Kinetics of the thermolysis of *para*-substituted benzylcobalamins and derivatives

FARUK NOME, MARCOS CAROLI REZENDE, CLAUDIA MARIA SABÓIA, AND ARLINDO CLEMENTE DA SILVA
Departamento de Química, Universidade Federal de Santa Catarina, 88.001-Florianópolis, S.C.-Brasil

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The thermolysis of five *para*-substituted benzylcobalamins was studied at different temperatures. In the presence of KCN the observed rates increase with the cyanide concentration until a constant value is attained at high [CN^-]. In both series the homolytic cleavage of the Co—C bond is slightly dependent on the *para*-substituent of the benzyl moiety, with ρ values of −0.1 and −0.2 when 5,6-dimethylbenzimidazole (Bzm) and cyanide are the axial ligands respectively. The Co—C bond is weakened by electron-donating axial ligands and the homolytic cleavage rates increase in the order H_2O < Bzm < CN.

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La thermolyse de cinq benzylcobalamines *para*-substituées a été étudiée à diverses températures. Les constantes de vitesse observées augmentent avec la concentration de cyanure jusqu'à une valeur constante à haute [CN^-]. Dans les deux séries, la rupture homolytique de la liaison Co—C dépend légèrement du *para*-substituant de la moitié benzylique, les valeurs de ρ étant respectivement −0,1 et −0,2 pour les ligands axiaux 5,6-dimethylbenzimidazole (Bzm) et cyanure. Les ligands axiaux affaiblissent la liaison Co—C et les constantes de vitesse de rupture homolytique augmentent dans l'ordre H_2O < Bzm < CN.

Introduction

The chemistry of the Co(III)—C bond plays a central role in the biochemistry of vitamin B_{12} (1, 2). As a consequence, the formation and cleavage of the Co—C bond of alkylcobalamins and cobinamides in various chemical processes have been topics of continuous interest in the vitamin B_{12} chemistry (1–14). Examples are found of homolytic and heterolytic cleavages and it is not always an easy task to decide which is the preferred pathway in many thermal decompositions. Even when a homolytic pathway is firmly established, the charge distribution in the transition state remains a subject of speculation. Although large kinetic effects arising from electronic factors are not to be expected in these homolytic processes, such effects do exist and can shed more light on the nature of the transition state of these cleavages. Changes in the ease of the Co—C bond breaking may be observed by either changing the charge of the Co atom, or of the alkyl moiety. Schrauzer and Grate (10) studied the thermolysis of benzylcobalamin and showed, on the basis of the products formed under aerobic and anaerobic conditions, that this is a homolytic process. We decided to study other substituted benzylcobalamins and evaluate the effect of these substituents on the rate of the Co—C bond cleavage. We were also interested in the effects of axial ligands on the cobalt atom, and how they might affect this thermolysis process. Such a *trans* effect should be larger than the result of altering the benzyl moiety, as the ligand is directly attached to the cobalt atom.

Experimental

Vitamin B_{12a} (aquocobalamin) and vitamin B_{12} (cyanocobalamin) were purchased from Merck, Sharp and Dohme. Diaquocobinamide was obtained from vitamin B_{12} following the procedures reported by Pratt and co-workers (14) and Friedrich and Bernhauer (15). The benzyl- and *p*-methylbenzylcobinamide and the various substituted benzylcobalamins **1** employed were prepared following Schrauzer's procedure (9). The products obtained were spectroscopically identical with those reported in the literature.

The spectroscopic characterization of all cobalamins and cobinamides prepared and the kinetic measurements were performed with a Shimadzu UV-210A spectrophotometer equipped with thermostatted water-jacketted cell compartments. The analysis of the organic products of the reactions was carried out with a gas chromatograph CG 370, equipped with an OV-17 column, retention times being identical with those of authentic samples.

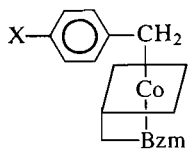
The aerobic decomposition of benzylcobalamins and cobinamides was studied in aqueous buffered solution at pH 7.0 by following the change of absorbance at 350 and 425 nm respectively. The spectral changes observed were identical with those reported by Schrauzer and Grate (10) with isobestic points at 370 and 480 nm. The decomposition of benzylcobalamins **1** in the presence of KCN was studied in aqueous buffered solution at pH 11, by monitoring the formation of the products at 367 nm. The spectral changes observed were similar to those described by Jencks and co-workers (11) for the thermolysis of (methoxycarbonyl)methylcobalamin in the presence of excess cyanide, which yields a mixture of cyano- and dicyanocobalamins (λ_{max}: 575, 540, and 370 nm).

Rate constants were obtained from linear plots of $\ln(A_\infty - A_t)$ vs. time. All plots were linear for at least 90% of the reaction, with correlation coefficients greater than 0.99. The activation parameters were calculated from Arrhenius plots of the rate constants at different temperatures.

Results and discussion

Benzylcobalamin decomposes in the presence of oxygen to form benzaldehyde and vitamin B_{12a} (9). The reaction is much slower under nitrogen because of recombination of the benzyl radical and the Co(II) species formed by the homolytic cleavage of the Co—C bond.

We have studied the thermolysis of five *p*-substituted benzylcobalamins **1** at pH 7.0 and different temperatures.



X = H, Me, MeO, Br, CO_2^-

1

The observed rate constants are given in Table 1. The activation parameters for the thermolysis process for each benzylcobalamin were calculated from the observed pseudo-first-order rate constants and are given in Table 2. For the sake of comparison and the discussion below, activation parameters for the benzyl- and *p*-methylbenzylcobinamide are also included in Table 2.

We have also followed the decomposition of cobalamins **1** in the presence of cyanide anion. As with the experiments in the absence of CN^-, the thermolysis is considerably slower

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TABLE 1. Observed rate constants for the thermolysis of *p*-substituted benzylcobalamins at pH 7 and various temperatures

Temperature (°C)	$10^3\ k_{obs}\ (s^{-1})$				
	X = H	X = Me	X = OMe	X = Br	X = CO_2^-
15	0.65	0.64	0.51	0.56	0.36
20	1.28	1.23	1.08	1.11	0.77
25	2.40	2.45	2.08	2.26	1.63
30	4.50	4.55	4.14	4.45	3.36
35	8.20	8.51	7.81	8.47	6.65

under nitrogen. Similarly to the reaction in the absence of CN^- the products were the corresponding benzaldehyde and 1,2-diarylethane in aerobic and anaerobic conditions respectively. Toluene, a product that could be formed by homolysis of the Co—C bond followed by electron transfer, was not detected under our experimental conditions. However, in this case, the spectral analysis of the products revealed the formation of a mixture of cyano- and dicyanocobalamin, both under aerobic and anaerobic conditions. The formation of a cobalt(III) species in a homolytic process can be explained by the disproportionation of the Co(II) species initially formed in the presence of excess cyanide, the Co(I) species being consumed by trace oxygen (16).

[1] $$2Co(II) + 2CN^- \overset{K_D = 0.28}{\rightleftharpoons} Co(III)(CN^-)_2 + Co(I)$$

As shown by Savéant and co-workers, this disproportionation is not as important when the axial ligand is water, hydroxide, or benzimidazole (16).

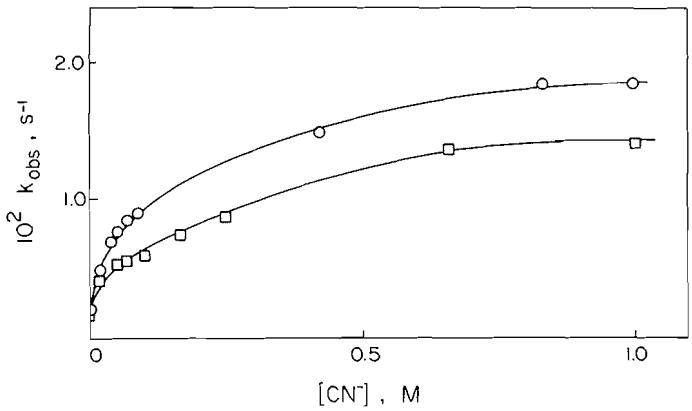
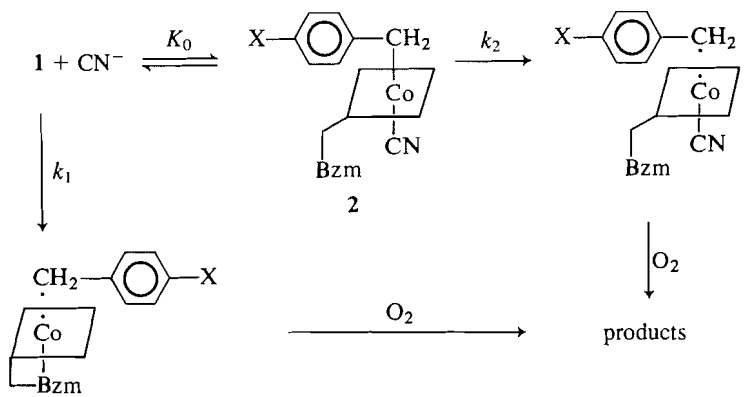


FIG. 1. Variation of k_{obs} as a function of the concentration of cyanide ion for the thermolysis of *p*-methoxybenzylcobalamin (○) and benzylcobalamin (□) at 25.0°C.

Table 3 lists the observed rate values for the decomposition of cobalamins **1** at 25°C, pH 11, and increasing concentrations of cyanide anion. The thermolysis rate is found to increase with [CN^-] until a constant value is reached. Such behaviour is illustrated for the benzyl- and the *p*-methoxybenzylcobalamin in Fig. 1, and has been described by Jencks and co-workers (11) in the decomposition of (methoxycarbonyl)methylcobalamin in the presence of cyanide. Our data can be rationalized by a mechanism that involves a preequilibrium between two cobalt species with different axial ligands, -CN and 5,6-dimethylbenzimidazole (Bzm), which undergo thermolysis at different rates.

[2]



At high cyanide concentrations the benzimidazole ligand is completely displaced by CN^-, the observed rate becoming constant and equal to k_2. Equation [3] relates the observed rate constant to the cyanide concentration.

[3] $$k_{obs} = (k_1 + k_2 \cdot K_0[CN^-])/(1 + K_0 \cdot [CN^-])$$

Since $k_{obs} = k_1$ when $[CN^-] = 0$, and $k_{obs} = k_2$ for sufficiently high concentrations of cyanide, the preequilibrium constant K_0 can be estimated by proper adjustment of eq. [3] to the experimental values. For the five cobalamins studied, the average K_0 value was $12 \pm 6\ M^{-1}$, not very different from the value of $22.7\ M^{-1}$ for a similar equilibrium involving the (methoxycarbonyl)methylcobalamin (11).

The observed rate values for the thermolysis of the five cobalamins in the presence of a high concentration of cyanide ($[CN^-] = 0.83\ M$) at various temperatures are given in Table 4. Under these conditions, these rates are equal to the rate values k_2, and the activation parameters derived from them (Table 5) correspond to the homolytic cleavage of the Co—C bond when -CN is the axial ligand. We can thus compare the two homolytic processes that differ in the nature of the axial ligand. Figure 2 is a Hammett plot of the thermolysis rate constants for all *p*-substituted benzylcobalamins. The ρ values are −0.1 and −0.2, in the absence and presence of cyanide respectively. The small values were expected for a homolytic process, but the negative sign in both cases is an indication of a slight nucleophilic character of the incipient benzyl radical in the transition state.

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TABLE 2. Activation parameters and calculated rate values at 25°C for the thermolysis of *p*-substituted benzylcobalamins and cobinamides

Substituent X	Axial ligand	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal mol^{-1} deg^{-1})	$\Delta G^{\ddagger}$ kcal mol^{-1}	$10^3 k_2^{25}$ (s^{-1})
H	Bzm	21.7±0.3	2.4±1.0	21.02	2.41
Me	Bzm	22.3±0.5	4.3±1.7	21.01	2.42
MeO	Bzm	23.4±0.6	7.7±1.9	21.10	2.11
Br	Bzm	23.5±0.5	8.1±1.6	21.06	2.26
CO_2^-	Bzm	25.0±0.5	12.8±1.6	21.22	1.72
H[a]	H_2O	28.6±1.3	14.4±4.1	24.30	0.0093
Me[b]	H_2O	27.2±1.4	10.1±4.7	24.20	0.011

[a]Parameters and rate values calculated from the following observed rate constants, k_{obs}: 9.4×10^{-5} (40°C), 1.95×10^{-4} (45°C), 3.98×10^{-4} (50°C), 7.80×10^{-4} (55°C), and 1.55×10^{-3} s^{-1} (60°C). [b]Observed rate constants, k_{obs}: 1.05×10^{-4} (40°C), 2.12×10^{-4} (45°C), 4.3×10^{-4} (50°C), 8.22×10^{-4} (55°C), and 1.60×10^{-3} s^{-1} (60°C).

TABLE 3. Observed rate constants for the thermolysis of *p*-substituted benzylcobalamins at 25°C and pH 11 in the presence of potassium cyanide

	$10^2 k_{obs}$ (s^{-1})				
10[KCN] (*M*)	X = H	X = Me	X = MeO	X = Br	X = CO_2^-
0	0.21	0.23	0.18	0.20	0.13
0.17	0.42	0.61	0.49	0.36	0.76
0.33	0.51	0.81	0.70	0.44	—
0.50	0.54	1.02	0.76	0.49	—
0.66	0.56	1.10	0.85	—	—
0.83	—	1.14	0.88	—	—
1.00	0.59	1.16	—	0.52	0.96
1.67	0.74	1.21	—	0.59	—
2.50	0.87	1.28	—	—	1.11
3.33	—	1.31	—	0.88	—
4.17	—	1.32	1.45	0.97	1.34
6.67	1.24	1.45	—	1.19	—
8.33	1.22	1.49	1.89	1.20	1.56
10.00	1.23	1.53	1.83	—	1.54

TABLE 4. Pseudo-first-order rate constants for the thermolysis of *p*-substituted benzylcobalamins at various temperatures and pH 11, in the presence of 0.83 *M* KCN

Temperature (°C)	$10^2 k_{obs}$ (s^{-1})				
	X = H	X = Me	X = MeO	X = Br	X = CO_2^-
15	0.598	0.687	0.750	0.537	0.790
20	0.876	1.03	1.18	0.826	1.12
25	1.22	1.49	1.89	1.20	1.56
30	1.69	2.09	2.91	1.80	2.23
35	2.33	3.01	4.45	2.60	3.04

The nature of the axial ligand was expected to play an important role in the homolytic cleavage of the Co—C bond. In fact, for the reaction in which water was the axial ligand (Table 2), the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the compounds studied are in the range of 27.2–28.6 kcal mol^{-1} and 10.1 – 14.4 eu respectively. When benzimidazole is the axial ligand, a slight decrease in $\Delta H^{\ddagger}$ (21.7–25.0 kcal mol^{-1}) is observed (Table 2). This trend is maintained when cyanide is the ligand, the range of $\Delta H^{\ddagger}$ values being 15.1–11.3 kcal mol^{-1}, but in this case a strong decrease in $\Delta S^{\ddagger}$ (−15.6 to −29.3 eu) is also observed (Table 5).

The changes observed in both enthalpy and entropy of activation are noteworthy and, as should be expected for reactions occurring through the same mechanism, a linear dependence of $\Delta H^{\ddagger}$ on $\Delta S^{\ddagger}$ is observed (graph not shown), implying a partial compensation of both factors. It is clear from Table 2 that the variations of $\Delta H^{\ddagger}$ predominate in the overall changes of $\Delta G^{\ddagger}$ for the reaction series.

It may be argued in the case of cobalamins that these activation parameters do not correspond solely to the homolytic cleavage of the Co—C bond. In fact, as pointed out by Schrauzer and Grate (10), the activation parameters for the thermolysis of the organocobalamins include a contribution from the base-on/base-off benzimidazole coordination equilibria. A comparison between benzylcobalamins and other related systems where these contributions are absent should be valid only if the benzimidazole coordination equilibria for all benzylcobalamins studied do not vary with the temperature, being cancelled in the calculation of the activation parameters. This was in fact observed by us with the *p*-substituted benzylcobalamins studied in this work. As was the case of benzylcobalamin itself (10), our cobalamins showed very small spectral changes in the temperature range of our experiments, indicating that variations of coordination equilibria with temperature are negligible.

The pronounced entropic change from positive (benzimida-

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TABLE 5. Activation parameters and calculated rate values at 25°C for the thermolysis of *p*-substituted benzylcobalamins in the presence of excess cyanide

Substituent X	E_a (kcal mol^{-1})	$\Delta H^{\neq}$ (kcal mol^{-1})	$\Delta S^{\neq}$ (cal mol^{-1} deg^{-1})	$\Delta G^{\neq}$ (kcal mol^{-1})	$10^2\, k_2^{25}$ (s^{-1})
H	11.9±0.4	11.3±0.4	−29.3±1.3	20.06	1.21
Me	12.9±0.4	12.3±0.4	−25.5±1.4	19.95	1.48
MeO	15.7±0.3	15.1±0.3	−15.6±1.0	19.80	1.87
Br	13.9±0.4	13.3±0.4	−22.7±1.3	20.05	1.22
CO_2^-	11.9±0.4	11.3±0.4	−28.7±1.2	19.91	1.58

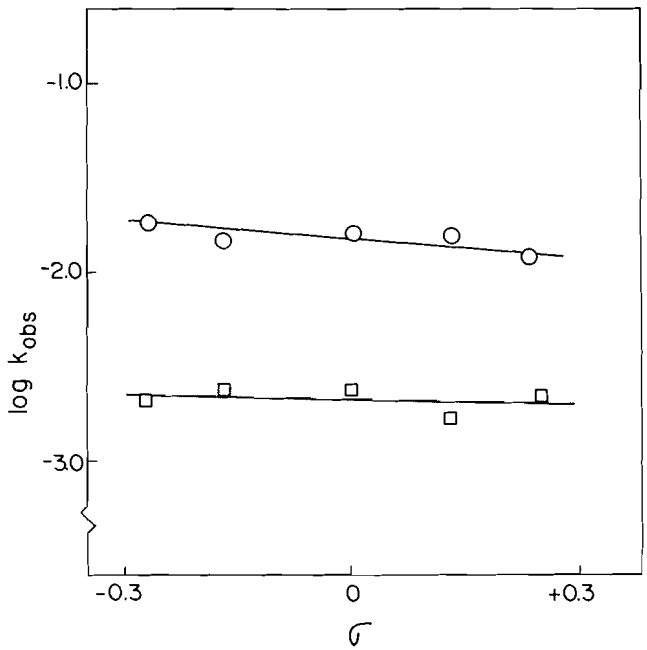

FIG. 2. Variation of log k_{obs} as a function of the substituent constant for the decomposition of **1** in the presence (○) and absence (□) of cyanide ion at 25.0°C.

TABLE 6. Co—C bond dissociation energies and rate constants for the Co—C cleavage of benzylcobinamides, cobalamins **1**, and the cyanoderivatives **2**

	Benzyl substituent			
	Benzyl		*p*-Methylbenzyl	
Axial ligand	D_{Co-C}[a] (kcal mol^{-1})	k_2^{25} (s^{-1})	D_{Co-C}[a] (kcal mol^{-1})	k_2^{25} (s^{-1})
H_2O	26.6±1.3	9.3×10^{-6}	25.2±1.4	1.10×10^{-5}
Bzm	19.7±0.3	2.41×10^{-3}	20.3±0.5	2.42×10^{-3}
CN	9.3±0.4	1.21×10^{-2}	10.3±0.4	1.48×10^{-2}

[a]Value calculated as $D_{Co-C} = \Delta H^{\neq} - 2.0$ kcal mol^{-1} (see ref. 12).

zole and water as axial ligands) to negative values when cyanide is coordinated to the cobalt(III) atom is, to the best of our knowledge, unprecedented. Following Schrauzer's tentative arguments (10), we may regard such an entropic change as the result of two opposing trends, an entropic gain due to the departure of the benzyl groups, and an entropy loss, when -CN is the axial ligand. Thus, the order imposed on the benzylcobalamin and benzylcobinamide by the benzyl group is lost in the transition state, which should be very nearly cobalt(II) in nature. When CN^- is the axial ligand, the order imposed by axial cyanide coordination is increased in going from the Co(III) to the Co(II) species and more than compensates the entropy gain due to the benzyl group departure. The overall result is then a net entropy decrease of the cyanide coordinated system.

Table 6 lists the rate constants at 25°C for the Co—C bond cleavage reaction of the benzyl and *p*-methylbenzylcobalamins in the presence and absence of cyanide ion, and the dissociation energies of the corresponding Co—C bond, estimated, according to Halpern (12), to be 2.0 kcal mol^{-1} less than the homolysis activation enthalpies. For the sake of comparison we also include the Co—C bond dissociation energies estimated from the thermolysis of the benzyl- and *p*-methylbenzylcobinamide at 25°C. Inspection of this table shows that the homolysis is facilitated by the increasing electron-donating ability of the axial ligand. By reducing the charge of the cobalt atom, the electron-donating axial cyanide weakens the Co—C bond considerably, as compared to the more stable cobalamin and cobinamide systems. This ground-state effect is much more important than an eventual transition state destabilization by the cyanide ligand, which renders more difficult the transition from Co(III) to Co(II) by increasing the electron density around the cobalt atom.

In conclusion, the present work extends Schrauzer's original studies on the homolytic cleavage of benzylcobalamin (10) by varying both the benzyl moiety and the substituent in the fifth coordination position. As anticipated, the homolytic fission is only slightly dependent on the nature of the *para* substituent of the benzyl moiety, but the negative values obtained argue for some small degree of nucleophilic character of the incipient benzyl radical in the transition state. Changing the axial substituent results in considerable changes in the rates of homolytic Co—C cleavage, such rates increasing in the order H_2O < Bzm < CN. It is noteworthy that, in spite of the large changes brought about by the replacement of the 5,6-dimethylbenzimidazole ligand by water or cyanide, the reaction mechanism and the mode of cleavage of the Co—C bond are essentially the same.

It is important to emphasize that, because of the particular steric and electronic labilization of the Co—C bond in benzylcobalamins, any mechanistic extension of our results to other organocobalamins should be made with caution.

Acknowledgements

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