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Alkali-Induced Decomposition of (2-Hydroxyalkyl)cobaloximes

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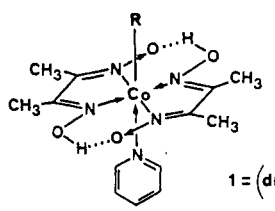
The mechanism by which (2-hydroxyethyl)(pyridine)cobaloxime decomposes in alkaline solution yielding acetaldehyde and cobaloxime(I) anion has been reinvestigated. The reaction is characterized by a complex hydroxide ion dependence, varying from second order in weakly basic solution to apparent first order near 0.2 N sodium hydroxide, with an extrapolation to zeroeth order in strongly alkaline solution. The reaction exhibits a negligible kinetic deuterium isotope effect [for (2-hydroxypropyl)(pyridine)cobaloxime-2-*d*] and is inhibited by excess pyridine or by cyanide ion. (Formylmethyl)cobaloxime is unreactive in alkaline solution and is therefore not an intermediate. A mechanistic pathway is suggested by the conversion of (3-hydroxypropyl)(pyridine)cobaloxime in $(CD_3)_2SO$–D_2O–NaOD into a *cis*-cobaloxime, with intramolecular ligation of the propyloxy substituent to cobalt, as observed by NMR spectroscopy. It is concluded that the hydride migration-displacement mechanism previously proposed for alkaline decomposition of (2-hydroxyethyl)(pyridine)cobaloxime is incorrect. Present evidence suggests that the rate-limiting step is conversion to a *cis*-cobaloxime, with a rapid subsequent σ- to π-complex conversion, ultimately yielding the enol of acetaldehyde. The reaction is actually second order in hydroxide but is simultaneously subject to first-order hydroxide inhibition.

Alkylcobaloximes (1) have been extensively employed as models for the much-studied naturally occurring organometallic species deoxyadenosylcobalamin (coenzyme B_{12}). Enzymes employing the latter cofactor catalyze a



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

number of important but mechanistically obscure biochemical reactions, including a series of internal redox reactions (for example, $CH_3CHOHCH_2OH \rightarrow CH_3CH_2CHO$, $HOCH_2CHOHCH_2OH \rightarrow HOCH_2CH_2CHO$, $H_2NCH_2CH_2OH \rightarrow CH_3CHO + NH_3$).[1] For these transformations, alkaline decomposition of (2-hydroxyethyl)(pyridine)cobaloxime, **2**, yielding acetaldehyde and the cobaloxime anion **3**, constitutes a plausible biomimetic process.[2] If the speculation is allowed that substrates become covalently bound in some fashion[3] to the metal cofactor in the enzyme catalytic cycle, then this transformation conceivably duplicates the carbonyl-generating step in the reactions cited. Consequently, the mechanism of the conversion **2** → **3** + CH_3CHO has attracted a good deal of attention, not only for its intrinsic interest but also for its potential biochemical significance.

$$\underset{\mathbf{2}}{(dmgH)_2(C_5H_5N)CoCH_2CH_2OH} \xrightarrow[H_2O]{OH^-} \underset{\mathbf{3}}{(dmgH)_2(C_5H_5N)Co^-} + CH_3CHO$$

The ease of decomposition of **2** is uncharacteristic of cobaloximes in general; most alkylcobaloximes are more stable under alkaline conditions. The discoverer of the acetaldehyde-yielding reaction, G. N. Schrauzer, has proposed a mechanism for the transformation.[2] With apparent support from several experimental observations, his scheme involves the oxyalkylcobaloxime anion undergoing a concerted hydride migration from the 2-position of the hydroxyalkyl moiety to the 1-position, displacing the metal as an anion. The indicated mechanism is summarized as **4**.

(1) For an extensive citation list of relevant references see: Toscano, P. J.; Marzilli, L. G. *Prog. Inorg. Chem.* **1984**, *31*, 105.

(2) (a) Schrauzer, G. N.; Windgassen, R. J. *J. Am. Chem. Soc.* **1967**, *89*, 143. (b) Schrauzer, G. N.; Sibert, J. W. *J. Am. Chem. Soc.* **1970**, *92* 1022. (c) Schrauzer, G. N.; Weber, J. H., Beckham, T. M. *J. Am. Chem. Soc.* **1970**, *92*, 7078. (d) Schrauzer, G. N. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 417; **1977**, *16*, 233.

(3) For the substrate activation step, present evidence points toward a homolytic mechanism, perhaps analogous to that operative in ribonucleotide reductase; see ref 1. Doubts have been expressed on the intermediacy of alkylcobalamin species in the catalytic cycle of diol dehydratase: Finke, R. G., Schiraldi, D. A., Mayer, B. J. *Coord. Chem. Rev.* **1984**, *54*, 1.

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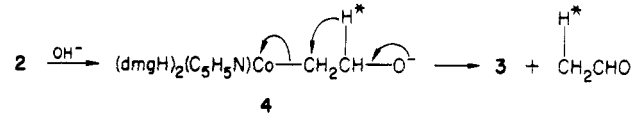

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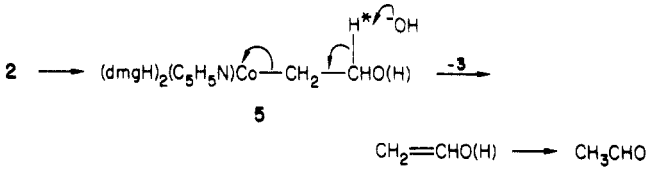
While superficially reasonable, this mechanism is sufficiently unique as to merit further critical examination. We have reopened the question of what actually happens in the alkaline decomposition of **2**. Evidence subsequently to be described suggests that **4** is incorrect and that the mechanism is considerably more complex than has been indicated by previous work.

Results

General Considerations. For the conversion $2 \rightarrow 3 + CH_3CHO$, at least two fundamentally different mechanisms are to be entertained. They are the hydride migration previously described (**4**) and an elimination process (**5**), whereby the enol or enolate of acetaldehyde is the penultimate product. The latter mechanism has previ-



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ously been dismissed because (2-methoxyethyl)(pyridine)cobaloxime (**6**) was said to be inert under the reaction conditions, failing to yield methyl vinyl ether.[2a,b] In fact, this finding is not completely correct. We have recently shown that (2-alkoxyalkyl)cobaloximes are indeed decomposed by alkali.[4] In 1.0 N sodium hydroxide at 25 °C, **6** is decomposed at a rate which is only 140 times slower than the reaction of **2**. However, the product of this decom-

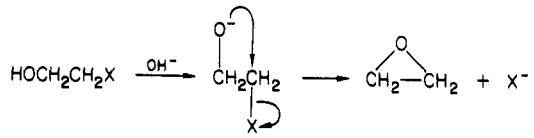
$$(dmgH)_2(C_5H_5N)CoCH_2CH_2OCH_3 \xrightarrow[H_2O]{OH^-} (dmgH)_2(C_5H_5N)CoOH + CH_2{=}CH_2 + HOCH_3$$

6

position is *not* an enol ether, but rather the alkali treatment yields fragmentation products cobaloxime(III), ethylene, and methanol.[4] Consequently, an ionizable function group (hydroxyl) does appear to be prerequisite for the aldehyde-producing reaction. It must be stated that this does not necessarily exclude an eliminative mechanism for **2**, as we shall show.

A choice between the mechanisms represented by **4** and **5** is in principle feasible by isotopic labeling (i.e., by following the fate of H* in **4** or **5**). Decomposition of **2** in D_2O should initially yield unlabeled CH_3CHO by **4** (H* retained) but should yield exclusively CH_2DCHO by **5** (H* lost to solvent). In practice, such a mechanistic discrimination cannot be realized experimentally. As Schrauzer had indicated[2b] (and we have confirmed), the major isolable product from such an experiment is CD_3CHO; the acetaldehyde produced exchanges with solvent exceedingly readily in solutions sufficiently alkaline to decompose **2**. It has not proven feasible to sweep acetaldehyde from solution prior to complete exchange, even with a vigorous gas purge of the reaction medium.

The most serious objection to the hydride migration mechanism (**4**) is its implausibility in light of precedent. Carbinols bearing substituents of high nucleofugicity on an adjacent carbon are well-known to yield oxiranes readily in alkaline media (**7**). It is not obvious how the nature of the leaving group [i.e., $(dmgH)_2(C_5H_5N)Co^-$ in **4**] could alter transition-state energetics so as to render hydride



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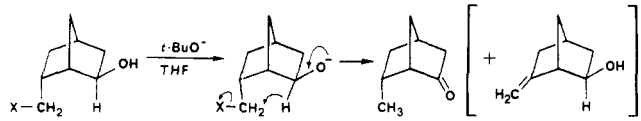
migration more favorable than the normal intramolecular nucleophilic displacement by oxygen. (Oxiranes may be excluded as reaction intermediates.[2b])

Examination of the literature revealed one possible precedent for **4**. The bicyclic bromoalkanol **8a** fragments in the presence of strong base, yielding in part methylnorcamphor, which implies internal hydride transfer (**9**).[5] This system cannot yield a tricyclic ether by intramolecular displacement because of steric constraints. Therefore, we prepared **8a** and converted it to the corresponding cobaloxime **8b** [X = $(dmgH)_2(C_5H_5N)Co$]. We reasoned that should the cobaloxime anion leaving group uniquely favor hydride migration because of some intrinsic property (e.g., the extreme polarizability of the incipient Co anion), then the alkaline decomposition of **8b** ought to proceed much more readily than that of **8a**. In fact, cobaloxime **8b** did appear to undergo the same reaction (**9**) but *no more readily* than did the precursor bromide **8a**. Both reactions

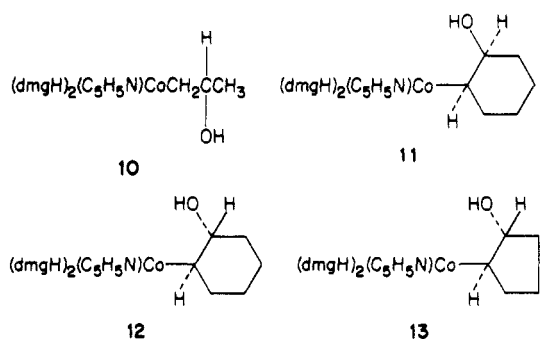


8a: X = Br
8b: X = $(dmgH)_2(C_5H_5N)Co$

9

require extended heating with an alkoxide, and both proceed at similar rates. Furthermore, the alkaline decomposition of **8b** is much slower than that of **2**; under comparable conditions we estimate that the relative rates differ by a factor of greater than 10^5. Ordinarily, a reaction occurring through an optimally aligned five-membered cyclic transition state such as **9** should be just as favorable as one occurring through a three-membered cyclic transition state.[6] Therefore, these results must cast doubt upon the validity of mechanism **4**. Since there is no reasonable expectation that hydride migration would compete with oxirane formation in the decomposition of **2**, it seems likely that some other mechanism takes precedence over either process to yield **3** and acetaldehyde.

Kinetics. Because of our doubts about the mechanism represented by **4**, we undertook a careful reexamination of the alkaline decomposition of (2-hydroxyalkyl)cobaloximes. The analogous substrates **10**–**13** were prepared



10 **11**

12 **13**

(4) Mock, W. L.; Bieniarz, C. *Organometallics* **1984**, *3*, 1279.

(5) Gwynn, D. E.; Skillern, L. *J. Chem. Soc., Chem. Commun.* **1968**, 490.

(6) Heine, H. W., Siegfried, W. *J. Am. Chem. Soc.* **1954**, *76*, 489. Böhme, H.; Sell, K. *Chem. Ber.* **1948**, *81*, 123. Nygard, B. *Abh. Dsch. Akad. Wiss. Berlin, Kl. Chem., Geol. Biol.* **1964**, 254; *Chem. Abstr.* **1965**, *62*, 5140. Freundlich, H.; Kroepelin, H. *Z. Phys. Chem.* **1926**, *122*, 39. Knipe, A. C.; Stirling, C. J. M. *J. Chem. Soc. B* **1967**, 808.

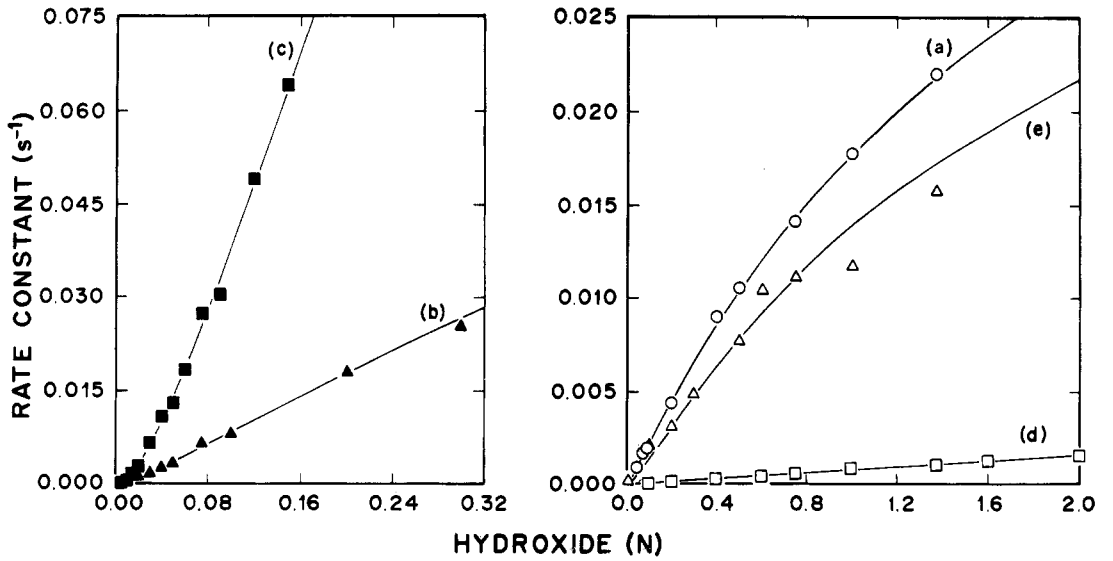


Figure 1. Dependence of pseudo-first-order rate constant upon sodium hydroxide concentration for decomposition of the following: **2** (a), ○; **10** (b), ▲; **11** (c), ■; **12** (d), □; and **13** (e), △. Lines are least-squares fit of data to an equation developed in Discussion.

for investigation of the effect of structure upon reactivity. We have examined both the hydroxide dependence and the effect of excess pyridine upon the course of decomposition for these substances. As will subsequently be shown, the reactivity pattern indicates a mechanism which is more complex than either **4** or **5**.

a. Hydroxide Dependence. Each of substances **10–13** decomposes analogously to **2** in aqueous alkali, yielding acetone from **10** and the corresponding cyclic ketone from **11–13**. As detailed in the Experimental Section, pseudo-first-order rate constants at various hydroxide ion concentrations were obtained spectrophotometrically (by following a decrease in alkylcobaloxime absorbance, 430 nm, at 25.0 ± 0.1 °C and 1.0 M ionic strength). The behavior of each of the substrates including **2** is given in Figure 1, a–e. The lines fitting the data in the figure correspond to a least-squares fit to an equation developed in the Discussion. The hydroxide dependence exhibited by the different substrates merits individual comment.

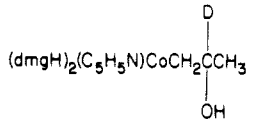
Although Schrauzer reported that decomposition of **2** was characterized by "first-order" dependence upon hydroxide,[2a,b] careful kinetic analysis reveals significant deviations from a linear correlation between rate and concentration of NaOH. Curvature in the plot (Figure 1, a) is quite evident at hydroxide concentrations greater than 0.5 N, suggesting that the reaction becomes *less* than first order in this region. On the other hand, at very low concentrations of NaOH the "first-order" dependence appears not to extrapolate linearly to zero base strength. The character of the hydroxide dependence in weak base is seen more clearly for **10** and especially for **11** (Figure 1, b and c). These substances are relatively more reactive in aqueous alkali, so that reaction velocities may be conveniently measured at NaOH concentrations of less than 0.05 N. In such medium the hydroxide dependence appears to be *higher* than first order.

A stereochemical bias in this reaction may be seen by comparison of **11**, **12**, and **13**. The cis and trans isomers of (2-hydroxycyclohexyl)(pyridine)cobaloxime (Figure 1, c and d) differ significantly in rate of decomposition with the trans isomer approximately 940 times less reactive. Schrauzer has previously made issue of the relative unreactivity of **12**, suggesting that its inertness supports the hydride migration mechanism.[2b] Such a process would be virtually impossible for the trans-(Co,OH)-disubstituted cyclohexane, since backside displacement of the cobalt moiety by hydride would be stereochemically unfeasible. The facts are that **12** does yield cyclohexanone as a product (confirmed by isolation of the 2,4-DNP derivative) and at a rate which is quite respectable (in 0.2 N NaOH, approximately one-fortieth that of **2**). Furthermore, *trans*-(2-hydroxycyclopentyl)(pyridine)cobaloxime (**13**), which would also require a front-site displacement of cobalt, is nearly as reactive as **2** (Figure 1, e). Hence, stereochemical evidence scarcely supports mechanism **4**. Perhaps coincidentally, these results are remarkably similar to authentic E_2 eliminations in five- and six-membered rings. It has been found that syn elimination is relatively favored for cyclopentanes and that the transition state for anti elimination in cyclohexanes is several kilocalories per mole more accessible than that for syn elimination.[7]

Finally, regarding Figure 1 it may be noted that **13** appears to show the same deviation from first-order hydroxide dependence at very high basicity that **2** does (although the experimental points are rather badly scattered). Substrates **10** and **11** reacted too rapidly to be examined in this region of alkalinity. On the other hand, the plot for **12** appears not to show a similar curvature, with an acceptable linear dependence upon hydroxide throughout the basicity range examined. In summary, the relative reactivities of the cobaloximes (25 °C, ca. 0.2 N NaOH) are as follows: **2**, 1.0; **10**, 4.0; **11**, 25; **12**, 0.027; and **13**, 0.68. The general form of the hydroxide dependence appears to be sigmoidal, with a *first*-order requirement for hydroxide near 0.2 N NaOH, extrapolating toward *second* order in weaker base, and (excepting **12**) extrapolating toward *zeroeth* order at very high alkalinity.

b. Kinetic Isotope Effect. Because interest focuses on the fate of the hydrogen atom which becomes detached from the carbinol reaction center, the kinetic consequences of deuterium substitution at this position were reinvestigated. Schrauzer reported a deuterium isotope effect (k_H/k_D) of 5.5 for **10** vs. **14** in 2 N sodium hydroxide.[2b] This is one of the points of evidence cited as supporting the hydride migration-displacement mechanism. It is not obvious to us that such a value is appropriate for a hydride transfer which substantially involves C–H bending modes (i.e., **4**). For the Cannizzaro reaction of benzaldehyde a

(7) Weinstock, J.; Pearson, R. G.; Bordwell, F. G. *J. Am. Chem. Soc.* **1956**, *78*, 3468, 3473. DePuy, C. H.; Morris, G. F.; Smith, J. S.; Smat, R. J. *J. Am. Chem. Soc.* **1965**, *87*, 2421.



14

k_H/k_D ratio of only 1.4 has been reported.[8] We prepared **14** and confirmed its extent of deuteration (>95%) by NMR. Identically prepared solutions of **10** and **14** were subjected to alkaline decomposition in an alternating sequence under identical conditions. The k_H/k_D value obtained (averaged over eight consecutive rate measurements in which substrates were alternated) was 1.06 ± 0.023. The ratio appears barely to be statistically significant (t-test, confidence coefficient ≥0.95). However, it does not distinguish between a small primary or a normal secondary isotope effect. Since the rate difference is nearly inconsequential, the possibility of preequilibrium loss of deuterium by exchange with solvent, due to reversibility of early stages of the reaction, had to be entertained. In a control experiment the decomposition of **10** was deliberately carried to 50% completion in alkaline deuterium oxide solvent, and the residual reactant was then recovered. Examination by NMR revealed no detectable incorporation of deuterium into the carbinol CH.

If must be concluded that either CH bond scission does not exhibit a significant primary kinetic isotope effect or that the bond is broken in a fast process *after* the rate-limiting step for the overall reaction. We cannot explain apparent disagreement with the original report of a sizeable isotope effect for **10** vs. **14**.[2b]

c. Pyridine Inhibition. The equilibria and kinetics of axial ligand exchange of pyridine for alkylcobaloximes in neutral aqueous solution has been studied by Kallen.[9] For example, the dissociation constant (K_d) at 25 °C for (2-methoxyethyl)(pyridine)cobaloxime (**6**, a model for **2**)

$$6 \underset{}{\overset{K_d(H_2O)}{\rightleftharpoons}} (dmgH)_2(H_2O)CoCH_2CH_2OCH_3 + C_5H_5N$$

is 7.04×10^{-4} M, and other alkylcobaloximes have similar values.[10] This is relevant to the preceding kinetic studies, because our substrate concentration was never greater than 6.0×10^{-5}M. Although our substrates were prepared as pyridine complexes, at this concentration the pyridine would be largely (>92%) dissociated. Hence, the kinetic data pertains to the aquo complex, in which the axial ligand position is filled by lyate species (or is unoccupied).

It was previously reported by Schrauzer[2b] that presence of the ligand pyridine in **2** accelerates its decomposition in alkaline medium by a factor of 4 relative to the corresponding complex with H_2O as ligand. In attempting to confirm this, we have examined the influence of excess pyridine upon the rate of decomposition of several of our substrates. As shown in Figure 2, the result is *complete inhibition* when the cobaloxime is saturated with pyridine. We have data for only **2**, **10**, and **11**, but in each case the kinetic results may be fitted (least squares) to a simple sigmoidal expression, $V = V_{max}/[1 + (C_5H_5N)/K_i]$, yielding an apparent inhibition constant. Values for the latter are as follows: **2**, $K_i = 1.9 \times 10^{-4}$ M (in 0.5 N NaOH); **10**, $K_i = 5.4 \times 10^{-4}$ M (in 0.1 N NaOH); and **11**, $K_i = 1.2 \times 10^{-3}$ M (in 0.05 N NaOH).

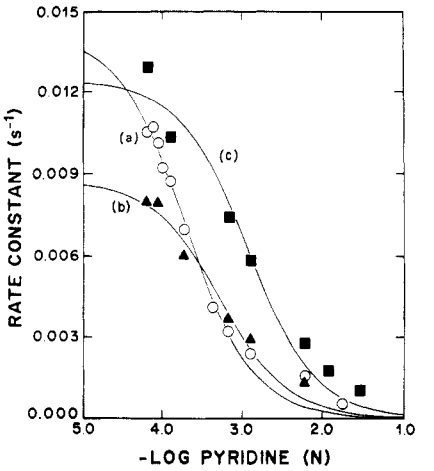


Figure 2. Dependence of pseudo-first-order rate constant upon pyridine concentration (logarithmic scale) for decomposition of the following: **2** (a), ○ (0.5 N NaOH); **10** (b), ▲ (0.1 N NaOH); and **11** (c), ■ (0.05 N NaOH). Lines are least-squares fit to a sigmoidal inhibition equation.

From the evidence in Figure 2 it must be concluded that the pyridine complexes are inert and that dissociation of pyridine is obligatory for alkaline decomposition. A cause for some concern is the fact that the K_i values listed above do not quite match expected values based on previous measurements of pyridine ligand dissociation constants for cobaloximes.[9] However, *rates* of pyridine dissociation (by spectrophotometric determination) have also been reported.[9] Examination of recorded rate constants for pyridine release reveals that they are of the same order of magnitude as our pseudo-first-order rate constants for alkaline decomposition. Therefore, at pyridine concentrations exceeding K_i (Figure 2), pyridine dissociation from the complex should be partially rate limiting. Because of this ambiguity no quantitative interpretation can be attached to our K_i values, which are presumably complex constants reflecting rates for more than one step. However, the conclusion that the pyridine complexes are inert toward hydroxide is valid regardless of this ambiguity and our rate measurements in the absence of excess pyridine are accurate, since equilibrium dissociation of the heterocyclic ligand was always attained by dilution before initiation of decomposition by incorporation of sodium hydroxide.

Finally, we report that decomposition of **2** is also prevented by ligation of cyanide ion. We have found that the hydroxyethyl group of **2** survives unchanged (>30% recovery) after 3.5 h of exposure to alkaline sodium cyanide solution (25 °C, 1.0 N NaCN, 1.0 N NaOH). No acetaldehyde was produced under such conditions. We therefore conclude that a satisfactory mechanism must account for the apparent fact that axial ligation to the sixth position of (2-hydroxyalkyl)aquocobaloximes is generally inhibitory for alkaline decomposition.

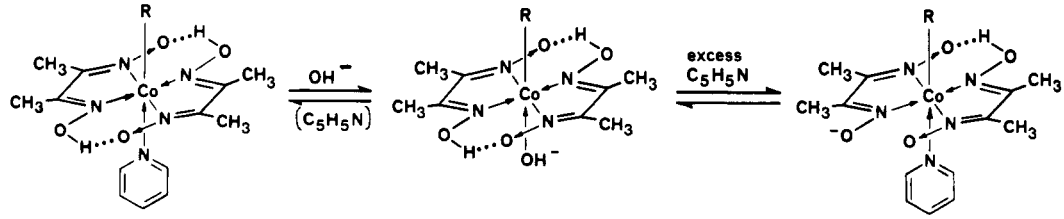
Intermediacy of (Formylmethyl)cobaloxime. One possible mechanism, which has not been mentioned until now, postulates a redox cycle involving the aldehyde **15**.

$$2 + OH^- \xrightarrow[(-py)]{-2H} \underset{\mathbf{15}}{(dmgH)_2(OH^-)CoCH_2CH{=}O} \xrightarrow{+2H} 3 + CH_3CHO$$

While such a scheme is not actually suggested by evidence previously cited, its general feature of separate oxidation and reduction steps merits consideration. Since a preparation of **15** as the pyridine complex **16** [$(dmgH)_2(C_5H_5N)CoCH_2CHO$] been recorded,[11] its intermediacy

(8) Miklukhin, G. P.; Rekasheva, A. F. *Zh. Obshch. Khim.* **1955**, *25*, 1146.
(9) Brown, K. L.; Lyles, D.; Pencovici, M.; Kallen, R. G. *J. Am. Chem. Soc.* **1975**, *97*, 7338.
(10) Kallen[9] reports formation constants; we have made the conversion to dissociation constants, which are employed in this article: $K_f = 1/K_d$.

Scheme I



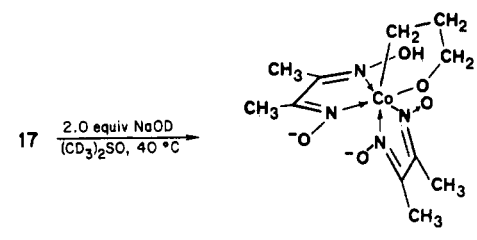
18: δ_{CH_3} 2.06 19: δ_{CH_3} 1.93 20: δ_{CH_3} 1.93, 1.72

may be readily tested. The aldehyde **16** was subjected to alkaline conditions both in the presence and in the absence of **2** (in 1.0–7.0 N NaOH, 25 °C). In the absence of **2** no acetaldehyde was produced, and **16** could be recovered unchanged in either case after 10 min. In kinetic comparison, the reactivity of **16** in 1.0 N NaOH was less than 0.0006 times that of **2**. Hence, in the absence of some external reductant, **15** may be excluded as an intermediate in the decomposition of **2**.[2a] (An oxidative scavenger was employed in our solutions for kinetic studies.) In fact, the alkaline stability of **16** is somewhat surprising. Because aldehydes exist partially as the hydrate (*gem*-diol) in aqueous solution, **16** would appear to meet the structural requirements for susceptibility to alkaline degradation and might have been expected readily to yield acetate anion by mechanism **4** (e.g., "semi-benzylic acid rearrangement").[12]

NMR of 17 in Alkaline Medium. (3-Hydroxypropyl)(pyridine)cobaloxime (**17**) is the homologue of **2**. Perturbations noted in the NMR spectrum of **17** in $(CD_3)_2SO$—D_2O—NaOD solutions are extremely suggestive of the mechanism by which **2** and its congeners decompose. However, before the behavior of **17** can be interpreted, it is necessary to review briefly the influence of NaOD upon less complicated alkylcobaloxime spectra. We have previously shown that the chemical shift of the methyl group protons of the coplanar dimethylglyoximato ligands can be used as an indicator for the ionization state of alkylcobaloximes.[4] As exemplified in **18–20**, a slight excess of NaOD causes replacement of axial ligand pyridine by hydroxide, with a concomitant upfield shift of the four equivalent methyl groups of the equatorial ligand system (**18** → **19**).[13] Addition of an excess of pyridine to the solution then causes an apparent splitting of the methyl group signal. The explanation for this phenomenon is that pyridine displaces hydroxide as axial ligand, and hydroxide then deprotonates the equatorial chelate system (**19** → **20**) (Scheme I). Note that pairs of methyl group substituents on the glyoximato moieties of **20** will be nonequivalent (proximal and distal to the oxyanion), provided that the remaining hydrogen bridge exchanges slowly on the NMR time scale. Such behavior has been observed for a number of alkylcobaloximes.

$$(dmgH)_2(C_5H_5N)CoCH_2CH_2CH_2OH$$
17

In contrast to **2**, (3-hydroxypropyl)(pyridine)cobaloxime (**17**) appears to be indefinitely stable in aqueous alkali, from which it may be recovered after several hours.[2a] When **17** is subjected to NaOD in $(CD_3)_2SO$–D_2O with ^1H NMR analysis as previously described, the initial behavior noted is exactly as presented in **18–20**. However, with the addition of *2 equiv* of NaOD to a solution of **17**, a further *time dependent* change in the NMR spectrum may be noticed. The methyl signal of the equatorial ligand system (singlet, four initially equivalent CH_3 groups) gradually undergoes further splitting and after 25 min at 40 °C is converted into *four* approximately equal singlets, at 0.49, 0.58, 0.69, and 0.88 ppm upfield from the signal of the residual CHD_2SOCD_3 of solvent. The new species produced was also examined by ^{13}C NMR spectroscopy. The same slow removal of degeneracy is observed upon addition of NaOD. Separate methyl signals at 26.48, 27.51, 27.75, and 27.88 ppm upfield from $(CD_3)_2SO$, and separate oximino carbon signals at 112.11, 110.29, 106.22, and 105.61 ppm downfield from $(CD_3)_2SO$ were observed after 25 min. Furthermore, these changes are fully reversible. Upon neutralization of the base or upon addition of excess pyridine, the original spectrum of **17** is restored. At this point **17** may be recovered unchanged from solution. Finally, these spectral perturbations are prevented by incorporation of cyanide ion, a tightly bound ligand for cobaloximes. In the presence of as much as 6 equiv of NaOD, the NMR spectrum of (3-hydroxypropyl)*cyano*cobaloxime remains unchanged.

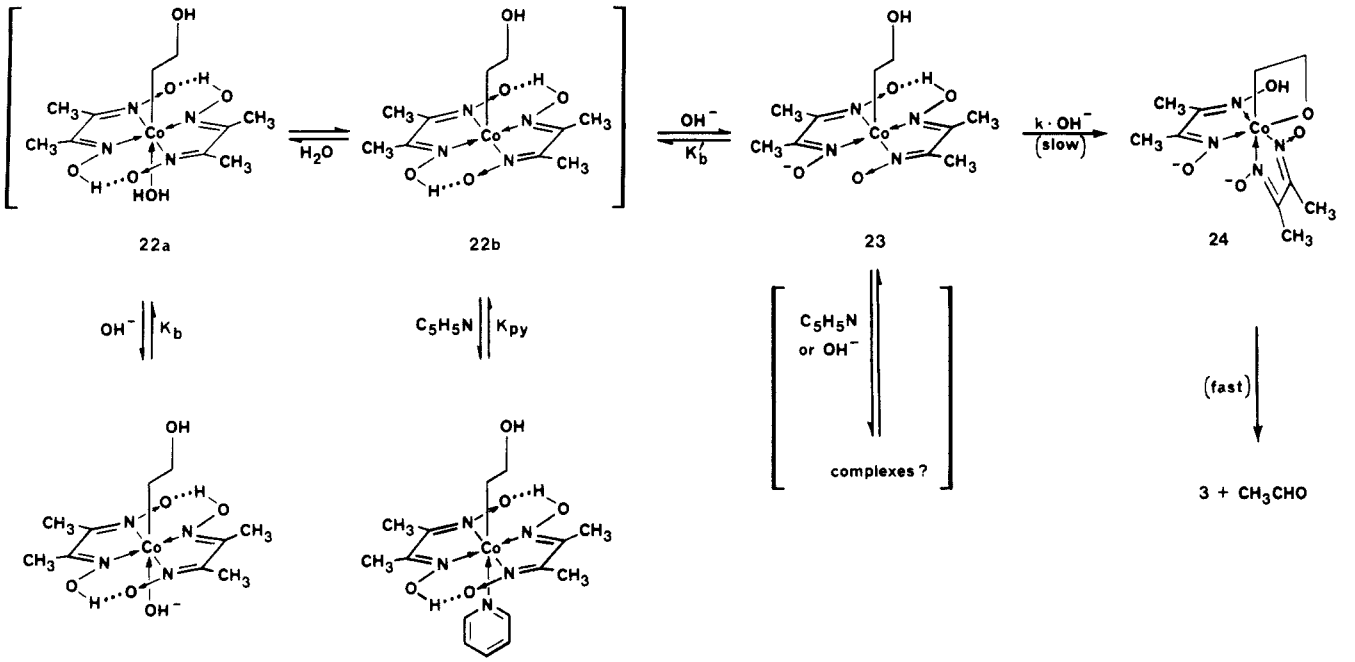


21

We suggest that the new species produced from **17** in alkaline dimethyl sulfoxide is **21**, a *cis*-cobaloxime.[14] The configuration of such a dianion would lack symmetry elements; therefore, **21** fulfills the requirement of a set of four nonequivalent methyl and oximino groups as noted by NMR. Intramolecular coordination by the hydroxypropyl substituent, which requires that one of the oximino groups be transposed into the ligand site formerly occupied by pyridine, would not be expected to compete with axial ligation by cyanide. Alkylcobaloxime binding of CN^- is ordinarily 30 000 times tighter than that of OH^-;[15] inhibition of formation of **21** by cyanide is quite reasonable. Also in support of the plausibility of the structure suggested for **21** is the observation that authentic *cis*-cobal-

(11) Silverman, R. B.; Dolphin, D. *J. Am. Chem. Soc.* **1974**, *96*, 7094.
(12) Cope, A. C.; Graham, E. S. *J. Am. Chem. Soc.* **1951**, *73*, 4702.
(13) Chemical shifts noted are for cobalt substituent R = CH_3. This methyl group also suffers an upfield shift upon addition of alkali: **18**, δ_{MeCo} 0.72; **19**, δ_{MeCo} 0.10; **20**, δ_{MeCo} 0.72.
(14) Structurally equivalent tautomers of **21** are not meant to be excluded. Some alternatives to **21**, such as an adduct of hydroxide to an oximino double bond, are inconsistent with the ^{13}C NMR data.
(15) Crumbliss, A. L.; Wilmarth, W. K. *J. Am. Chem. Soc.* **1970**, *92*, 2593.

Scheme II



oximes have previously been characterized, including examples of X-ray crystallographic structure determination.[16] Several attempts to isolate **21** were unsuccessful, because of its facile reversion to **17**. Although **17** does not undergo alkaline decomposition analogously to **2** and even though comparable NMR perturbations cannot be detected during decomposition of $(CD_3)_2SO$–D_2O–NaOD solutions of **2**, we suggest that the formation of **21** is of the utmost relevance to the mechanism of the conversion **2** → **3** + CH_3CHO.

Discussion

Since the hydride migration-displacement mechanism proposed by Schrauzer (**4**) is incompatible with the characteristics of this reaction as outlined in the preceding paragraphs, the pertinent question is whether a more acceptable alternative can be formulated. We believe that the accumulation of **21** in strongly basic medium provides the key to the fate of the (2-hydroxyalkyl)cobaloximes in alkaline solution. Should an analogous species be formed as an *obligatory intermediate* in the decomposition of **2**, then it would immediately be apparent why (2-methoxyethyl)(pyridine)cobaloxime (**6**) fails to undergo a similar transformation, and why an excess of pyridine (or cyanide) inhibits the reaction of **2**. Of equal significance is the fact that the conversion **17** → **21** is not instantaneous but occurs at approximately the same rate as **2** → **3** + CH_3CHO in aqueous alkali. This allows for the possibility that ligand reorganization is in fact rate limiting in the case of **2**, which conveniently provides an explanation for the absence of a kinetic deuterium isotope effect for the overall transformation (e.g., **10** vs. **14**). Therefore, we suggest that formation of a *cis*-cobaloxime from **2** constitutes the slow step of the reaction, with a rapid subsequent decomposition yielding the cobaloxime anion **3** and acetaldehyde. We now show that this mechanism can be accommodated to the hydroxide dependence manifested in Figure 1 and that the overall process is chemically plausible.

The general form of the hydroxide dependence can be fitted by the assumption that the reaction is *second* order in NaOH at very low hydroxide concentration (Figure 1, c), becoming *first* order as alkalinity increases (ca. 0.1 N NaOH), with the hydroxide dependence ultimately tending to level off (*zeroeth* order, Figure 1, a and e). The transition from second-order to first-order behavior can be explained with reference to what is known about *hydroxide ligation* to alkylcobaloximes. An acid dissociation constant for alkyl*aquo*cobaloximes has been determined by Kallen:[9] $(dmgH)_2(H_2O)CoR \rightleftharpoons (dmgH)_2(OH^-)CoR + H^+$, pK_a of ~12. Dissociation of a proton from an aquo ligand is of course indistinguishable from coordination by hydroxide ion in aqueous solution, so that for hydroxide ligation, a pK_b of ~2 is expected ($pK_b = pK_w - pK_a$).[15] In other words, for **2** the transition from second-order to first-order dependence on hydroxide concentration (at ca. 0.01 NaOH) coincides with formation of (hydroxyethyl)*hydroxo*cobaloxime anion. The simplest interpretation which follows is that the decomposition reaction is actually *uniformly second order* in hydroxide but becomes simultaneously subject to *first-order* hydroxide inhibition. Stated differently, coordination by hydroxide ion prevents decomposition, just as does pyridine or cyanide ion ligation. This interpretation is quite plausible, should equatorial ligand reorganization be rate limiting as previously postulated, and such behavior would yield a *net first-order dependence* on hydroxide at higher alkalinity.

Scheme II summarizes our proposed analysis of the kinetics of decomposition of cobaloxime **2** and its analogues. As the experimental pyridine dependence indicates, the active form of the cobaloxime is formally the aquo complex **22a**. This species is kinetically indistinguishable from a pentacoordinate species (**22b**) having a free ligand position, which is presumably the true active intermediate. It has previously been shown that H_2O is bound weakly to alkylcobaloximes.[9] (2-Methoxyethyl)aquocobaloxime exists extensively as the pentacoordinate species in aqueous solution.[17] As shown in Scheme II,

(16) (a) Ablov, A. V.; Simonov, Y. A.; Malinovskii, S. T.; Bologa, O. A.; Malinovskii, T. I. *Dokl. Akad. Nauk SSSR* **1975**, *221*, 605. Malinovskii, S. T.; Simonov, Y. A.; Ablov, A. V., Malinovskii, T. I.; Samus, I. D.; Bologa, O. A. *Dokl. Akad. Nauk SSSR* **1977**, *232*, 326. The *cis*-cobaloxime dimer described in these articles has been examined by us and shown to have an NMR spectrum similar to that of **21**. (b) Alcock, N. W.; Atkins, M. P.; Curzon, E. H.; Golding, B. T.; Sellars, P. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1238. (c) Methylcobaloxime has been reported to be converted in part into a species having a similar NMR spectrum: Brown, K. L. *J. Am. Chem. Soc.* **1979**, *101*, 6600. A *cis*-cobaloxime dimer seems to us to be a more plausible structure than that proposed.

Table I. Kinetic Parameters for Alkaline Decomposition of (2-Hydroxyalkyl)(pyridine)cobaloximes According to Scheme I[a]

substr	k, M^{-1} s^{-1}	K_b, M	K_b', M
2	3.3 (± 2.1)	0.017 (± 0.010)	2.1 (± 0.3)
10	9.5 (± 2.0)	0.024 (± 0.005)	2.1[b]
11	21.2 (± 2.1)	0.066 (± 0.010)	2.1[b]
12	0.027 (± 0.017)	0.06 (± 0.04)	(2.1)[b,c]
13	0.66 (± 0.02)	0.066[d]	2.1[b]

[a] Tolerances are standard errors from least-squares fitting of data (Figure 1) to an equation given in Discussion. [b] Assumed identical to value for 2. [c] Data fitted to the equation for Scheme I without perturbation from the K_b' equilibrium (see Discussion). [d] Assumed identical with value for 11 (because of the scatter of points).

second-order kinetic dependence on hydroxide is explained by postulating first that the equatorial ligand system undergoes deprotonation yielding **23**, analogously to the pyridine model complexes described in the Results section (e.g., **18** → **20**). Ionization permits rearrangement of **23** to the *cis*-cobaloxime **24**, which transformation consumes a *second* equivalent of hydroxide. The conversion **23** → **24** constitutes the slow step for the overall reaction. The presumed rapidly ensuing decomposition of **24**, yielding **3** and CH_3CHO, will be considered subsequently.

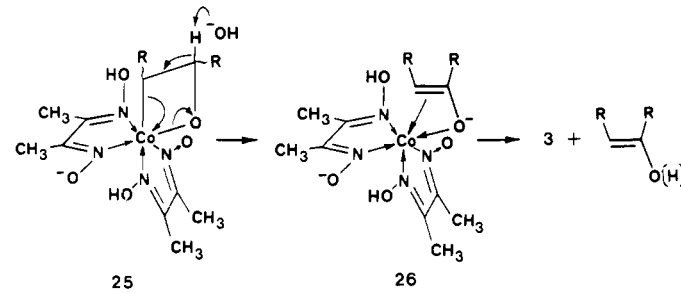
The kinetic expression for the mechanism in Scheme I is given by the following equation, in which [**22**] = [**22a**] + [**22b**].

$$-\mathrm{d}[\mathbf{22}]/\mathrm{d}t = \frac{k[\mathbf{22}][OH^-]^2/(K_b' + [OH^-])}{1 + [OH^-]/K_b + [C_5H_5N]/K_{py}}$$

Kinetic data for each of the substrates examined has been fitted to this equation by the method of least squares, and the curves accommodating the data in Figure 1 show that the interpretation is quite successful. Kinetic parameters for each of the substrates, as obtained by iterative adjustment, are shown in Table I. The rate constants (k) correspond to the formation of **24**, and these values presumably represent the true relative reactivities in genesis of the postulated *cis*-cobaloxime (allowing only for an uncertainty in the ratio [**22b**]/[**22a**], which should be greater for **11**–**13**).[18] The hydroxide inhibition constants K_b, which are responsible for curvature in the plots at low NaOH concentration, all correspond excellently with expected values based upon known pK_a values for the alkylaquocobaloximes **22a**, as previously described.[9] The equation shown also provides for pyridine inhibition (K_{py}). However, we have not fitted the experimental pyridine dependence to this equation. As indicated in the Results section, the known rate of pyridine dissociation from alkyl(pyridine)cobaloximes is not rapid relative to the overall decomposition reaction under the conditions which we have employed.

Not previously commented upon is K_b', the basicity constant for ionization of the equatorial ligand system of **22**, yielding the reactive intermediate **23**. This term is responsible for curvature in the plots at very high alkalinity (Figure 1, a and e). As the concentration of NaOH is increased so as to approach K_b', the equilibrium **22** ⇌ **23** is shifted to the right, and a transition from apparent first-order to zeroeth-order dependence on hydroxide ensues. While a value for K_b' could be determined with any accuracy only for **2**, it is significant that the number is in reasonable agreement with previous estimates of the corresponding ionization constants for alkyl(*pyridine*)cobaloximes. For such species a pK_a of 13.3–14.0 has been recorded (equivalent to a K_b' of ca. 0.5).[9] Furthermore, we have detected this mode of ionization by NMR.[4] As described in the Results section, in the presence of excess pyridine (which prevents hydroxide ion ligation to the metal), addition of NaOD to a $(CD_3)_2SO$–D_2O solution of most alkyl(pyridine)cobaloximes yields two separate resonances for the previously equivalent methyl groups of the chelating ligand system. This was interpreted as resulting from ionization of one of the bridging protons (**20**). While an identical K_b' value would not be expected of the **22** in the absence of pyridine coordination to cobalt, a similar value is reasonable.[19] In summary, the hydroxide dependence characterizing the decomposition of **2** and its analogues is adequately explained by Scheme II, using only proton dissociations which have independent substantiation (K_b, K_b'). Furthermore, Scheme II rationalizes the unreactivity of (methoxyethyl)(pyridine)cobaloxime (**6**), and also the observed inhibition by pyridine or cyanide, as well as the absence of a significant kinetic deuterium isotope effect for the decomposition reaction.

Scheme III



We now consider the conversion of the pivotal intermediate **24** to the observed products of the reaction, cobaloxime anion **3** and acetaldehyde. Since this occurs subsequent to the rate-limiting step, necessarily we must rely on chemical inference. This latter phase of the reaction is kinetically inaccessible to examination. However, we suggest that the process which is indicated in Scheme III is quite plausible. Proton abstraction (**25**) allows collapse of the *cis*-cobaloxime to a π-complex of Co(I), **26**, which can subsequently release the enolate (or enol) of acetaldehyde. The most convincing feature of the mechanism embodied in Schemes II and III is that it invokes a well-precedented principle of organometallic chemistry, namely, σ- and π-complex interconversion. The apparent uniqueness of the cobaloxime anion as a leaving group (i.e., suppression of oxirane formation) is thereby rationalized.

Although our mechanism appears consistent with the available evidence for the reaction, because of its complexity it should be regarded as tentative at the present time. Two aspects specifically require further comment. Decomposition of **13** by this mechanism requires the intermediacy of a bicyclic ring system involving trans-fused five- and four-membered rings (albeit incorporating Co). While the apparent steric strain is not so serious as to rule out the mechanism, it is surprising that **13** is nearly as reactive as **2**. It may be that the major barrier to the

(17) Kallen[9] estimates for the equilibrium $(dmgH)_2(HOH)CoCH_2CH_2OCH_3$ ⇌ $(dmgH)_2CoCH_2CH_2OCH_3$, K = 1.2 (aqueous solution, 25.0 °C, ionic strength 1.0 M).

(18) Note that K_i values for pyridine inhibition (and also K_b) are larger for **11** than for **2** and **10**. For isopropyl(pyridine)cobaloxime, the K_d value is three times greater than for **6**, and the amount of "pentacoordinate" species in the aquo complex is correspondingly greater.[9]

(19) The observed value of K_b' may also reflect additional modes of hydroxide inhibition. If hydroxide ion can produce an inert complex by coordination to **23**, as well as induce decomposition by yielding **24**, then a systematic perturbation of the true value of K_b' results.

reaction is associated with reorganization of the equatorial ligand system of cobalt. Secondly, the slowly reacting substrate **12** does not show a curvature in its hydroxide dependence at very high alkalinity (Figure 1, d), as might have been anticipated by the behavior of **2** and **13**. We suggest that this may be a consequence of a change in rate-limiting step. Because the decomposition is slow, formation of a *cis*-cobaloxime intermediate from **12** may have opportunity to approach equilibrium in strongly basic solution (compare **17**). The hydroxide-induced breakdown of this species (Scheme III) may then become kinetically significant, with the result that the reaction coincidentally appears uniformly first order in sodium hydroxide.[20] Alternatively, **12** and **13**, which are activated by having the cobalt attached to a branched carbon atom, may in fact be reacting by a conventional E_2 β-elimination mechanism, yielding a free enol without necessity of reorganization of the cobalt ligand system. For the other substrates, the hypothesis that ligand reorganization is rate-limiting leads to an expectation that there should be only a mild dependence of rate upon structure of the hydroxyalkyl moiety. The values for the rate constant k are rather similar for **2**, **10**, and **11** (Table I).

In conclusion, we suggest that the multistep mechanism embodied in Schemes II and III best accommodates the evidence pertaining to the alkaline decomposition of **2**. At the present time we prefer not to draw extensive biochemical inferences from this study. However, we would note that the ligand system of the naturally occurring cobalamins is not strictly coplanar, with an incipient distortion toward the geometry of **21** caused by the trans-disubstituted junction of the A and D rings of the biomolecule. A tetradentate ligand system for which the inherent conformational preference is intermediate between trans (square planar) and cis geometry would, of course, facilitate interconversion of coordination isomers of a bound metal ion. Therefore, we suggest that our interpretation may indeed have relevance to problems of cobalamin reaction mechanisms.

Experimental Section

Organocobaloximes used in this study were prepared by standard techniques, generally by hydroxyalkylation of (pyridine)cobaloxime(I) anion in alcoholic solution under a reducing atmosphere.[2,21] Complete characterization of these substances is difficult. They are frequently obtained as amorphous powders which 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 suitable CHN elemental analysis (±0.4% unless otherwise noted).

The following substances have been previously reported (our preparative yield in parentheses): **(2-hydroxyethyl)(pyridine)cobaloxime**,[2a,b] **2** (89%); **(2-methoxyethyl)(pyridine)cobaloxime**,[2b] **6** (62%); **(2-hydroxypropyl)(pyridine)cobaloxime, 10**, and **(2-hydroxypropyl)(pyridine)cobaloxime-*2-d***,[2a] **14** (49%); ***trans*-(2-hydroxycyclohexyl)(pyridine)cobaloxime**,[2a,22] **12** (38%); **(formylmethyl)(pyridine)cobaloxime**,[11] **16** (59% from hydrolysis of the acetal, itself produced in 4% yield); **(3-hydroxypropyl)(pyridine)cobaloxime**,[2a] **17** (67%).

Preparation of 8b. From 0.860 g (7.5 mmol) of dimethylglyoxime, 0.890 g (3.8 mmol) of cobaltous chloride hexahydrate, pyridine, and 0.161 g (0.79 mmol) of *endo*-6-(bromomethyl)-*exo*-2-norbornanol[5,23] (**8a**) there was obtained by the procedure of Schrauzer[21] 0.289 g of **[(*exo*-2-hydroxynorborn-*endo*-6-yl)methyl](pyridine)cobaloxime, 8b** (75%): ^{1}H NMR ($CDCl_3$) δ 8.6–7.1 (5 H, m, C_5H_5N), 4.1 (1 H, s, OH), 2.1 (12 H, s, CH_3), 2.1–0.9 (12 H, m, norbornylmethyl). Anal. ($C_{21}H_{32}O_5N_5Co$) C, H, N.

A preparative decomposition was carried out by refluxing a dilute solution of **8a** or **8b** with a sixfold excess of potassium *tert*-butoxide in tetrahydrofuran for 16 h.[5] Gradual formation of product, *endo*-6-methylnorcamphor, could be followed by IR (increasing absorbance at 1740 cm^{-1}, norcamphor carbonyl) or by silica TLC (ethyl acetate eluent, for **8b** R_f 0.13, for product R_f 0.63). The half-life of **8b** in 2.0 N NaOH at 25 °C appeared to be ≥46 days.

Preparation of 11. To a solution of **3**, prepared from 4.76 g (20 mmol) of cobaltous chloride hexahydrate, 4.64 g (40 mmol) of dimethylglyoxime, 1.61 g (20 mmol) of pyridine, 2.4 g (60 mmol) of sodium hydroxide, and 0.19 g (5 mmol) of sodium borohydride in ca. 70 mL of aqueous methanol was added under a nitrogen atmosphere 5.38 g (30 mmol) of *trans*-2-bromocyclohexanol in 10 mL of methanol. After stirring for 13 h the solution was filtered and added to 150 mL of water containing 1 mL of pyridine. The aqueous solution was extracted with methylene chloride (5 × 50 mL). The organic extract was dried, concentrated, and diluted with pentane. A yellow precipitate (1.084 g) was collected. This material was submitted to preparative silica TLC (eluent acetone). The desired product (R_f 0.7) was recovered, giving 0.217 g of ***cis*-(2-hydroxycyclohexyl)(pyridine)cobaloxime, 11** (2%): ^{1}H NMR ($CDCl_3$) δ 8.6–7.2 (5 H, m, C_5H_5N), 3.42 (1 H, s, OCH), 2.20 (12 H, s, CH_3), and 1.8–0.8 (9 H, m, ring H). Anal. Calcd for $C_{19}H_{30}O_5N_5Co$: C, 48.82. Found: C, 46.52. Anal. ($C_{19}H_{30}O_5N_5Co$) H, N. For comparison, **12**: ^{1}H NMR ($CDCl_3$) δ 8.6–7.3 (5 H, m, C_5H_5N), 2.9 (1 H, m, OCH), 2.20 (12 H, s, CH_3), 2.3–0.8 (9 H, m, ring H); **12** also analyzes low for carbon.

Preparation of 13. From 4.76 g (20 mmol) of cobaltous chloride hexahydrate, 4.64 g (40 mmol) of dimethylglyoxime, pyridine, and 2.94 g (35 mmol) of cyclopentene oxide there was obtained by the procedure of Schrauzer[21] 1.81 g of ***trans*-(2-hydroxycyclopentyl)(pyridine)cobaloxime, 13** (20%): ^{1}H NMR ($CDCl_3$) δ 8.6–7.1 (5 H, m, C_5H_5N), 3.5–3.1 (1 H, m, OCH), 2.17 (12 H, s, CH_3), 2.2–0.7 (7 H, m, ring H). Anal. Calcd for $C_{18}H_{28}O_5N_5Co$: N, 15.45. Found: N, 15.90. Anal. ($C_{18}H_{28}O_5N_5Co$) C, H. An attempted preparation of the cis isomer of **13** was unsuccessful.

Solution Kinetics. Rate measurements were obtained from decay of the substrate absorption (VIS) subsequent to mixing solutions of hydroxyalkylcobaloxime with excess alkali. Measured volumes of individual substrate stock solutions were temperature adjusted and then added together to a 10-cm path length quartz cell in a spectrophotometer with a thermostated cell compartment (at 25.0 ± 0.1 °C). In every case the initial substrate concentration was 6.0 × 10^{-5} M (i.e., well below the pyridine dissociation constant). 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 twice-distilled water which was heated to boiling prior to addition of sodium hydroxide and careful sealing of all stock solutions. This is of consequence, since the apparent nonlinear hydroxide dependence in our kinetics at low alkalinity might have been caused by carbonate buffering. Such is not the case; in one series of kinetic runs (for **10**) the alkalinity was verified by pH meter readings (glass electrode), and in any event in a concurrent investigation utilizing the same sodium hydroxide solutions, an *opposite* curvature in pH dependence was noted.[4] Constant ionic strength (1.0 M) was maintained by addition of sodium chloride (unless the concentration of NaOH was ≥1.0 N). In preliminary experiments difficulty was encountered in obtaining satisfactorily reproducible exponential decays in kinetic runs. This was attributed to nonuniform accumulation of the cobaloxime anion **3** after exhaustion of unavoidable dissolved O_2. The problem was solved by addition of a trace of sodium periodate to the kinetic

(20) Examination of **12** in (CD_3)SO–D_2O–NaOD showed detectable perturbations of the NMR spectrum as the substance decomposes. However, at no time was the spectrum sufficiently well-resolved as to warrant a claim of detection of an intermediate analogous to **21**.

(21) Schrauzer, G. N. *Inorg. Synth.* **1968**, *11*, 61.

(22) Jensen, F. R.; Madan, V.; Buchanan, D. H. *J. Am. Chem. Soc.* **1970**, *92*, 1414.

(23) Berson, J. A.; McRowe, A. W.; Bergman, R. G.; Houston, D. *J. Am. Chem. Soc.* **1967**, *89*, 2563. Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 2544.

runs (0.0011 M) to function as an oxidative scavenger (converting Co(I) to Co(III) as rapidly as formed). In control experiments the rates obtained were shown to be independent of periodate concentration in this range of molality. Furthermore, the approximate rate constants obtained anaerobically[2] (in the absence of periodate) by monitoring the accumulation of cobaloxime anion **3** did not differ significantly. In a similar set of control experiments rates were shown not to be a function of sodium chloride concentration.

Rates (Figures 1 and 2) were determined by monitoring disappearance of absorption due to the (hydroxyalkyl)aquocobaloxime 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. Tolerances listed in the Results and Discussion sections are standard errors as obtained from nonlinear least-squares curve fitting. For the kinetic deuterium isotope effect determination, the following series of pseudo-first-order rate constants were obtained in rapid succession (0.20 N NaOH): **10**, 0.0184; **14**, 0.0168; **10**, 0.0190; **14**, 0.0185; **10**, 0.0202; **14**, 0.0192; **10**, 0.0201; **14**, 0.0189 (±0.0005) s^{-1}. Kinetic data for other substrates (i.e., for Figures 1 and 2) is recorded in the Ph.D. thesis of C.B.[24]

Registry No. **2**, 15218-81-2; **3**, 53790-02-6; **8a**, 20379-85-5; **8b**, 98065-09-9; **10**, 15218-82-3; **11**, 75716-05-1; **12**, 59598-34-4; **13**, 98065-10-2; **14**, 98065-12-4; **17**, 15228-01-0; **21**, 98065-11-3; CH_3CHO, 75-07-0; *endo*-6-methylnorcamphor, 20569-37-3; *trans*-2-bromocyclohexanol, 2425-33-4; cyclopentene oxide, 285-67-6; acetone, 67-64-1; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3.

(24) Bieniarz, C. Ph.D. Thesis, University of Illinois at Chicago, 1982; *Diss. Abstr. Int. B* **1982**, *43*, 136.

Organoboranes. 42. One-Carbon Homologation of Organoboranes. Synthesis of Homologated Boronic Acids and Esters from Boronic Esters

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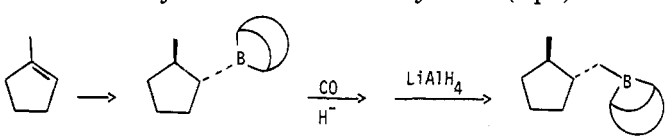
Received March 18, 1985

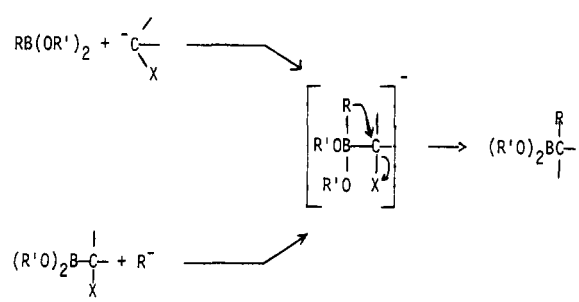
One-carbon-homologated boronic acid and esters were prepared from alkylboronic esters by the reaction with (dichloromethyl)lithium, $LiCHCl_2$, followed by reduction with KIPBH. One-carbon homologation of representative dialkylborinic esters and trialkylboranes was achieved by the reaction with $LiCHCl_2$, followed by trapping the first intermediate, the one alkyl migrated product, with KIPBH at −100 °C. Oxidation of the one-carbon-homologated organoborane intermediates, $RB(OR')_2 \rightarrow RCH_2B(OR')_2$, afforded homologated primary alcohols, RCH_2OH.

The utility of boranes in organic synthesis stems in large part from the high regio- and stereoselectivity of their transformations. Application of this chemistry hinges on the availability of regio- and stereochemically pure organoboranes. As part of an ongoing program in the synthesis of boranes not available via hydroboration,[2] we were interested in a convenient method for the one-carbon homologation of organoboranes. Recently we developed practical methods for extending the alkyl chain via carbonylation of *B*-alkyl-9-borabicyclo[3.3.1]nonane (*B*-alkyl-9-BBN) in the presence of potassium triisopropoxyborohydride (KIPBH), followed by reduction of the intermediate by lithium aluminum hydride[3] (eq 1).



(1)

Scheme I



Unfortunately, there is not available at present a simple procedure to convert the homologated *B*-alkyl-9-BBN into the homologated boronic esters, $RCH_2B(OR')_2$.

Generally, carbanionic reagents bearing potential leaving group(s), such heteroatom substituents as halogen, oxygen, or sulfur, at the α-position, homologate organoboranes. A large number of such reagents have been successfully applied for such transformations[4-6] (eq 2–4).

In many of these reactions, only one of the three alkyl groups of a trialkylborane is utilized. In some cases, the

(1) (a) Postdoctoral research associate on Grant CHE 79-18881 of the National Science Foundation. (b) Postdoctoral research associate on Grant 2 R01 GM 10937-22 of the National Institutes of Health. (c) Visiting Professor on a grant from the Ministry of Education of the Republic of Korea.

(2) (a) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1974**, *73*, 1. (b) Brown, H. C.; Sinclair, J. A. *Ibid.* **1977**, *131*, 163. (c) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316.

(3) Brown, H. C.; Ford, T. M.; Hubbard, J. L. *J. Org. Chem.* **1980**, *45*, 4067.

(4) Tufariello, J. J.; Lee, L. T. C. *J. Am. Chem. Soc.* **1966**, *88*, 4757.

(5) Tufariello, J. J.; Wojtkowski, P.; Lee, L. T. C. *J. Chem. Soc., Chem. Commun.* **1967**, 505.

(6) Musker, W. K.; Stevens, R. R. *Tetrahedron Lett.* **1967**, 995.

0276-7333/85/2304-1925$01.50/0