are much less dependent on pH than the values of K. The pH dependence of K is attributed to the protonation of 5,6-dimethylbenzimidazole moiety, which results in a "base-on" to "base-off" conversion:


$$\qquad (5)$$
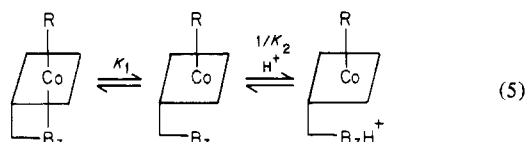
In a study of the cyanide reaction with cyanocobalamin, Reenstra and Jencks have estimated the pK_a of protonated 5,6-dimethylbenzimidazole of $NCB_{12}CN-B_zH^+$ as 5.0 (1.0 M KCl, 25 °C).[6] We have adopted this value with the assumption that a small change in temperature does not significantly affect pK_2. On the basis of this value, and a previously determined spectrophotometric method,[7] we have estimated the pK_1's for CH_3-B_{12} and $C_2H_5-B_{12}$ to be 2.0 and 1.3, respectively (1.0 M NaCl, 23 °C).

Assuming the variation of k in the pH range 0.558–3.0 can be neglected (i.e., k for both "base-on" and "base-off" CH_3-B_{12} is $\sim 10^{-2}$ s^{-1}) and using an equation previously derived for K that incorporates both "base-on" and "base-off" CH_3-B_{12},[7] we estimate K values for "base-on" and "base-off" CH_3-B_{12} are $\sim 7 \times 10^4$ and $\sim 2 \times 10^3$ M^{-1}, respectively. However, it must be noted that the assumption of a constant k value may not be justified, thus introducing a great error in the K values.

The pK_1 values for CH_3-B_{12} and $C_2H_5-B_{12}$ indicate that the 5,6-dimethylbenzimidazole ligand is much less tightly coordinated in $C_2H_5-B_{12}$ than in CH_3-B_{12}. Therefore, even at pH 3, the predominant species of $C_2H_5-B_{12}$ is in the "base-off" form. This prevents us from obtaining a meaningful analysis of the pH dependence of k and K values. Nevertheless, k and K for $C_2H_5-B_{12}$ obtained at pH 1.30 can be apparently assigned to that of "base-off" $C_2H_5-B_{12}$.

The most notable feature of the present study is the comparable magnitudes in both k and K for the "base-off" CH_3-B_{12} and $C_2H_5-B_{12}$. This is in sharp contrast to that of the electrophilic attack at the α-carbon of alkylcobalamins or other B_{12}-model compounds by an electrophile such as Hg^{2+}[8] and thus favors an electron-transfer mechanism. This mechanism is similar to the chemical and electrochemical one-electron oxidation of alkylcobaloximes recently delineated by Halpern.[8]

$$R-B_{12}, \; AuCl_4{}^- \underset{}{\overset{k_{et}}{\rightleftharpoons}} R-B_{12}{}^+, \; AuCl_4{}^{2-} \qquad (6)$$
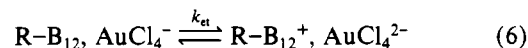
Two modes could account for the cleavage of Co–C bonds of $R-B_{12}{}^+$ cations. The first one is a homolytic scission of the Co–C bond to generate an alkyl radical, which abstracts a chlorine atom from a second $AuCl_4{}^-$. This mode is similar to the homolytic scission of the Co–C bond of a one-electron-oxidized dimethylcobalt macrocycle.[9] The second mode is a nucleophilic displacement of $R-B_{12}{}^+$ to generate a B_{12r}, which then reacts with another $AuCl_4{}^-$. This mode is similar to the one-electron oxidative dealkylation of alkylcobaloximes or other B_{12}-model compounds.[10] Unfortunately, our present study does not allow us to distinguish these two mechanisms.

(6) Reenstra, W. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 5780.
(7) Fanchiang, Y.-T., unpublished results.
(8) For a recent review, see: Halpern, J. "B$_{12}$"; Dolphin, D., Ed.; Wiley: New York, 1982; Vol. 1, p 501.
(9) Tamblyn, W. H.; Klinger, R. J.; Hwang, W. S.; Kochi, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 3161.
(10) (a) Abley, P.; Dockal, E. R.; Halpern, J. *J. Am. Chem. Soc.* **1972**, *94*, 659. (b) Halpern, J.; Chan, M. S.; Hanson, J.; Roche, R. S.; Topich, J. A. *Ibid.* **1975**, *97*, 1606. (c) Halpern, J.; Chan, M. S.; Roche, T. S.; Tom, G. M. *Acta Chem. Scand., Ser. A* **1979**, *A33*, 141.

Additions and Corrections

1981, Volume 20

Ralph G. Pearson,* Howard W. Walker, Heiko Mauermann, and Peter C. Ford: Hydrogen Migration Mechanism for Ligand Substitution Reactions in Metal Carbonyl Hydrides.

Page 2742. The second sentence in the second paragraph should read: "Furthermore a kinetics study showed a second-order rate law and no deuterium isotope effect when DWCp(CO)$_3$ was used." The fourth sentence of the fourth paragraph should read: "(A) In acetone at −70 °C H$_2$Fe(CO)$_4$ reacts within *30* min with PPh$_3$...."—Ralph G. Pearson

1982, Volume 21

J. D. Lydon, R. C. Elder, and Edward Deutsch*: Synthesis and Characterization of Coordinated Disulfides. Single-Crystal Structural Analysis of [(en)$_2$Co(S(SC(CH$_3$)$_2$COOH)C(CH$_3$)$_2$COO)]-(ClO$_4$)$_2$·H$_2$O.

Page 3192. In Table V, the y coordinate of atom O(4) was published as −0.4534 (6). It should have been 0.4534 (6); the minus sign was in error.—R. C. Elder