Alkali-Induced Decomposition of (2-Alkoxyalkyl)cobaloximes

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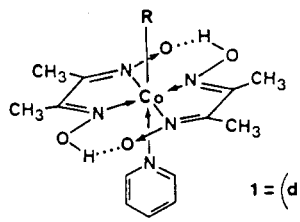
Decomposition of tetrahydrofurfuryl(pyridine)cobaloxime by aqueous sodium hydroxide results in fragmentation to 4-penten-1-ol and cobaloxime(III). Several other (2-alkoxyalkyl)(pyridine)cobaloximes behave analogously. The reaction is of mixed kinetic order in hydroxide and is inhibited by pyridine. Intermediates may be detected by NMR spectroscopy. A mechanism is proposed in which tetrahydrofurfurylhydroxocobaloxime anion or dianion (from deprotonation of the chelating ligand system) undergoes a spontaneous cleavage with elimination of alkene and alcohol.

The readily accessible alkylcobaloximes (1) [derivatives of bis(dimethylglyoximato)cobalt] have been intensively studied as models for the important coenzyme vitamin B_{12} (5′-deoxyadenosylcobalamin). In particular, (2-hydroxyalkyl)(pyridine)cobaloximes (e.g., 1, R = CH_2CH_2OH) are decomposed by aqueous base, and this reaction (liberating ketones or aldehydes)[1] has been considered as an analogue of certain inadequately understood rearrangements in which the biochemical cofactor participates.[2] We have reinvestigated the reactivity of such species.[3] This article focuses on (2-alkoxyalkyl)(pyridine)cobaloximes (e.g., 1, R = $CH_2CH_2OCH_3$); our conclusions will be shown to differ from previous interpretations by other investigators.

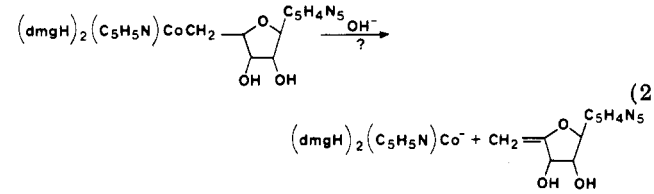


1 = $(dmgH)_2(C_5H_5N)CoR$

The *acid*-induced decomposition of (2-hydroxyalkyl)cobaloximes has recently been carefully reexamined.[4] In general, the mechanism appears to involve reversible formation of an olefinic π-complex, with subsequent release of an alkene from the metal ion. There is adequate evidence that (2-alkoxyalkyl)cobaloximes decompose similarly in acidic solution (eq 1).[1,5]

$$(dmgH)_2(HOH)CoCHRCHR'OH \overset{H^+}{\rightleftharpoons} (dmgH)_2(HOH)Co^{\bullet} \bullet (CHR{=}CHR') \longrightarrow (dmgH)_2(HOH)Co^{+} + CHR \square CHR' \quad (1)$$

As regards the reactivity of (2-alkoxyalkyl)cobaloximes in *alkaline* solution, there have previously been no detailed studies. Schrauzer has stated that (2-methoxyethyl)(pyridine)cobaloxime can be recovered unchanged from strongly basic solution,[6] an observation which we find must be qualified. He has also reported that 5′-deoxyadenosyl(pyridine)cobaloxime decomposes in aqueous alkali to yield the cobaloxime(I) anion and an elimination product of the 5′-deoxyadenosyl moiety (eq 2).[6] The pseudo-first-order rate constant for this reaction at 27 °C in 1 N sodium hydroxide was reported to be 1.6×10^{-3} s^{-1}.

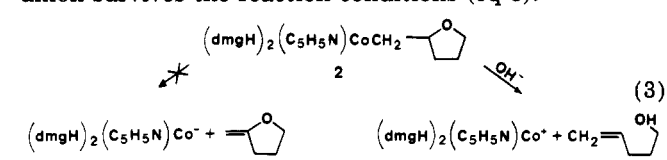


(2)

This transformation has been considered as a plausible model for the biochemical activation process of the cobalamins, in which the adenosyl moiety is believed to be dissociated from the metal prior to the cofactor's participation in catalytic reactions.

Results

Product Identification. In order to facilitate product characterization, we adopted tetrahydrofurfuryl(pyridine)cobaloxime (2) as our model substrate, since it appears to contain the essential functionality of the adenosine moiety. An aqueous solution of this substance readily decomposes upon addition of dilute sodium hydroxide. Extraction of the reaction mixture yielded 4-penten-1-ol, and not the expected enol ether. In the previous report on fragmentation of deoxyadenosylcobaloxime, the supposed product was not actually characterized.[6] However, it was claimed that the cobaloxime(I) anion was a coproduct. In our hands the reaction of 2 yields only cobaloxime(III), and we have explicitly excluded formation of cobaloxime(I) by a control experiment showing that the anion survives the reaction conditions (eq 3).



(3)

In order to verify the generality of the reaction, a number of other (2-alkoxyalkyl)(pyridine)cobaloximes were prepared and submitted to alkaline decomposition. The results, which are summarized in Table I, are quite analogous to the transformation just described. The relative reactivities do not show any interpretationally significant variation with structure.[7] The secondary cobaloxime substrates (entries 6 and 8 in Table I) are in fact more rapidly decomposed; however, this correlates with known steric destabilization of such branched organometallics. It may be noted that (2-hydroxy-2-methylpropyl)(pyridine)cobaloxime (entry 7), which lacks hy-

(1) Schrauzer, G. N.; Windgassen, R. J. *J. Am. Chem. Soc.* **1967**, *89*, 143.
(2) Babior, B. M.; Krouwer, J. S. *CRC Crit. Rev. Biochem.* **1979**, *6*, 35.
(3) Bieniarz, C. Ph.D. Thesis, University of Illinois at Chicago, 1982.
(4) Espenson, J. H.; Wang, D. M. *Inorg. Chem.* **1979**, *18*, 2853.
(5) (a) Golding, B. T.; Holland, H. L.; Horn, U.; Sakrikar, S. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 959. (b) Hogenkamp, H. P. C.; Rush, J. E.; Swenson, C. A. *J. Biol. Chem.* **1965**, *240*, 3641. (c) Johnson, A. W.; Shaw, N. *J. Chem. Soc.* **1962**, 4608.
(6) Schrauzer, G. N.; Sibert, J. W. *J. Am. Chem. Soc.* **1970**, *92*, 1022.
(7) At one time we entertained a mechanism in which the ether oxygen participating in the fragmentation first enters the ligand sphere of the metal by intramolecular chelation. Hence, substrates with better coordination potential were prepared (entries 2–6 in Table I). The kinetic data provide no support for this idea.

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Table I. Cobaloxime Substrates Yielding Alkaline Fragmentation Products

	substrate[a]	product(s)[b]	rate of decomp,[c] $s^{-1} \times 10^3$
1	$OCH_2CH_2CH_2CHCH_2Co(dmgH)_2(C_5H_5N)$ (2)	$CH_2{=}CHCH_2CH_2CH_2OH$	47.4 (±1.0)
2	$HOCH_2CH_2OCH_2CH_2Co(dmgH)_2(C_5H_5N)$	$(CH_2{=}CH_2)^d + HOCH_2CH_2OH$	3.02 (±0.02)
3	$CH_3OCH_2CH_2OCH_2CH_2Co(dmgH)_2(C_5H_5N)$	$(CH_2{=}CH_2)^d + CH_3OCH_2CH_2OH$	2.31 (±0.04)
4	$HOCH_2CH(OCH_3)CH_2Co(dmgH)_2(C_5H_5N)$	$CH_2{=}CHCH_2OH + CH_3OH$	48.8 (±1.2)
5	$CH_3OCH_2CH(OCH_3)CH_2Co(dmgH)_2(C_5H_5N)$	$(CH_2{=}CHCH_2OCH_3 + CH_3OH)^d$	4.96 (±0.06)
6	$(CH_3OCH_2)_2CHCo(dmgH)_2(C_5H_5N)$	$CH_2{=}CHCH_2OCH_3 + CH_3OH$	>100[e]
7	$(CH_3)_2COHCH_2Co(dmgH)_2(C_5H_5N)$	$CH_2{=}C(CH_3)_2$	0.47 (±0.03)
8	*cis*-$CH(OCH_3)CH_2CH_2CH_2CH_2CHCo(dmgH)_2(C_5H_5N)$	$CH{=}CHCH_2CH_2CH_2CH_2 + CH_3OH$	>100[e]
9	$CH_3OCH_2CH_2Co(dmgH)_2(C_5H_5N)$	$(CH_2{=}CH_2 + CH_3OH)^d$	1.60 (±0.02)
10	$(C_2H_5O)_2CHCH_2Co(dmgH)_2(C_5H_5N)$	$(CH_2{=}CHOC_2H_5 + C_2H_5OH)^d$	1.18 (±0.05)

[a] dmgH = dimethylglyoximato; C_5H_5N = pyridine. [b] Coproduct cobaloxime(III). [c] Pseudo-first-order rate constant in 0.50 N NaOH at 57.5 °C. [d] Product not actually identified. [e] Very rapid, apparently biphasic decay exhibited.

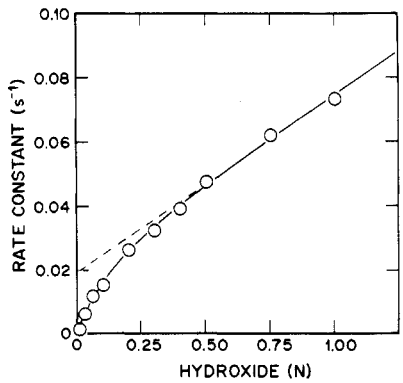


Figure 1. Dependence of pseudo-first-order rate constant on hydroxide concentration for **2** at 57.5 °C.

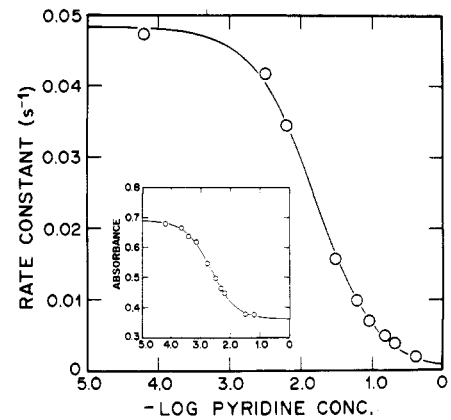


Figure 2. Dependence of pseudo-first-order rate constant on pyridine concentration for **2** in 0.50 N NaOH (57.5 °C). Inset: dependence of absorbance (444 nm) on pyridine concentration for **2** at 57.5 °C.

drogens β to the metal and hence cannot yield a ketonic product,[1] also undergoes this reaction. It had previously been reported that (2-methoxyethyl)(pyridine)cobaloxime (entry 9) can be recovered unchanged from 50% KOH solution.[6] While this may be true, it would seem that one must work quickly to do so. For this substance we find a half-life of less than 7 min in 0.5 N NaOH at 57.5 °C.

Kinetics. Dilute solutions of the primary (alkoxyalkyl)(pyridine)cobaloximes (Table I) exhibit pseudo-first-order decay in strongly alkaline solution as monitored spectrophotometrically. Rate constants at a fixed hydroxide concentration are recorded in Table I. As next described for the first substrate **2**, a series of experiments was carried out to determine the kinetic order in hydroxide and to assess the influence of excess pyridine on the course of the reaction. Details of the kinetic analysis may be found in the Experimental Section, with a summary of the results to follow.

(a) Hydroxide Dependence. The pseudo-first-order rate constants for decomposition of our model substrate, tetrahydrofurfuryl(pyridine)cobaloxime (**2**), appear to increase linearly with hydroxide ion concentrations above 0.3 N (Figure 1). However, there is a considerable deviation at lower base strengths (compare curve with dashed line). Such nonlinearity is indicative of a complex mechanism. The solid line accommodating the data in Figure 1 corresponds to a best fit on the assumption that the reaction is of *mixed* order in hydroxide at low base strength, becoming *first* order as the alkalinity increases. This interpretation follows from the mechanism that is developed in the Discussion.

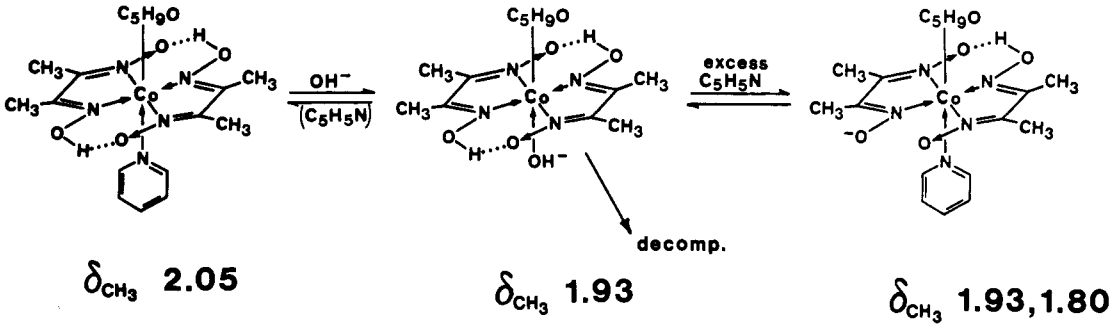
(b) Pyridine Inhibition. The rate of alkaline decomposition of **2** is greatly retarded by the presence of potential ligands such as pyridine, ammonia, or cyanide. The dependence of the pseudo-first-order rate constant on pyridine concentration is shown in Figure 2 for a sodium hydroxide concentration of 0.50 N. The data were satisfactorily fitted to a sigmoidal curve, yielding an apparent inhibition constant, K_i = 0.015 (±0.001) M. Quite evidently pyridine renders the substrate inert to alkaline decomposition. Although the substance submitted to our kinetic runs was a pyridine complex, in the absence of excess pyridine apparently the cobaloxime is largely dissociated (hydrolyzed) at the concentrations of substrate employed, and it is the aquo complex that suffers decomposition.

In order to confirm this conclusion a spectrophotometric determination of the equilibrium constant at 57.5 °C for conversion between aquocobaloxime and (pyridine)cobaloxime was undertaken. By absorbance readings at 444 nm upon solutions of **2** in the absence of alkali but in the presence of various pyridine concentrations, a sigmoidal dependence shown also in Figure 2 (inset) was obtained. From this a dissociation constant may be determined

$$K_d = [(dmgH)_2(HOH)CoC_5H_9O]\cdot[C_5H_5N]/[(dmgH)_2(C_5H_5N)CoC_5H_9O]$$

A value was obtained by least-squares curve fitting: K_d = 0.0021 (±0.0001) M. This number confirms that in the absence of added pyridine our cobaloximes exist almost completely in the aquo form at the concentrations investigated kinetically (0.000 06 M). However, this true dissociation constant (K_d) is 7.3 times *smaller* than the ap-

Scheme I



parent pyridine inhibition constant (K_i) measured kinetically in 0.5 N sodium hydroxide. The discrepancy is not within experimental error; its rationalization is a key piece of mechanistic evidence (see Discussion).

NMR of Intermediates. The behavior of **2** in strongly basic media was examined by NMR spectroscopy. The decomposition of concentrated solutions of **2** yielding 4-penten-1-ol can be conveniently followed by proton NMR in $(CD_3)_3S{=}O$ solution containing 2 equiv of 40% NaOD in D_2O. The conversion is prevented by addition of an excess of pyridine, as is the case in dilute aqueous solution. There are informative changes under these circumstances in the chemical shift of the *methyl* signal arising from the coplanar dimethylglyoximato chelate component of the cobaloxime (four equivalent CH_3 groups). Upon addition of alkali to solutions of **2**, this singlet promptly undergoes an upfield shift of 0.12 ppm. We attribute this to displacement of ligand pyridine by the negatively charged hydroxide, a transformation which has adequate precedent.[8] This species then appears to undergo decomposition as previously described. If the decay is arrested by addition of an excess of pyridine, then the methyl signal is split into *two equal resonances*, separated by 0.13 ppm. This is attributed to reestablishment of pyridine ligation, with concurrent ionization of one of the bridging protons in the equatorial ligand system.[8] The changes are summarized in Scheme I. Note that pairs of methyl groups of the ionized chelate structure will be *nonequivalent*, provided that proton exchange involving the remaining hydrogen bridge is slow on the NMR time scale.[9]

Identical behavior was noted when CD_3ONa/CD_3OD was used as the base in $(CD_3)_2S{=}O$ solution, indicating that hydroxide is not unique in initiating this decomposition. Furthermore, the presence of 2.5 equiv of cyanide ion also completely inhibited decay in these strongly alkaline solutions. Cyanide is known to be a tightly bound ligand for cobaloximes; its affinity is more than 200 times greater than that of pyridine (and more than 30 000 times greater than that of hydroxide).[10] These results confirm the interpretation given in Scheme I.

Discussion

Alkali-induced decomposition of the (2-alkoxyalkyl)cobaloximes that we have investigated uniformly yields a fragmentation reaction providing cobaloxime(III), alkene, and alcohol. These are in fact the same products expected to arise from acid-induced decomposition.[4,5] As mentioned in the Introduction, a previous report has suggested that 5′-deoxyadenosyl(pyridine)cobaloxime does not follow this reaction course in basic solution but rather undergoes β-elimination to yield anhydroadenosine and cobaloxime(I).[6] If this claim is correct, then the additional functionality of the nucleoside fundamentally alters the course of reaction. We have undertaken to provide a definitive mechanism for those substrates for which the product identification is firm (Table I).

Since all primary substrates have similar rates of decomposition, there is no basis in structure–reactivity correlations for defining a mechanism. However, the dependence of rate upon hydroxide and pyridine concentrations, plus the NMR spectral perturbations, provides stringent constraints upon an acceptable mechanism. Complete inhibition by pyridine ligation indicates that the reactive species is an aquo complex; i.e., the (alkoxyalkyl)cobaloxime in which the exchangable ligand is H_2O or OH^-. Pertinent evidence regarding the ionization of aquocobaloximes has been provided by Kallen.[8] Simple alkylaquocobaloximes undergo deprotonation in aqueous base, with a pK_a value of 12.2–13.0, attributed to conversion to an alkyl*hydroxo*cobaloxime anion. Simple alkyl(*pyridine*)cobaloximes also ionize, but only in relatively more strongly alkaline solution (pK_a of 13.5–14.0).[8] The latter deprotonation was attributed to loss of a bridging proton from the chelate system, as we believe was detected for **2** by NMR in $NaOD/(CD_3)_2S{=}O$ (Scheme I).

We may now explain the hydroxide dependence of the pseudo-first-order rate constants for **2**, as shown in Figure 1. The values rise linearly with increasing hydroxide concentration in highly alkaline medium (i.e., apparent first-order dependence on OH^-). However, in more weakly basic solutions the rate falls off abruptly. The key observation is that the change in slope (at ca. 0.2 N NaOH) correlates with the first ionization of alkylaquocobaloximes (pK_a = 12–13). Therefore, it is a reasonable assumption that the linear region of Figure 1 corresponds to a reaction first order in each of hydroxide ion and (alkoxyalkyl)-hydroxocobaloxime anion. The most plausible role of this second hydroxide is removal of one of the bridging hydrogens from the chelate system, producing a dianion. However, to account for the curvature in Figure 1 at low basicity, we find it necessary to assume that the tetrahydrofurfurylhydroxocobaloxime monoanion also decomposes spontaneously, without the necessity of further ionization. Our proposed mechanism is given in Scheme II.

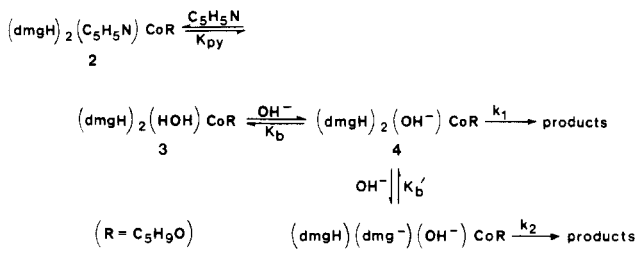
For the mechanism of Scheme II the appropriate kinetic expression may be derived as in the equation shown below. A least-squares fit of our data to this expression is shown as the solid line in Figure 1. The parameters (rate and

(8) Brown, K. L.; Lyles, D.; Pencovici, M.; Kallen, R. G. *J. Am. Chem. Soc.* **1975**, *97*, 7338.

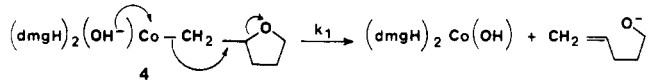
(9) Exchange involving such protons has previously been shown to be retarded in aqueous solution by the intramolecular hydrogen bonding: Hibbert, F. *Acc. Chem. Res.* **1984**, *17*, 115. Dimethyl sulfoxide solvent is also known to render hydroxyl proton exchange slow in NMR analysis. The splitting of the chelate resonance is not associated with an asymmetric environment provided by the tetrahydrofurfuryl moiety; simpler alkylcobaloximes show the same behavior.

(10) Crumbliss, A. L.; Wilmarth, W. K. *J. Am. Chem. Soc.* **1970**, *92*, 2593.

Scheme II



Scheme III



equilibrium constants) so obtained are as follows. The first-order rate constant for decay of the tetrahydrofurfurylhydroxocobaloxime anion **4** is $k_1 = 0.028$ (±0.006) s^{-1}. Since the second basicity constant K_b' is unknown, we can only specify for the parallel decomposition of **5** a second-order rate constant, $k_2/K_b' = 0.050$ (±0.004) s^{-1} M^{-1}. (We do not exclude the possibility that decomposition is synchronous with deprotonation of **4**; this would imply general base catalysis.) The value of K_b, the first basicity constant (linking **3** and **4**), is defined by the curvature in Figure 1, and the fitted value is $K_b = 0.17$ (±0.04) N (NaOH). This number correlates quite well with the previously recorded data for ionization of alkylaquocobaloximes. This kinetically measured K_b value corresponds to a pK_a value of 12.3 (at 57.5 °C, $pK_w = 13.08$) for the conjugate acid (**3**). The recorded pK_a value for (2-methoxyethyl)aquocobaloxime is 12.2 (at 25 °C, measured by ligand dissociation rates).[8]

$$-d(4)/dt = \frac{(4)[k_1 + (k_2/K_b')(OH^-)]}{1 + [K_b/(OH^-)][1 + (C_5H_5N)/K_{py}]}$$

Finally, the value of the pyridine dissociation constant K_{py} (as obtained by fitting the kinetic data to the equation) is $K_{py} = 0.0041$ (±0.0008) M. This number is in reasonable agreement with the spectrophotometrically determined value of K_d for this ligand (Figure 2, $K_d = 0.0021$ M). It may be recalled that the *apparent* inhibition constant secured from Figure 2 was $K_i = 0.015$ M, a value which is 7.3 times greater than K_d. This discrepancy is reconciled by the kinetic equation. According to the mechanism in Scheme II, pyridine and hydroxide compete for the same ligand binding site. Although pyridine is *inhibitory*, hydroxide is *activating* toward decomposition. Because the data for Figure 2 was obtained (necessarily) at a concentration of base where hydroxide ligation is substantial, a perturbation of the true pyridine ligand dissociation constant is introduced into the kinetic data, as is implicit in the kinetic equation. This can only be so if hydroxide ligation is competitive; therefore, this behavior uniquely substantiates our mechanistic interpretation.[11]

The noteworthy feature of the reactivity of (2-alkoxyalkyl)cobaloximes is that coordination of hydroxide anion to the exchangable ligand position of the metal induces carbon–cobalt bond cleavage with resulting formation of cobaloxime(III) plus alkene and alkoxide (Scheme III). This fragmentation is not brought about by pyridine (uncharged ligand) nor by cyanide anion.[12] While cyanide is an avid coordinating species, it is capable of accommodating back-donation of electron density from filled d orbitals of cobalt to empty antibonding orbitals of the ligand. Hence, a sufficient accumulation of charge on the metal is not attained with cyanide coordination. Not surprisingly, a further ionization of the chelate system accelerates the hydroxide-induced heterolysis (k_2 step of Scheme II).

The alkaline decomposition of (2-alkoxyalkyl)cobaloximes constitutes a new type of reactivity for these models of vitamin B_{12}.[11] It is apparent that a suitable leaving group on the 2-position of the organo substituent is required for this reactivity to be present. The previously known[4,5] acid-induced decomposition of such substrates proceeds by creating electron deficiency at the 2-position of the organoligand as a result of protonation of the ether oxygen. In this work we have shown that an alternative process yielding the same products exists, and that it is induced by increasing the electron density around the cobalt center, which then causes heterolysis and concomitant elimination of the alkoxy substituent. It is conceivable that these processes might operate concurrently in the activation step of some cobalamin biochemical metabolic reactions, where simultaneous general acid and general base catalysis may be brought about enzymically at neutral pH.

Experimental Section

Organocobaloximes used in this study were prepared by standard techniques,[6,13] generally by alkoxyalkylation of (pyridine)cobaloxime(I) anion in alcoholic solution under a reducing atmosphere. Complete characterization of these substances is difficult. They are frequently obtained as amorphous powders that decompose without melting upon heating. Our criteria of purity is an acceptable proton NMR spectrum without extraneous resonances, homogeneity on silica thin-layer chromatography, plus a correct CHN elemental analysis (±0.4%, unless otherwise noted).

Tetrahydrofurfuryl(pyridine)cobaloxime (2). From 9.52 g (0.04 mol) of cobalt chloride hexahydrate, 9.28 g (0.08 mol) of dimethylglyoxime, and 8.21 g (0.04 mol) of (2-bromomethyl)-tetrahydrofuran[14] in alkaline methanolic reducing solution (Schrauzer's procedure),[6,13] there was obtained 8.64 g (48%) of tetrahydrofurfuryl(pyridine)cobaloxime, which was recrystallized from aqueous methanol (1:1): ^1H NMR ($CDCl_3$) δ 8.6–7.1 (5 H, m, py), 3.82–3.02 (3 H, m, CH_2, CH), 2.15 (12 H, s, CH_3), and 2.4–0.95 ppm (6 H, m, CH_2). Anal. ($C_{18}H_{28}O_5N_5Co$) C, H, N.

In order to identify the product of alkaline decomposition of this substance, 4.0 g of the cobaloxime and 60 mL of 2.0 N sodium hydroxide was stirred and heated at 50 °C for 24 h. After recovery of unreacted starting material by filtration, ether extraction followed by distillation gave a 28% yield of 4-penten-1-ol, bp 30 °C (0.5 mm), identified by comparison of its NMR spectrum.[15] Similar decomposition in $(CD_3)_2S{=}O$ with concurrent NMR analysis of the reaction mixture reveals no competing decomposition modes.

Identification of the coproduct as cobaloxime(III) rather than cobaloxime(I) rests on the following evidence. Alkaline decomposition of (2-hydroxyethyl)cobaloxime is known rapidly to give

(11) Methyl(pyridine)cobaloxime also decomposes in alkali, yielding methane: Brown, K. L. *J. Am. Chem. Soc.* **1979**, *101*, 6600. Although the mechanism may be related to that for **2**, more complex processes were proposed; see also: Brown, K. L.; Hessley, R. K. *Inorg. Chem.* **1980**, *19*, 2410. To us the intermediate **5** seems especially plausible according to NMR evidence; however, we cannot exclude kinetically equivalent tautomers for the k_2 branch of Scheme II; e.g., $(dmgH)_2(O^{2-})CoR$ in place of **5**.

(12) The more reactive 5′-deoxyadenosylcobalamin system is cleaved in this fashion by cyanide: see ref 5b,c.

(13) Schrauzer, G. N.; Windgassen, R. J. *J. Am. Chem. Soc.* **1967**, *89*, 1999. Schrauzer, G. N. *Inorg. Synth.* **1968**, *11*, 61.

(14) Smith, L. H. "Organic Syntheses"; Wiley: New York, 1964; Coll. Vol. III, p 793.

(15) "Sadtler Standard Spectra" Proton NMR Coll.; Sadtler Research Lab.: Philadelphia, 1980; spectrum 968.

solutions of cobaloxime(I) anion, which have a characteristic intense blue color. To an aqueous suspension of 3.64 g of (2-hydroxyethyl)(pyridine)cobaloxime was added sufficient pyridine (13.9 g) to retard its rate of alkaline decomposition to a velocity similar to that of tetrahydrofurfuryl(pyridine)cobaloxime.[3] The reaction vessel was thoroughly purged with nitrogen gas, and the solution was then made 2 N in sodium hydroxide. After 1 h the solution had the blue color of cobaloxime(I), showing that under the conditions for alkaline decomposition of tetrahydrofurfuryl(pyridine)cobaloxime, the cobaloxime(I) anion could be detected visually, were it formed. In contrast, corresponding solutions (ex pyridine) from tetrahydrofurfuryl(pyridine)cobaloxime turn brown after a similar time period under strictly anaerobic conditions.

(2-(2-Hydroxyethoxy)ethyl)(pyridine)cobaloxime. This substance was similarly prepared from 2-(2-chloroethoxy)ethanol[16] in 22% yield: ^{1}H NMR ($CDCl_3$) δ 8.6–7.1 (5 H, m, py), 3.8–3.2 (4 H, m, CH_2), 2.9 (2 H, t, CH_2), 2.15 (12 H, s, CH_3), 1.62 ppm (2 H, t, CH_2). Anal. ($C_{17}H_{28}O_6N_5Co$) C, H, N.

The product of alkaline decomposition of this substance was recovered by continuous extraction of the reaction mixture with ether and was identified as ethylene glycol (NMR). The coproduct is presumed to be ethylene.

(2-(2-Methoxyethoxy)ethyl)(pyridine)cobaloxime. This substance was similarly prepared from 1-(2-chloroethoxy)-2-methoxyethane[17] in 63% yield: ^{1}H NMR ($CDCl_3$) δ 8.6–7.1 (5 H, m, py), 3.42 (4 H, s, CH_2CH_2), 3.31 (3 H, s, CH_3), 3.18 (2 H, t, CH_2), 2.12 (12 H, s, CH_3), and 1.58 ppm (2 H, t, CH_2). Anal. ($C_{18}H_{30}O_6N_5Co$) C, H, N.

The product of alkaline decomposition of this substance was recovered as above and was identified as 2-methoxyethanol (NMR).

(2-Methoxy-3-hydroxypropyl)(pyridine)cobaloxime. This substance was similarly prepared from 1-bromo-2-methoxy-3-propanol (from 2-propenol and *N*-bromosuccinimide in methanol[18]) in 50% yield: ^{1}H NMR ($CDCl_3$) δ 8.6–7.1 (5 H, m, py), 3.6–3.1 (3 H, m, CH_2CH), 3.1 (3 H, s, CH_3), 2.1 (12 H, s, CH_3), and 1.5–0.9 ppm (2 H, m, CH_2). Anal. ($C_{17}H_{28}O_6N_5Co$) C, H; N: calcd, 15.31; found, 14.50.

For product identification from alkaline decomposition of this substance, a reaction was carried out in $(CD_3)_2S{=}O$ solution with sodium deuteroxide as base. Analysis of the reaction mixture by NMR revealed after 3 days at 25 °C the products 3-propen-1-ol and methanol.

(2,3-Dimethoxypropyl)(pyridine)cobaloxime. This substance was similarly prepared from 1-chloro-2,3-dimethoxypropane[19] in 20% yield: ^{1}H NMR ($CDCl_3$) δ 8.6–7.1 (5 H, m, py), 3.36 (3 H, s, CH_3), 3.21 (3 H, s, CH_3), 3.2 (1 H, m CH), 2.8 (2 H, t, CH_2), 2.18 (12 H, s, CH_3), and 1.2 ppm (2 H, m, CH_2). Anal. ($C_{18}H_{30}O_6N_5Co$) C, H, N.

A product analysis for this substance was not carried out but is inferred by analogy.

(1,3-Dimethoxy-2-propyl)(pyridine)cobaloxime. Bromomethoxylation of 3-methoxy-1-propene as above was found to give a 9:1 mixture of 2-bromo-1,3-dimethoxypropane and 1-bromo-2,3-dimethoxypropane by NMR analysis. From this mixture was prepared as before (1,3-dimethoxy-2-propyl)(pyridine)cobaloxime in 4.5% yield after fractional recrystallization from aqueous methanol: ^{1}H NMR (C_6D_6) δ 8.4–6.7 (5 H, m, py), 3.9–3.2 (4 H, m, CH_2CH_2), 3.3 (6 H, s, CH_3), 1.9 (12 H, s, CH_3), and 2.2–1.9 ppm (1 H, m, CH). Anal. ($C_{18}H_{30}O_6N_5Co$) H, N; C: calcd, 45.85; found, 45.23. The isomeric primary cobaloxime could be identified by NMR in the crude product (30% of initial mixture).

Product identification for the alkaline decomposition of this substance was carried out in $(CD_3)_2S{=}O$ solution as above, showing 3-methoxy-1-propene and methanol after 5 h.

Other Cobaloximes. The following substrates listed in Table I, which have been previously reported, were prepared and characterized by NMR: **(2-hydroxy-2-methylpropyl)(pyridine)cobaloxime,**[6] product of alkaline decomposition identified as isobutene by NMR; ***cis*-(2-methoxycyclohexyl)(pyridine)cobaloxime,**[20] products of alkaline decomposition identified as cyclohexene and methanol by NMR; **(2-methoxyethyl)(pyridine)cobaloxime,**[6] products of alkaline decomposition (ethylene, methanol) not identified; and **(2,2-diethoxyethyl)(pyridine)cobaloxime,**[21] products of alkaline decomposition (ethyl vinyl ether, ethanol) not identified.

Table II

[NaOH], N	$[C_5H_5N]$, M	rate const, $s^{-1} \times 10^3$
0.01	0.00006	1.32 (±0.02)
0.03	0.00006	6.12 (±0.12)
0.06	0.00006	11.88 (±0.13)
0.10	0.00006	15.30 (±0.36)
0.20	0.00006	26.0 (±0.3)
0.30	0.00006	32.3 (±0.7)
0.40	0.00006	39.1 (±0.8)
0.50	0.00006	47.4 (±1.0)
0.75	0.00006	62.3 (±2.9)
1.00	0.00006	74.1 (±4.0)
0.50	0.00306	41.6 (±0.9)
0.50	0.00606	34.4 (±0.5)
0.50	0.0301	15.64 (±0.26)
0.50	0.0601	9.72 (±0.20)
0.50	0.0901	6.92 (±0.14)
0.50	0.150	4.86 (±0.11)
0.50	0.210	3.74 (±0.10)
0.50	0.420	1.89 (±0.05)

Solution Kinetics. Rate measurements were obtained from decay of the substrate absorption (VIS) subsequent to mixing solutions of cobaloxime with excess alkali. Measured volumes of individual substrate stock solutions were preheated and then added together to a 10-cm path length quartz cell in a spectrophotometer with a thermostated cell compartment (at 57.5 ± 0.1 °C). In every case the initial substrate concentration was 6.0×10^{-5} M (i.e., $<<K_d$). Kinetic runs were carried out with sodium hydroxide always present in at least 100-fold excess over cobaloxime concentration, ensuring pseudo-first-order conditions. Precautions taken to exclude carbon dioxide from alkaline solutions included use of doubly distilled water that was heated to boiling prior to addition of sodium hydroxide and careful sealing of all stock solutions. Constant ionic strength (1.0 M) was maintained by addition of sodium chloride. Cobaloxime stock solutions were handled only in subdued light. In preliminary experiments difficulty was encountered in obtaining stable spectrophotometric end points for kinetic runs. This was attributed to spontaneous reduction of the Co(III) product by the organic coproducts or, perhaps, to some minor side reaction. The problem was solved by addition of a trace of sodium periodate to the kinetic runs (0.0011 M), to function as an oxidative scavenger. In control experiments the rates obtained were shown to be independent of periodate concentration in this range of molality. In a similar set of control experiments rates were shown not to be strongly influenced by ionic strength (NaCl).

Rates were determined by monitoring disappearance of absorption due to the (alkoxyalkyl)cobaloxime at 430 nm for several half-lives. Pseudo-first-order rate constants were obtained by directly fitting absorbance readings to an exponential decay function by the method of least squares. Replicate runs were routinely made, with derived rate constants agreeing within 5%. Pyridine dependence experiments were carried out by incorporating twice distilled pyridine in various concentrations into the cobaloxime stock solution immediately prior to the kinetic runs. Kinetic data for substrates other than **2** are listed in Table I. For **2** the hydroxide and pyridine dependences (data for Figures 1 and 2) are listed in Table II (average of duplicate runs in each case). Tolerances listed (here and in the Results and Discussion) are standard errors as obtained from nonlinear least-squares curve

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fitting.

Registry No. 1 (R = $HOCH_2CH_2OCH_2CH_2$), 90343-24-1; 1 (R = $CH_3OCH_2CH_2OCH_2CH_2$), 40982-08-9; 1 (R = $HOCH_2CH(OCH_3)CH_2$), 90343-25-2; 1 (R = $CH_3OCH_2CH(OCH_3)CH_2$), 90343-26-3; 1 (R = $(CH_3OCH_2)_2CH$), 90367-59-2; 1 (R = $(CH_3)_2COHCH_2$), 90367-60-5; 1 (R = *cis*-$CH(OCH_3)CH_2CH_2CH_2CH_2CH$), 29863-11-4; 1 (R = $CH_3OCH_2CH_2$), 40982-05-6; 1 (R = $(C_2H_5O)_2CHCH_2$), 54195-50-5; 1 (R = $HOCH_2CH_2$), 15218-81-2; **2**, 37824-55-8; $CH_2{=}CHCH_2CH_2CH_2OH$, 821-09-0; $HOCH_2CH_2OH$, 107-21-1; $CH_2{=}CH_2$, 74-85-1; $CH_3OCH_2CH_2OH$, 109-86-4; $CH_2{=}CHCH_2OH$, 107-18-6; CH_3OH, 67-56-1; $CH_2{=}CHCH_2OCH_3$, 627-40-7; $CH_2{=}C(CH_3)_2$, 115-11-7; $CH{=}CHCH_2CH_2CH_2CH_2$, 110-83-8; $CH_2{=}CHOC_2H_5$, 109-92-2; C_2H_5OH, 64-17-5; cobalt chloride, 7646-79-9; dimethylglyoxime, 95-45-4; (2-bromomethyl)tetrahydrofuran, 1192-30-9; 2-(2-chloroethoxy)ethanol), 628-89-7; 1-(2-chloroethoxy)-2-methoxyethane, 52808-36-3; 1-bromo-2-methoxy-3-propanol, 90321-38-3; 1-chloro-2,3-dimethoxypropane, 34680-56-3; 3-methoxy-1-propene, 627-40-7; 2-bromo-1,3-dimethoxypropane, 90321-39-4; 1-bromo-2,3-dimethoxypropane, 90321-40-7.

Synthesis and Properties of Pinanediol α-Amido Boronic Esters

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The use of (+)-pinanediol as the chiral directing group for the synthesis of several α(*R*)-α-amido boronic esters and acids, which are boronic acid analogues of *N*-acyl-L-amino acids, has been explored. RBO_2Pin (Pin = *cis*-pinane-2,3-diyl) was homologated to (*S*)-$RCHClBO_2Pin$, which was converted to (*R*)-$RCH(NHAc)BO_2Pin$ and, for R = isopropyl, to (*R*)-$RCH(NHCOAc)B(OH)_2$ by previously reported methods. Where R = isobutyl, methyl, or (benzyloxy)methyl, zinc chloride catalysis was required for the homologation step. Two (*S*)-acetamido boronic esters (R = isopropyl, isobutyl) were made from (−)-pinanediol. Acylation of the unstable α-amino boronic ester intermediate with carbobenzyloxy chloride was accomplished in the synthesis of $PhCH_2CH(NHCOOCH_2Ph)BO_2Pin$, but attempted boron trichloride cleavage of the pinanediol boronic ester to the acid also cleaved the benzyloxy group. Hydroboration of allyl halides or allyl benzyl ether with (1,2-phenyldioxy)borane has yielded γ-substituted boronic esters. These were converted to (+)-pinanediol esters and converted by the general route outlined above to α-acetamido δ-substituted boronic esters. (Pinanediyldioxy)borane has been prepared and found to be a sluggish hydroborating agent.

Introduction

Homologation of boronic esters with (dichloromethyl)lithium to form α-chloro boronic esters has been shown to be highly efficient[1] and to result in exceptionally high chiral selectivity if pinanediol is used as the chiral directing group.[2,3] The conversion of (+)-pinanediol (*S*)-1-chloro-2-phenylethane-1-boronate to the corresponding α-acetamido boronic ester and acid has been described.[4,5] This boronic acid analogue of *N*-acetyl-L-phenylalanine has been shown to be a competitive inhibitor of chymotrypsin.[4] In the present study, the use of pinanediol boronic esters as intermediates for the synthesis of other chiral α-amido boronic esters has been explored.

Results

Homologation Conditions. The previously reported route to an α-amido boronic acid[4,5] proved directly applicable to the conversion of (+)-pinanediol 2-propaneboronate (**1a**) to (+)-pinanediol (*S*)-1-chloro-2-methylpropane-1-boronate (**2a**), which with *N*-lithiohexamethyldisilazane yielded the (*R*)-1-[bis(trimethylsilyl)amino]-2-methylpropane-1-boronate (**3a**). Acetic acid and acetic anhydride converted **3a** to (+)-pinanediol (*R*)-1-acetamido-2-methylpropane-1-boronate (**4a**), the first intermediate in the sequence that was isolated and characterized. The need for the silylated intermediate in order to circumvent the instability of α-amino boronic esters has been discussed previously.[5]

Cleavage of the pinanediol group with boron trichloride[2] completed the route synthesis of (*R*)-(−)-1-acetamido-2-methylpropane-1-boronic acid (**5a**), the boronic acid analogue of *N*-acetylvaline. Philipp and Maripuri have found that this compound is a moderately active inhibitor of elastase.[6] (−)-Pinanediol (*S*)-1-acetamido-2-methylpropane-1-boronate, the enantiomer of **4a**, was also prepared. Philipp and Maripuri have found that equilibration with aqueous boric acid removes the pinanediol satisfactorily for purposes of testing for enzyme inhibition and have found the resulting boronic acid to be a good inhibitor of penicillinase.[7]

In sharp contrast to the easy synthesis of **2a**, homologation of (+)-pinanediol 2-methylpropane-1-boronate (**1b**) with (dichloromethyl)lithium yielded only 15–33% of (+)-pinanediol (*S*)-1-chloro-3-methylpropane-1-boronate (**2b**), which was isolated by chromatography. Conversion

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