Model Studies of Coenzyme B_{12} Dependent Diol Dehydratase. 2.[1] A Kinetic and Mechanistic Study Focusing upon the Cobalt Participation or Nonparticipation Question

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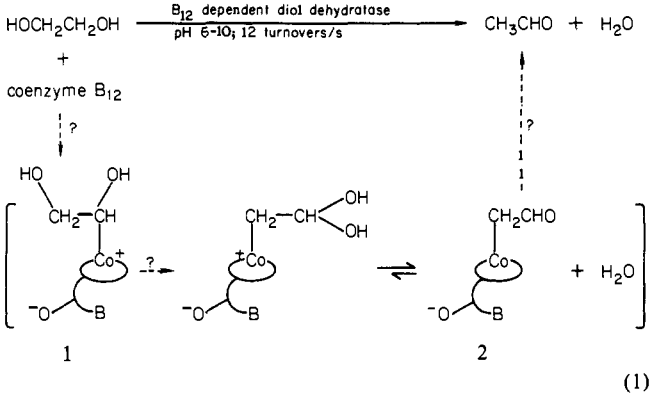
Abstract: In the preceding paper[1] model analogues of the putative diol dehydratase intermediates [Co]–$CH(OH)CH_2OH$ (**1**) and [Co]–CH_2CHO (**2**) ([Co] = coenzyme B_{12}) were synthesized and characterized by using the $Co[C_2(DO)(DOH)_{pn}]$ B_{12} model system, with the unstable, postulated intermediate **1** being prepared in a carbonate-protected form (**3**), $CH_2O(C{=}O)OCH$–$Co[C_2(DO)(DOH)_{pn}]Cl$. The CH_3O^-/CH_3OH catalyzed deprotection of **3** and subsequent formation of 100% $Co^{II}[C_2(DO)(DOH)_{pn}]Cl$, 95% CH_3CHO, and 50% each of $CH_3OCO_2CH_3$ and $CH_3OCO_2^-$ were also described, as were experiments suggesting the noninvolvement of $OHCCH_2Co[C_2(DO)(DOH)_{pn}]Cl$ in this reaction. In the present manuscript, a kinetic and mechanistic study of this methanolysis reaction, **3** + CH_3O^-/CH_3OH, is presented and evidence for the formation of α-hydroxy, Co–$CH(OH)CH_2OR$, complexes such as **1** is provided. Nitroxide radical trapping and added 1,5,6-trimethylbenzimidazole experiments are described, and the possible intermediates consistent with these experiments are presented. Cyclic voltammetry, literature precedent, and Meyerstein's related observations with coenzyme B_{12} are provided as interpretation for the CH_3CHO-inhibiting, but Co(I)- and $HOCH_2CHO$-producing, side reaction induced by the added axial ligand. Evidence against cobalt participation pathways involving Co(I) and Co(III) is described, and additional mechanistic experiments probing the apparent, nonformation of Co–CH_2CHO (**6**) are presented. The results obtained (1) provide good evidence against cobalt participation in the rearrangement step, (2) rule out the often cited, but unverified, Co(III) π-complex mechanism, (3) demonstrate that base-on cobalt participation is not only unnecessary, it introduces a CH_3CHO-inhibiting side reaction, and (4) provide evidence that, when combined with literature stereochemical and other studies, suggest that it is the protein and not the cofactor which has the more significant role in diol dehydratase.

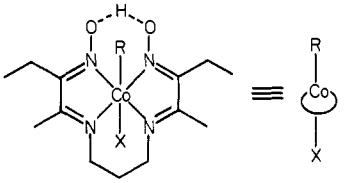
The question of cobalt participation in the coenzyme B_{12} dependent, diol dehydratase rearrangement reaction (eq 1), whether



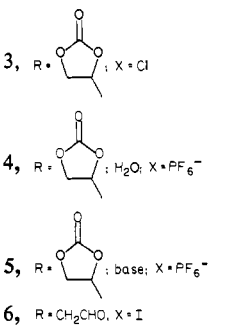
(1)

or not the diol substrate is converted to the B_{12}-bound form **1**, and whether or not **1** rearranges to the formylmethyl complex **2**, is a long-standing question in mechanistic coenzyme B_{12} chemistry. In the preceding manuscript,[1] following a brief introduction to the cobalt participation question and its literature, we reported the full details of the synthesis and characterization of **1** in a carbonate-protected form (Chart I, complex **3**). The B_{12} model complex employed is our modification[2a,b] of Costa's coenzyme B_{12} model, $RCo[C_2(DO)(DOH)_{pn}]X$ (Chart I), which is a closer B_{12} mimic—on the basis of charge,[2b] electrochemical,[2b] axial lability,[2c,d] symmetry,[2e] and other considerations[2c]—than is the much more widely used cobaloxime B_{12} model or any other Schiff base model

Chart I[a]



$RCo[C_2(DO)(DOH)_{pn}]X$



[a] Base = 1,5,6-trimethylbenzimidazole

system. Also reported were the catalytic deprotection of **3** by MeO^- in MeOH and the resultant, facile "rearrangement"[3] reaction to yield an unprecedented 95% CH_3CHO and other products, including 100% of $Co^{II}[C_2(DO)(DOH)_{pn}]Cl$ (eq 2).

Since the stoichiometry (eq 2) suggested by mass and charge balance that a $\cdot CH_2CHO$ intermediate was formed and required a H· source to be completely balanced, experiments were also described showing that the RCH_2OH solvent (R = H, Ph) is the H· source, at least in the case of R = Ph where the more easily

(1) Part 1: Finke, R. G.; McKenna, W. P.; Schiraldi, D. A.; Smith, B. L.; Pierpont, C. *J. Am. Chem. Soc.* **1983**, preceding paper in this issue.

(2) (a) Finke, R. G.; Smith, B. L.; McKenna, W. P.; Christian, P. A. *Inorg. Chem.* **1981**, *20*, 687. (b) Elliott, C. M.; Hershenhart, E.; Finke, R. G.; Smith, B. L. *J. Am. Chem. Soc.* **1981**, *103*, 5558. (c) See the discussion and references in footnote 20 of ref 2b. Additional references on the axial lability of $Co[(DO)(DOH)_{pn}]$ complexes are listed in ref 2d. (d) Guschl, R. J.; Brown, T. L. *Inorg. Chem.* **1973**, *12*, 2815; **1974**, *13*, 959. (e) See the discussion in: Salem, L.; Eisenstein, O.; Anh, N. T.; Burgi, H. B.; Davequet, A.; Segal, G.; Veillard, A. *Nouv. J. Chim.* **1979**, *1*, 335.

(3) Strictly speaking, the reactions $HOCH_2CH_2OH \rightarrow CH_3CHO + H_2O$ or $HOCH_2CHOH \rightarrow \cdot CH_2CHO + H_2O$ are not "rearrangements", since the reactant and the carbon-containing products are not isomers. The reaction (eq 1) is generally referred to as one of the B_{12} dependent rearrangements, however, and we will occasionally follow this usage in the present manuscript.

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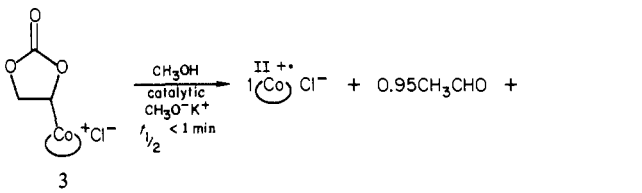


3

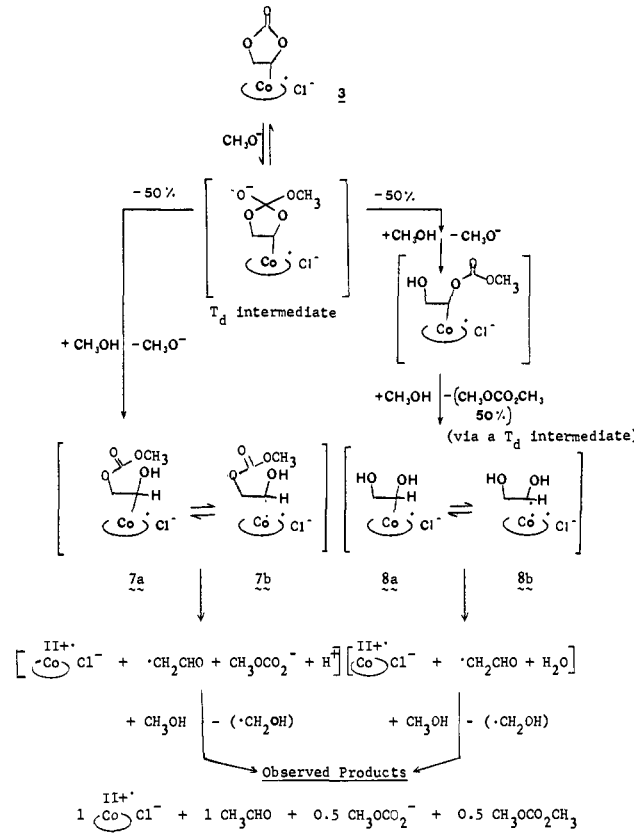
$$0.5CH_3OCO_2CH_3 + 0.5CH_3OCO_2^-K^+ \quad (2)$$

identifiable PhĊHOH derived product, PhCHO, could be detected. The preceding manuscript also described the synthesis of the formylmethyl model complex, $OHCCH_2Co[C_2(DO)(DOH)_{pn}]I$ (**6**), its characterization, and its relatively high stability, behavior consistent with all other known formylmethyl complexes.[1] The results strongly suggested that the formylmethyl complex **6** is not involved in the reaction (eq 2) and therefore that cobalt does not participate in eq 2.

The sum of the synthetic, stoichiometry, and formylmethyl product studies was interpreted in terms of Scheme I, where MeO^- attack at the carbonyl carbon produces the expected tetrahedral (T_d) intermediate, followed by its statistical opening each of the two possible ways to give the two α-hydroxy intermediates **7** and **8** (Scheme I), thereby accounting for the observed 50% each of $CH_3OCO_2^-$ and $CH_3OCO_2CH_3$. Rapid, Co–CH(OH)R cobalt–carbon bond homolysis in **7** and **8** was then postulated, the overall reaction of **3** + MeO^- apparently serving merely to provide 50% each of $HOCH_2ĊHOH$ and $CH_3OCO_2CH_2ĊHOH$ and 100% $Co^{II}[C_2(DO)(DOH)_{pn}]Cl$. The remaining steps (Scheme I), consist of the very well precedented[4] radical fragmentation, $HOCH_2ĊHOH \rightarrow H_2O + \cdot CH_2CHO$, and the MeO^--dependent $CH_3OCO_2CH_2ĊHOH + CH_3O^- \rightarrow CH_3OCO_2^- + CH_3OH + \cdot CH_2CHO$, followed by H· abstraction from the CH_3OH solvent to give CH_3CHO and the other products (eq 2 and Scheme I). These remaining steps all apparently occur without the need of any cobalt participation. The postulated rapid homolysis of the cobalt–(α-hydroxyl)carbon bond is supported by very recent studies[5] that strongly suggest that first row transition-metal–(α-hydroxy)carbon bonds[5] are especially weak, simply due to the relatively high stability of metal radicals, like Co(II)·, and α-hydroxy radicals, like $HOCH_2ĊHOH$, consistent with the inherent weakness of Co–C bonds, BDE generally $\lesssim$30 kcal/mol.[6]

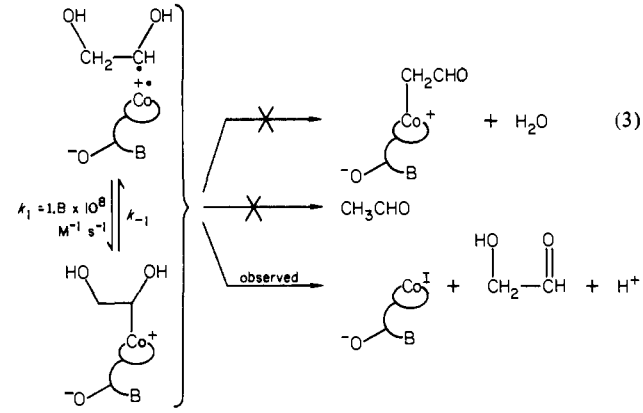
However, a number of other possible mechanisms can be postulated consistent with the observed stoichiometry (eq 2), and it is these mechanisms and the questions they raise that form the basis for the present study. For example, six other possible sites for MeO^- attack on **3** besides the carbonyl carbon exist, reactions that have precedent primarily in the work of Brown,[7] although

Scheme I



they are ca. 10^6 slower than the present methanolysis reaction. Reversible homolysis of the Co–C bond in **3**, to Co· and $\overline{OCH_2(C{=}O)ĊHO}$, followed by MeO^- attack on the organic radical is also conceivable in the absence of kinetic and other studies. One also cannot fully rule out the often discussed $Co(III)^+/HOCH_2CHOH^-$, $Co(I)^-/HOCH_2CHOH^+$, and Co–CH(OH)CH_2OH mechanisms (Scheme II) without further experiments and additional interpretation of the existing data. If the Co(II)· and $HOCH_2ĊHOH$ pathway (Scheme II) is correct or at least occurs approximately as shown in Scheme I, it raises questions of why radical-derived products such as $HOCH_2$(OH)CH–CH(OH)CH_2OH, $OHCCH_2CH_2CHO$, or Co–CH_2CHO are apparently not observed (eq 2).

Finally, we note that Meyerstein's most recent pulse radiolysis study[8] (eq 3) is especially interesting and relevant to the present



(3)

(stable at pH 3–10 for ca. 1 s)

work. On the surface, this work would appear to show that cobalt

(4) (a) Pikaev, A. K.; Kartasheva, L. I. *Int. J. Radiat. Phys. Chem.* **1975**, *7*, 395. (b) Buley, A. L.; Norman, R. O. C.; Pritchett, R. J. *J. Chem. Soc. B* **1966**, 849. (c) Livingston, R.; Zeldes, H. *J. Am. Chem. Soc.* **1966**, *88*, 4333. (d) Gilbert, B. C.; Larkin, J. P.; Norman, R. O. C *J. Chem. Soc., Perkin Trans. 2* **1972**, 794. (e) Bansal, K. M.; Grätzel, M.; Henglein, A.; Janata, E. *J. Phys. Chem.* **1973**, *77*, 16. (f) Venter, P. J.; van der Linde, H. J.; Basson, R. A. *J. Chem. Soc., Chem. Commun.* **1972**, 187. (g) Burchill, C. E.; Perron, K. M. *Can. J. Chem.* **1971**, *49*, 2382. (h) Steenken, S.; Schulte-Frohlinde, D. *Tetrahedron Lett.* **1973**, 653. (i) Steenken, S. *J. Phys. Chem.* **1979**, *83*, 595.

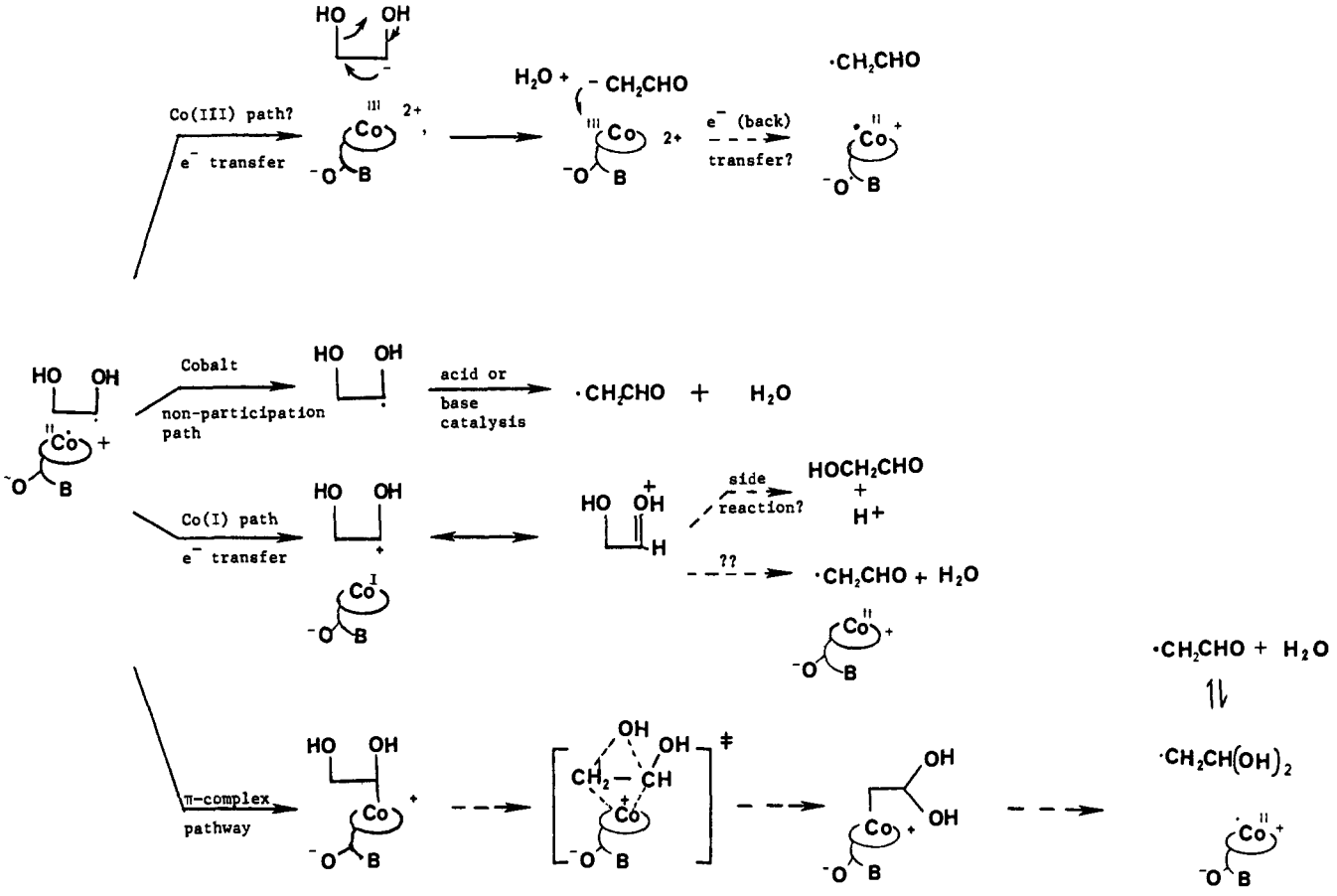
(5) (a) Gladysz, J. A.; Selover, J. C.; Strouse, C. E. *J.* Am. *Chem. Soc.* **1978**, *100*, 6766. (b) Vaughn, G. D.; Gladysz, J. A. *Ibid.* **1981**, *103*, 5608. (c) Casey, C. P.; Jones, W. D. *Ibid.* **1980**, *102*, 6154 and reference 1 therein. (d) Espenson, J. H.; Bakač, A. *Ibid.* **1980**, *102*, 2488. (e) Bakač, A.; Espenson, J. H. *Ibid.* **1981**, *103*, 2721; **1981**, *103*, 2728. (f) Brown, K. L.; Clark, G. R.; Headford, C. E. L.; Marsden, K.; Roper, W. R. *Ibid.* **1979**, *101*, 503. (g) Wayland, B. B.; Woods, B. A.; Minda, V. M. *J. Chem. Soc., Chem. Commun.* **1982**, 634. (h) Kirker, G. W.; Bakač, A.; Espenson, J. *J. Am. Chem. Soc.* **1982**, *104*, 1249. (i) Thorn, D. L.; Tulip, T. H. *Organometallics* **1982**, *12*, 1580.

(6) (a) Halpern, J. *Acc. Chem. Res.* **1982**, *15*, 238 and references therein. (b) Finke, R. G.; Smith, B. L.; Mayer, B. J.; Molinero, A. A. *Inorg. Chem.* **1983**, *22*, 3677.

(7) (a) Brown, K. L. *J. Am. Chem. Soc.* **1979**, *101*, 6600. (b) Brown, K. L. *J. Chem. Soc., Chem. Commun.* **1981**, 598. (c) Brown, K. L.; Hessley, R. K. *Inorg. Chim. Acta* **1981**, *53*, L115. (d) Brown, K. L. *Ibid.* **1978**, *31*, L401. (e) Brown, K. L.; Hessley, R. L. *Inorg. Chem.* **1980**, *19*, 2410. (f) Golding, B. T.; Kemp, T. J.; Sell, C. S.; Sellars, P. J.; Watson, W. P. *J. Chem. Soc., Perkin Trans. 2* **1978**, 839.

(8) Mulac, W. A.; Meyerstein, D. *J. Am. Chem. Soc.* **1982**, *104*, 4124.

Scheme II. Often Discussed but Unverified Rearrangement Steps



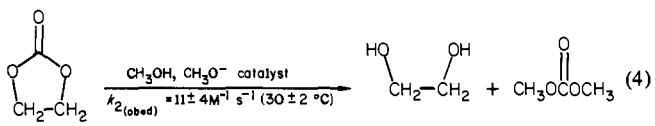
participation, i.e., **1** formation, is a hindrance yielding only a side reaction to Co(I) and $HOCH_2CHO$, although only visible spectral evidence for the cobalt products were obtained, the assumed organic products being formed in only minute, nonidentifiable amounts. Meyerstein's study certainly raises the question of why the present model study works so well, yielding 95% CH_3CHO, and which model study—if either—is more relevant to diol dehydratase.

The synthesis of **3** and its methanolysis reaction (eq 2), have clearly raised more questions than they answered,[1] at least at this point, yet **3** provides a clean system for further study. Experiments probing the above questions and the precise mechanism for the methanolysis of **3** (eq 2) are the focus of the present manuscript.

Results

Preliminary discussion will also be provided in this section as it is needed to understand why certain experiments were performed or why certain results were obtained.

Kinetic Studies and the Initial Site of CH_3O^- Attack. Kinetic and other studies were used to probe the initial site of CH_3O^- attack on **3**. As a control, the kinetics of CH_3O^--catalyzed deprotection of simple ethylene carbonate were determined by following the loss of the ν_{CO} = 1805 cm^{-1} carbonyl band in the IR, a reaction affording the previously established products[1] (eq 4). The linear first-order ln plots and the complete reaction under



(4)

conditions where $[CH_3O^-] \ll 1$ equiv clearly establish the catalytic nature of the deprotection. The observed results, although not highly precise due to the fast rates and limit of ±2 °C temperature control in the IR spectrophotometer, define k_2(obsd) = 11 ± 4 M^{-1} s^{-1} at 30 ± 2 °C, $t_{1/2}$ = 32 s, for example, for a run using 2×10^{-3} M ethylene carbonate and 4.5×10^{-3} M CH_3O^-.

The methanolysis of **3** gave clean, reproducible kinetics at $1-2 \times 10^{-2}$ M **3**, with the appearance of the λ_{max} = 520 nm, Co(II), product showing linear first-order ln plots over 90–95% reaction. The rate law, $+d[Co(II)]/dt = k_2(obsd)\,[3][MeO^-]$, showed a k_2(obsd) = 3.3 ± 0.8 M^{-1} s^{-1} (at 25 °C), and the *kinetics* were unchanged by 1.0 equiv. of added nitroxide radical trap, 1.0 to 20.5 equiv of added 1,5,6-trimethylbenzimidazole, 100 equiv of added I^-, or the Co(I) trap N_2O (Table I). (The *products* are changed under some of these conditions, however; vide infra.) The kinetic data, especially the linear first-order (not second-order) plots observed at $[MeO^-] \ll 1$ equiv and complete reaction under these conditions, prove the reaction is catalytic in MeO^-.

The kinetic results establish that simple ethylene carbonate and **3** react at the same rate within experimental error (once the temperature difference and a statistical factor of 2 are taken into account; see Discussion) and thus strongly suggest the initial site of attack is the carbonyl carbon as anticipated. Some additional, confirming, experiments were done, however, since six additional sites of MeO^- attack are at least possible (Figure 1). Simple $RCo[C_2(DO)(DOH)_{pn}]X$ complexes (e.g., R = *n*-Bu–, X = Br) were treated with 1 equiv of CD_3O^- in CD_3OD and examined by visible and ^1H NMR spectroscopy. The λ_{max} 475 nm characteristic of the presence of the R group and the NMR spectra were essentially unchanged, other than the loss of the δ 2.5 –N=C(CH_3)– signal in the NMR probably due to deuteration as observed in cobaloximes by Brown,[7] results that argue against attack at positions 1–5 (and, in part, position 6) (Figure 1).

The fact that simple, non-carbonate-containing, cobalt alkyls are stable to the reaction conditions, that ethylene carbonate and **3** react at essentially identical rates, and that Co–C bond cleavage from attack at positions 1–3 in cobaloximes is ca. 10^6 slower than the reaction of **3** + MeO^- leave no alternative other than the expected pathway, initial attack at the carbonyl carbon. Attack at the "underneath", axial base position 5 is furthermore rigorously ruled out by the kinetic nondependence of added 1,5,6-tri-

Table I. Kinetic Data for the Methanolysis of 3

run	[3]	[MeO⁻]	equiv of MeO⁻	temp, °C	observed pseudo-first-order rate constant, s^{-1}	second-order rate constant, $M^{-1}\ s^{-1}$	comments[a]
1	6.89×10^{-3}	1.11×10^{-2}	1.6	22.5	2.88×10^{-2}	2.59	
2	5.73×10^{-3}	1.60×10^{-2}	2.8	22.5	4.85×10^{-2}	3.03	
3	6.49×10^{-3}	1.11×10^{-2}	1.7	22.5	3.83×10^{-2}	3.45	
4	6.7×10^{-3}	8.36×10^{-3}	1.2	22.5	2.10×10^{-2}	2.51	
5	1.30×10^{-2}	1.78×10^{-2}	1.4	22.5	3.79×10^{-2}	2.13	
6	1.30×10^{-2}	1.11×10^{-2}	0.85	22.5	2.06×10^{-2}	1.86	1.0 equiv of Tempone
7	1.24×10^{-2}	1.11×10^{-2}	0.9	22.5	3.00×10^{-2}	2.70	1.0 equiv of Tempone
8	8.90×10^{-3}	1.32×10^{-2}	1.48	22.5	2.50×10^{-2}	1.89	1.0 equiv of Tempone
9	1.54×10^{-2}	1.17×10^{-2}	0.80	22.5	3.00×10^{-2}	2.60	1.0 equiv of Bz
10	1.24×10^{-2}	1.11×10^{-2}	0.90	22.5	3.00×10^{-2}	2.70	N_2O added
11	1.33×10^{-2}	9.3×10^{-3}	0.70	22.5	3.80×10^{-2}	4.09	100 equiv of I^-
12	2.00×10^{-2}	9.3×10^{-3}	0.47	22.5	1.60×10^{-2}	1.72	100 equiv of I^-
13	1.04×10^{-2}	1.04×10^{-2}	1.0	25	3.50×10^{-2}	3.37	
14	1.04×10^{-2}	2.18×10^{-2}	2.1	25	1.10×10^{-1}	5.05	
15	1.86×10^{-2}	1.86×10^{-2}	1.0	25	4.35×10^{-2}	2.47	
16	1.93×10^{-2}	6.43×10^{-3}	0.3	25	1.86×10^{-2}	2.90	
17	1.86×10^{-2}	1.86×10^{-2}	1.0	25	3.79×10^{-2}	2.04	
18	9.30×10^{-3}	9.30×10^{-3}	1.0	25	3.20×10^{-2}	3.44	
19	9.30×10^{-3}	9.30×10^{-3}	1.0	25	3.80×10^{-2}	4.09	
20	9.30×10^{-3}	1.86×10^{-2}	2.0	25	8.09×10^{-2}	4.35	
21	9.30×10^{-3}	4.65×10^{-3}	0.5	25	1.30×10^{-2}	2.79	
22	9.30×10^{-3}	2.33×10^{-2}	2.5	25	9.30×10^{-2}	3.99	
23	9.30×10^{-3}	9.30×10^{-3}	1.0	25	4.20×10^{-2}	4.52	
24	9.30×10^{-3}	9.30×10^{-3}	1.0	25	3.10×10^{-2}	3.33	1.0 equiv of Bz
25	9.30×10^{-3}	9.30×10^{-3}	1.0	25	3.55×10^{-2}	3.82	1.1 equiv of Bz
26	9.30×10^{-3}	9.30×10^{-3}	1.0	25	3.10×10^{-2}	3.33	1.0 equiv of Tempone
27	1.50×10^{-2}	1.30×10^{-2}	0.9	25	2.73×10^{-2}	2.10	20.5 equiv of Bz; follow Co(I), 626 nm

[a] Bz = 1,5,6-trimethylbenzimidazole.

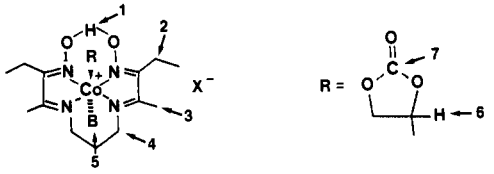


Figure 1. Seven possible sites of MeO^- attack.

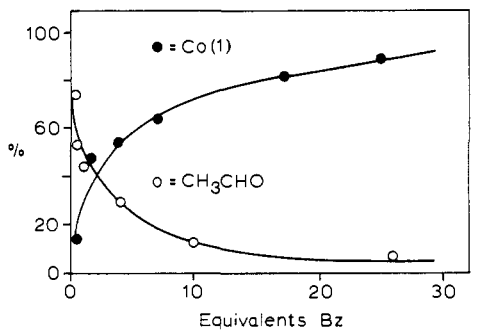
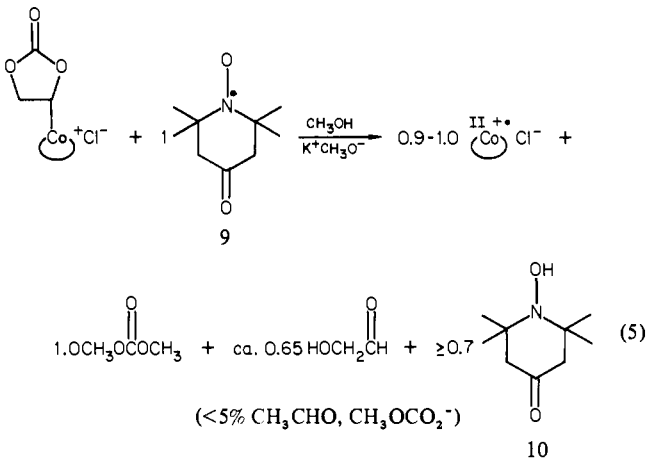


Figure 2. CH_3CHO yield (uncorrected for losses due to aldol chemistry) and the Co(I) yield vs. equivalents of added 1,5,6-trimethylbenzimidazole (Bz).

methylbenzimidazole, under conditions from 0% bound (no added base) to >98% bound (ca. 20 equiv, K_{assoc}[1] = 90 ± 20 M^{-1}) and the nondependence upon 100 equiv of I^- (Co(III) prefers $I^- > Br^- > Cl^-$).[9] A major point is that only attack at the carbonyl carbon can account for the observed products, especially $CH_3OCO_2CH_3$, in any mechanisms we have been able to write. Finally, the kinetic results, product studies, independence of the rates upon added nitroxide, and other data summarized in the footnote[10] unequivocally rule out the prior homolysis mechanism, $Co\text{-}\overline{CH\text{-}O(C{=}O)OCH_2} \rightleftharpoons Co\cdot + \cdot\overline{CHO(C{=}O)OCH_2}$.

Nitroxide Radical Trapping Studies. Early in these studies, it was observed that even 1 equiv of radical traps such as *N-tert*-butyl-α-phenylnitrone, galvanoxyl, duroquinone, or the nitroxide 2,2,6,6-tetramethyl-4-oxopiperidinyl-*N*-oxyl (**9**, eq 5) would significantly reduce the CH_3CHO yield to <ca. 5%. The nitroxide



(9) Dodd, D.; Johnson, M. D. *Organomet. Chem. Rev.* **1973**, *52*, 1. See p 45.

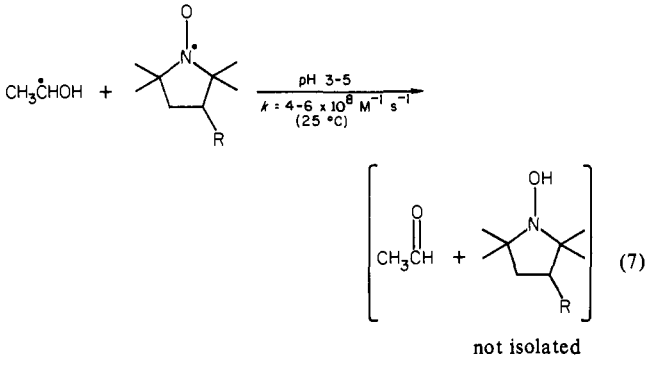
(10) If such a prior homolysis existed, a rate $\alpha\ [3]^{1/2}[CH_3O^-]$ is expected under at least some conditions and rapid decomposition (trapping) by nitroxide[6b] would be required (but is not observed) since k_{obsd} (methanolysis) = 3.3 $M^{-1}\ s^{-1}$. Furthermore, $\overline{OCH_2CHOC{=}O} \rightarrow \cdot CH_2CHO + CO_2$ (+ $CH_3O^- \rightarrow CH_3OCO_2^-$, *but no* $CH_3OCO_2CH_3$) would be expected if 1 equiv of CH_3CHO is formed, or $\overline{OCH_2CHOC{=}O} + Co\cdot \rightarrow Co\text{-}H + \overline{OCH{=}CH\text{-}OC{=}O}$ (+ $CH_3O^- \rightarrow HOCH_2CHO + CH_3OCO_2CH_3$) is possible if only ca. 50% CH_3CHO is observed (along with 50% $HOCH_2CHO$), none of which are consistent with the observed products. Thus the rate $\alpha[3]^1[CH_3O^-]$, the stability of **3** to nitroxide (**9**) in CH_3OH at 25 °C, and the 1 equiv of CH_3CHO and 0.5 equiv each of $CH_3OCO_2^-$ and $CH_3OCO_2CH_3$ observed rule out this pathway.

9 subsequently proved most valuable, and with a combination of spectroscopic techniques, control experiments, air-free chromatography to isolate the easily oxidized hydroxylamine product **10**, and patience to establish the conditions necessary to directly observe the base-sensitive glycoaldehyde product ($HOCH_2CHO$) by ^1H NMR, the stoichiometry shown in eq 5 was determined. One can follow the loss of the nitroxide **9** ($\nu_{CO}(CH_3OH)$ = 1720 cm^{-1}) and the appearance of the hydroxylamine *N*-hydroxy-2,2,6,6-tetramethyl-4-piperidone (**10**) ($\nu_{CO}(CH_3OH)$ = 1709 cm^{-1}) by careful IR studies, although the hydroxylamine **10** was isolated and identified by its ^1H NMR spectrum, which superimposed with authentic **10** prepared, isolated, and crystallized following hydrogenation of **9**. ESR studies comparing the spectra of the free nitroxide (5.9×10^{-3} M) with and without added carbonate compound **3** (1.4×10^{-3} M) showed identical spectra, demonstrating that nitroxide binding as an axial base to **3** has $K_{assoc} < 2$ M^{-1} (assuming 1% bound nitroxide would have been detected) and, therefore, that **3** with an axial nitroxide is less likely to be involved in this nitroxide redox radical trapping reaction.

The nitroxide results are clearly of interest, especially the observation that some intermediate(s) after the rate-determining step (the kinetics were unchanged by added nitroxide), which normally gives CH_3CHO and 50% each of $CH_3OCO_2CH_3$ and $CH_3OCO_2^-$, has (have) been intercepted and now gives, instead, $HOCH_2CHO$ and *only* $CH_3OCO_2CH_3$. The cobalt-bound intermediates Co–$CH(OH)CH_2OH$ (**7**) and Co–$CH(OH)CH_2OCO_2CH_3$ (**8**) or, more likely, their Co–C bond cleavage products, the α-hydroxy radicals $\cdot CH(OH)CH_2OH$ and $\cdot CH(OH)CH_2OCO_2CH_3$ are the only possible intermediates that will account for these results. No good precedent exists for the direct oxidation of $M-C(OH)R_2$ complexes by nitroxides, although Espenson has studied the metal oxidation of $(H_2O)Cr-CH(OH)R^{2+}$ complexes[11] (eq 6), and we note that, as a class, the

$$(H_2O)_5Cr^{III}CRR'OH + Cu^{2+}\ (\text{or } Fe^{3+}) \xrightarrow[(\text{at 1 M } H^+)]{k \sim 0.5\ s^{-1}} Cr(H_2O)_6^{2+} + M^+ + RCOR' + Cu^+\ (\text{or } Fe^{2+}) \quad (6)$$

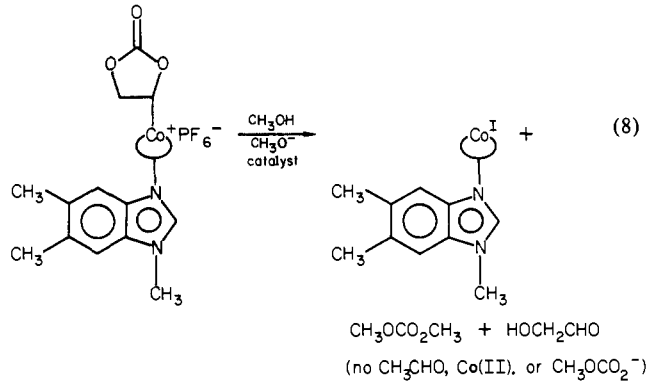
relatively new $M-C(OH)R_2$ complexes are little studied; i.e., a better precedent may be subsequently discovered. On the other hand, direct precedent exists[12] for the diffusion-controlled oxidation of $\cdot C(OH)R_2$ radicals by the weak oxidants nitroxides ($E_{1/2} \simeq -0.15$ V (SCE)[13] at pH 6–8) (eq 7). The oxidized $OHCCH_2OCO_2CH_3$ would then undergo ready methanolysis, $OHCCH_2OCO_2CH_3 \rightarrow OHCCH_2OH + CH_3OCO_2CH_3$, to yield another 50% of $CH_3OCO_2CH_3$ but no $CH_3OCO_2^-$ as observed.



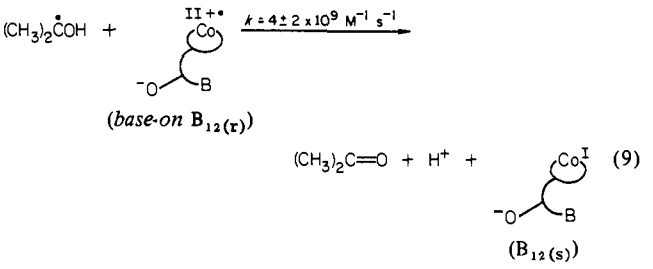
(7)

One other piece of evidence strongly suggests that the nitroxides are trapping noncaged, freely diffusing radicals. It is known that such radicals are completely scavenged by even a few equivalents of good traps, such as O_2 or nitroxides.[14] In a separate study, we have shown that 1 equiv of nitroxide will trap a significant fraction of the free $PhCH_2\cdot$ radicals produced by thermolysis of the Co–C bond of 1×10^{-4} M $PhCH_2Co[C_2(DO)(DOH)_{pn}]I$.[6b] In the above studies, 1 equiv of added nitroxide nearly completely inhibits CH_3CHO formation (eq 5). (It is likely that some ($\lesssim$5%) CH_3CHO is produced but that it is consumed by MeO^--catalyzed aldol formation.)

Axial 1,5,6-Trimethylbenzimidazole Effects. Added 1,5,6-trimethylbenzimidazole (eq 8), a close mimic of the 1-alkyl-5,6-dimethylbenzimidazole present in B_{12}, does not affect the observed kinetics yet drastically alters the observed products, i.e., is also involved (as base-on Co(II); vide infra) in intercepting an intermediate after the rate-determining step. The results, summarized in Figure 2 and eq 8, reproduce and explain for the first time the observations made by Meyerstein[8] (eq 3). The sequential addition of 1,5,6-trimethylbenzimidazole causes a smooth decrease in the CH_3CHO yield, a decrease that correlates with the increasing percentage of base-on RCo^{III}, and a smooth increase in Co(I) (with decreasing Co(II)), Figure 2. A control reaction demonstrated that most of the CH_3CHO decrease was not due to CH_3O^-/1,5,6-trimethylbenzimidazole catalyzed aldol or other chemistry. There is also a gradual decrease in the $CH_3OCO_2^-$ yield from 50 → 0% and a concomitant increase in $CH_3OCO_2CH_3$ from 50 → 100%, as documented in the Experimental Section, and by mass and charge balance there must be a parallel increase in $HOCH_2CHO$. The possibility was considered that the observed effect of added 1,5,6-trimethylbenzimidazole was due to the axial base shifting the equilibrium, $2Co(II) \rightleftharpoons Co(I) + Co(III)$, to produce Co(III), which then oxidized intermediates such as $HOCH_2\dot{C}HOH$. This was ruled out, however, by showing added authentic $\{Co^{III}[C_2(DO)(DOH)_{pn}]X\}^+PF_6^-$ did not alter the methanolysis products.[15] The results are again most easily interpreted in terms of the α-hydroxy radicals $HOCH_2\dot{C}HOH$ and $CH_3OCO_2CH_2\dot{C}HOH$ giving $HOCH_2CHO$ and $CH_3OCO_2CH_2CHO$ (+ MeO^-/MeOH → $CH_3OCO_2CH_3$ + $HOCH_2CHO$) and an electron for Co(II) + e → Co(I), especially with the precedent that such reactions occur at diffusion-controlled rates, at least with *base-on* $B_{12(r)}$ (eq 9).[16] The fact that no CH_3CHO



(8)



(9)

(11) For a mechanistic study, see ref 8d,e.
(12) Nigam, S.; Asmus, K. D.; Willson, R. L. *J. Chem. Soc., Faraday Trans 1* **1976**, *72*, 2324.
(13) Gaffney, B. J. In "Spin Labeling, Theory and Applications"; Academic Press: New York, 1976; p 186.
(14) (a) Bawn, C. E. H.; Mellish, S. F. *Trans. Faraday Soc.* **1951**, *47*, 1223. (b) Waits, H. P.; Hammond, G. S. *J. Am. Chem. Soc.* **1964**, *86*, 1911. (c) Noyes, R. M. *Ibid.* **1955**, *77*, 2042. (d) See also ref 6b.

(15) The insignificance of this possible Co(III) → Co(II) reduction reaction was anticipated since such reductions are slow on even a cyclic voltammetry time scale of seconds.[2b] A good example of this is the failure of F^- + $CH_2{=}CHOSiMe_3$ (→ $\dot{C}H_2CHO$ + $(CH_3)_3SiF$) + $I-Co(III)[C_2(DO)(DOH)_{pn}]^+I^-$ to give reduction to $\cdot CH_2CHO$ + $\cdot Co(II)$ followed by coupling to $Co-CH_2CHO$ (**6**). Instead, proton transfer from the ligand's –O···H···O– position was observed.[1]

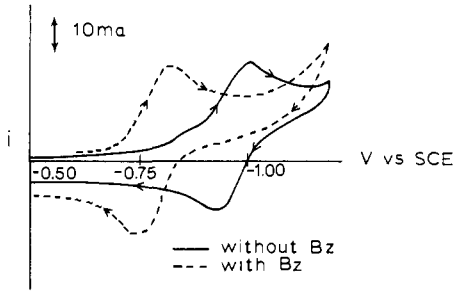
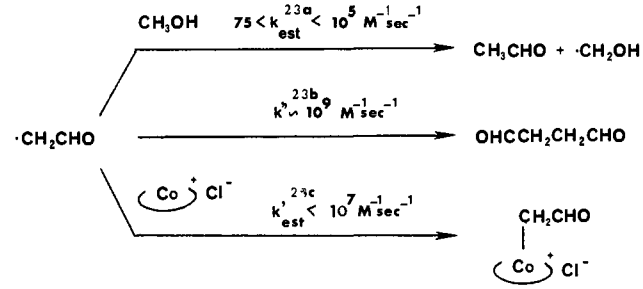


Figure 3. Cyclic voltammogram of $\{Co^{II}[C_2(DO)(DOH)_{pn}]\}^+I^-$ in CH_3OH with and without added 1,5,6-trimethylbenzimidazole (Bz).

or $CH_3OCO_2^-$ is observed, the expected products from a freely diffusing, $CH_3OCO_2\dot{C}HOH$ radical, strongly suggests that this reduction reaction is either concerted with Co–C bond cleavage in Co–$CH(OH)CH_2OR$ (R = $COCH_3$, H; **7**, **8** in Scheme I), or that the redox reaction occurs before the resultant Co· and ·$CH(OH)CH_2OR$ radicals can escape the cage.

This CH_3CHO-inhibiting, axial base induced, side reaction certainly shows that *base-on cobalt participation is not only unnecessary, it is a hindrance*! It also raises the question of the exact origins and explanation for the axial base effect. Since, broadly speaking, the effect could be either kinetic and/or thermodynamic in origin, the cyclic voltammetry of $\{Co^{II}[C_2(DO)(DOH)_{pn}]\}^+X^-$ with and without axial 1,5,6-trimethylbenzimidazole in CH_3OH, at Pt with $Bu_4N^+PF_6^-$ electrolyte, was examined. The results (Figure 3) show a largely reversible, $E_{1/2}$ = –0.86 V (SCE), i_{pa}/i_{pc} = 0.73, ΔE_p = 64 ± 2 mV, one-electron wave at 100 mV/s scan rate *in* CH_3OH, quite similar, although somewhat more negative, of the Co(II)/Co(I) $E_{1/2}$ = –0.71 V (SCE) *in* CH_3CN we previously reported.[2b] Interestingly, in CH_3OH, the addition of 30 equiv of 1,5,6-trimethylbenzimidazole shifts the peak to $E_{1/2}$ = –0.69 V (SCE), i_{pa}/i_{pc} = 0.87, $\Delta E_p \simeq$ 66 ± 2 mV (Figure 3); *the Co(II)/Co(I) reduction is now 170 mV easier.* Given the weak binding of most ligands to $Co^{II}[C_2(DO)DOH]_{pn}^+$ yet the stronger, known imidazole binding[17] to $Co^I[C_2(DO)(DOH)_{pn}]$, it is likely this thermodynamic effect is achieved primarily by axial base binding and stabilization of cobalt(I) rather than cobalt(II).[18] In addition to this thermodynamic effect of the axial base, kinetic effects on the rates of Co(II)/Co(I) reduction probably exist, and Savéant, Lexa, and Faure's recent work[19d] with B_{12} suggests that the stronger binding 1,5,6-trimethylbenzimidazole would *slow*, not increase, the Co(II) + e → Co(I) electron transfer. Additional studies will be required to fully understand the CH_3CHO inhibiting effect of added axial 1,5,6-trimethylbenzimidazole, but it is clear that base-on cobalt participation hinders the rearrangement reaction.[19]

Scheme III. Some Possible Reactions of ·CH_2CHO



Tests for Co(I) and Co(III) Pathways. As noted in Scheme II, pathways involving electron transfer and the formation of $Co(I)^-/HOCH_2CHOH^+$ or $Co(III)^+/HOCH_2CHOH^-$ are at least conceivable, so experiments were designed to test for these possible Co(I) or Co(III) pathways.

The literature indicates that Co(I) but not Co(II) is selectively oxidized by N_2O, although the rates cited vary from 10^2 to 10^7 M^{-1} s^{-1} and even the products are not fully defined in all cases.[20] Control reactions showed that $Co^{II}[C_2(DO)(DOH)_{pn}]X$ did not react with N_2O while blue $Co^I[C_2(DO)(DOH)_{pn}]$ reacted immediately, giving a blue to yellow (Co(III)) color change. When the methanolysis of **3** was performed in N_2O-saturated MeOH, no change from the usual rates or products (eq 2) was observed. The experiments with added 1,5,6-trimethylbenzimidazole, which produce Co(I) in the presence of $HOCH_2CHO$ but no further reaction and *no* CH_3CHO (eq 8), also argue effectively against the Co(I) pathway in *our reaction* (*eq 2*). (Similar arguments can be made for Meyerstein's studies using B_{12}, eq 3, a reaction that also produces Co(I) and $HOCH_2CHO$ but no CH_3CHO or Co–CH_2CHO.)

The Co(III) pathway, producing $Co(III)^+$ and $HOCH_2CHOH^-$, can be ruled out on the basis of the observed products, since $HOCH_2CHOH^-$ should be rapidly protonated in CH_3OH (even if in a CH_3OH cage with $Co(III)^+$) and no $HOCH_2CH_2OH$ is observed[1] under conditions where as little as 5% of added $HOCH_2CH_2OH$ was detectable by ^1H NMR. Furthermore, 100 equiv of I^-, which has a relatively high affinity for Co(III), caused no change in the observed products. Another major problem with the Co(II)/Co(III) electron-transfer mechanism is that this couple *shows a slow electron transfer*, slow even on a cyclic voltammetry time scale of a few seconds, in both B_{12} and B_{12} models.[2b,19b]

The above data argue against possible Co(III) and Co(I) pathways, as well as against a pathway forming 50% each of Co(III) and Co(I) followed by its disproportionation to give the observed 100% Co(II).

Additional Experiments with the Co–CH_2CHO, Formylmethyl Complex (6). Evidence for a ·CH_2OH Intermediate. In the preceding paper,[1] the formylmethyl complex **6** was prepared and found to be largely stable over at least 1 h to MeO^-/MeOH, or MeO^-/MeOH plus 1,5,6-trimethylbenzimidazole. Since all the cobalt-participation mechanisms (Scheme II) either produce ·CH_2CHO in a solvent cage with Co(II)· or produce Co–CH_2CHO directly (e.g., the π-complex mechanism, Scheme II), the absence

(16) (a) Endicott, J. F.; Netzel, T. L. *J. Am. Chem. Soc.* **1979**, *101*, 4000. (b) Espenson finds[16c] that $Co(diamine)_3^{3+}$ complexes are reduced at rates $\sim 10^5$ M^{-1} s^{-1} by $(CH_3)_2\dot{C}(OH)$ at pH ≈ 7, 25 °C. (c) Espenson, J. H.; Shirmura, M.; Bakač, A., submitted for publication.

(17) Costa, G.; Mestroni, G.; Tauzher, G. *J. Chem. Soc., Dalton Trans.* **1972**, 450.

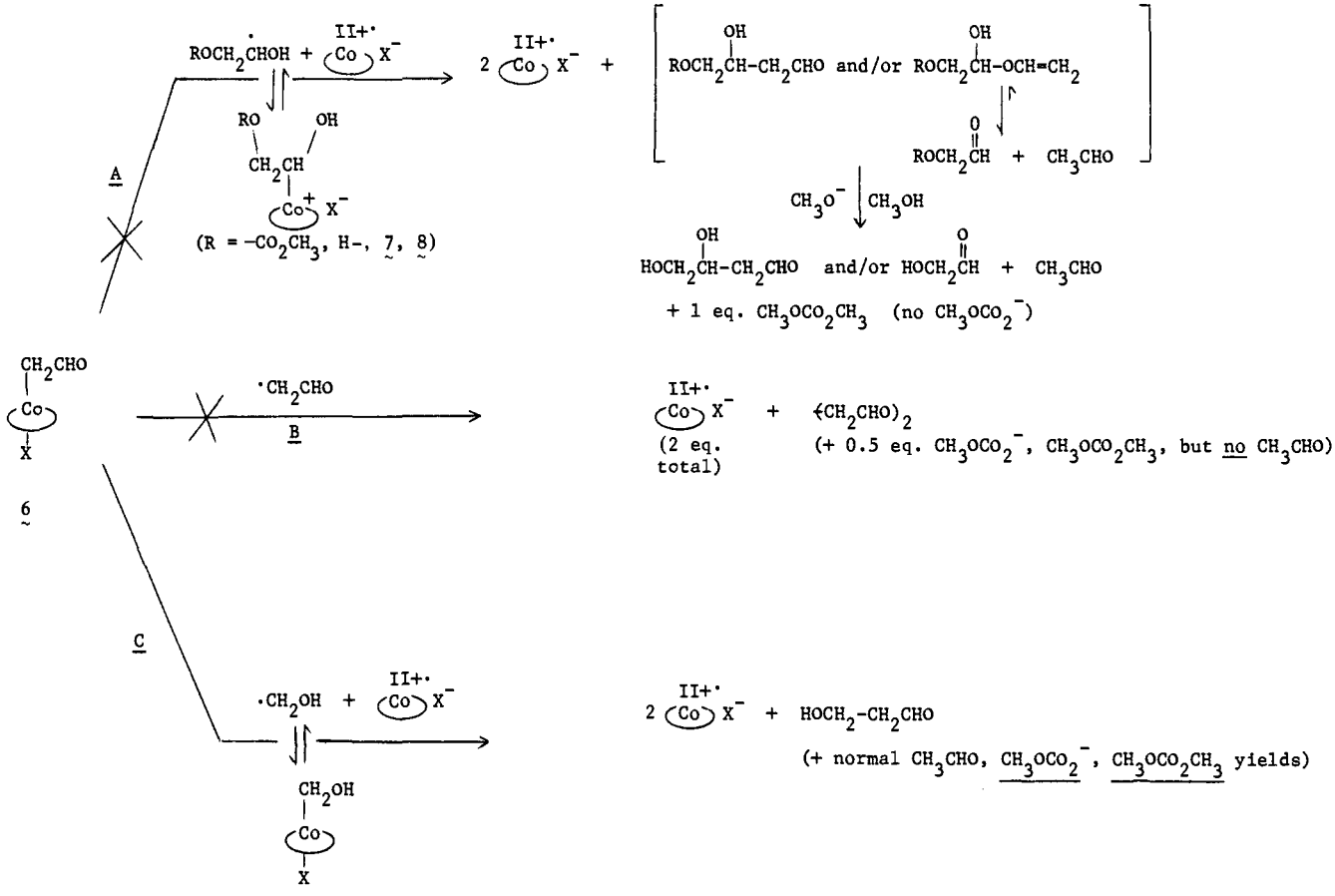
(18) (a) Endicott, J. F.; Lilie, J.; Kuszaj, J. M.; Ramaswamy, B. S.; Schmonsees, W. G.; Simic, M. G.; Glick, M. D.; Rillema, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 429. (b) Schneider, P. W.; Phelan, P. F.; Halpern, J. *Ibid.* **1969**, *91*, 77. (c) Lexa and Savéant have found that CN^- binds better than benzimidazole to Co(II) in $B_{12(r)}$. Lexa, D.; Savéant, J. M.; Zickler, J. *J. Am. Chem. Soc.* **1980**, *102*, 2654.

(19) (a) An interesting point that emerges from Lexa and Savéant's thorough electrochemical studies of coenzyme B_{12}[19b,d] is that *in* H_2O, the Co(II) ($B_{12(r)}$, base-off)/Co(I) ($B_{12(s)}$, base-off) $E_{1/2}$ = –0.742 V (SCE) while the Co(II) ($B_{12(r)}$, base-*on*)/Co(I) ($B_{12(s)}$, base-*off*) $E_{1/2}$ = –0.851 V (SCE), 109 mV harder,[19c] the axial base destabilizing Co(II) in the case of B_{12}. Unfortunately, the B_{12} Co(II) (base-*off*)/Co(I) (base-*on*) $E_{1/2}$ value required for a direct comparison to the model's electrochemistry reported herein is one of the few pieces of data unavailable from the studies of Lexa and Savéant. Their data show, however, that Co(I), $B_{12(s)}$, prefers to be in the *base-off* form,[19c] the opposite result found for the $Co[C_2(DO)(DOH)_{pn}]$ model. Their recent data[19b] combined with their earlier work[19b,c] demonstrate that in B_{12}, base-off Co(II) is reduced both thermodynamically easier and kinetically faster, strongly suggesting that it is base-off $B_{12(r)}$ that is involved in Meyerstein's observed $B_{12(r)} \rightarrow B_{12(s)}$ reaction.[8] (b) A listing of Lexa and Savéant's work is provided in footnote 9 of ref 2b. Their very recent work, parts 7–9, is given in ref 19d. (c) Lexa, D.; Savéant, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 2652. (d) Faure, D.; Lexa, D.; Savéant, J. M. *J. Electroanal. Chem.* **1982**, *140*; part 7, p 269; part 8, p 285; part 9, p 297.

(20) (a) Blackburn, R.; Kyaw, M.; Swallow, A. J. *J. Chem. Soc., Faraday Trans. 1* **1977**, *73*, 250. (b) Elroi, H.; Meyerstein, D. *J. am. Chem. Soc.* **1978**, *100*, 5540. (c) Tait, A. M.; Hoffman, M. Z.; Hayon, E. *Ibid.* **1976**, *98*, 86. (d) Banks, R. G. S.; Henderson, R. J.; Pratt, J. M. *J. Chem. Soc. A* **1968**, 2886. (e) Finaly, T. H.; Valinsky, J.; Sato, K.; Abeles, R. H. *J. Biol. Chem.* **1972**, *247*, 4197. (f) Schrauzer, G. N.; Seck, J. A.; Holland, R. J. *Z. Naturforsch., C* **1973**, *28C*, 1.

(21) (a) Golding, B. T. In "Vitamin B_{12}"; Dolphin, D., Ed.; Wiley-Interscience: New York, 1982; Vol. 1, Chapter 15. (b) Golding, B. T.; Sell, C. S.; Sellars, P. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 961. (c) Golding, B. T.; Radom, L. *J. Am. Chem. Soc.* **1976**, *98*, 6331. (d) See also ref 7f. (e) Russell, J. J.; Rzepa, H. S.; Widdowson, D. A. *J. Chem. Soc., Chem. Commun.* **1983**, 625. For a discussion of this recent, interesting work see ref 36, footnote 7c.

Scheme IV



of any Co–CH_2CHO complex (**6**) in the methanolysis of **3** (eq 2) was taken as a strong argument against the cobalt participation mechanisms, assuming no significant barrier for Co· + ·CH_2CHO → Co–CH_2CHO exists. For the methanolysis of **3** then, it would appear that Co–$C(OH)R_2$ bond homolysis in **7** and **8** (Scheme I) followed by cage escape by the $ROCH_2\dot{C}HOH$ radicals (R = H, CH_3OCO–) before their fragmentation[21] to ·CH_2CHO + ROH readily explains the observed results.

The possible reactions available to a ·CH_2CHO radical[22] and their estimated absolute rate constants based on literature precedent[23a,b] are shown in Scheme III. Using the observed results, $[CH_3CHO]/[Co–CH_2CHO\ (\mathbf{6})] > 95/5$ and $[CH_3OH]/[Co(II)]_{av} = 4 \times 10^3$, one estimates k' for Co· + ·CH_2CHO → Co–CH_2CHO as $k'(\text{est}) < 10^7\ M^{-1}\ s^{-1}$, if the assumed mechanism (Scheme III) is correct.[23c] This result is somewhat surprising. One estimate for the partially delocalized, partially oxygen centered[22a,b] ·CH_2CHO ↔ CH_2=CHO· radical plus Co(II)· exists,[22c] $k \sim 8 \times 10^7\ M^{-1}\ s^{-1}$, although the B_{12} model system employs an uncharged ligand and was later noted to be a poor model system.[8] For Co· + CH_3· the rates are fast, $8 \times 10^7\ M^{-1}\ s^{-1}$ for CH_3· + $Co(DMG)_2py$[24a] and 25 times faster for $B_{12(r)}$· + CH_3·, $2 \times 10^9\ M^{-1}\ s^{-1}$.[24b] Given the above considerations, additional studies of the Co–CH_2CHO complex **6** were required, especially studies of its stability during the functioning methanolysis of **3**, with and without nitroxides or 1,5,6-trimethylbenzimidazole.

When 0.9 equiv of Co–CH_2CHO (**6**) was added to 1.0 equiv of **3** and treated with MeO^-/MeOH, the Co–CH_2CHO complex was, in fact, *completely consumed* with 1.8 ± 0.1 equiv of Co(II) (λ_{max} 520 nm), no Co–CH_2CHO, **6**, by IR, UV-visible, or NMR ($\nu_{CO} = 1650\ cm^{-1}$; λ_{max} 392 nm; δ 8.97, 1.56 (Co–CH_2CHO)) *but with the usual CH_3CHO, $CH_3OCO_2^-$ and $CH_3OCO_2CH_3$ yields being observed.* When the experiment was repeated, but with 1.8 equiv of Co–CH_2CHO (**6**) added, the observed products included 1.8 ± 0.1 equiv of Co(II) (λ_{max} 520 nm), 0.8 ± 0.1 equiv of Co–CH_2CHO, **6**, ($\nu_{CO} = 1650\ cm^{-1}$; λ_{max} 392 nm; δ 8.57, 1.56 (Co–CH_2CHO)), and again CH_3CHO, $CH_3OCO_2^-$, and $CH_3OCO_2CH_3$ in their usual yields, demonstrating that Co–CH_2CHO is consumed stoichiometrically, not catalytically.

If 1.0 equiv each of **3**, the nitroxide **9** (eq 5), and Co–CH_2CHO, **6**, were treated with MeO^-/MeOH, 50 ± 20% (70 ± 30% corrected for decomposition) of the formylmethyl complex survived, with the other products consisting of 80 ± 10% Co(II) (λ_{max} 520 nm), 100 ± 10% $CH_3OCO_2CH_3$ ($\nu_{CO} = 1755\ cm^{-1}$), and no detectable (<5%) CH_3CHO or $CH_3OCO_2^-$. The nitroxide appears to be trapping the same intermediate(s) it trapped earlier (eq 5, 7), before this intermediate(s) can consume Co–CH_2CHO, **6**.

When 1.0 equiv of **3** and **6** and 25 equiv of 1,5,6-trimethylbenzimidazole are combined and treated with MeO^-/MeOH, 80 ± 5% of the formylmethyl complex survives, with the other products being 1.0 equiv of $CH_3OCO_2CH_3$, 85 ± 10% Co(I), 20 ± 5% Co(II), and no (<5%) CH_3CHO.

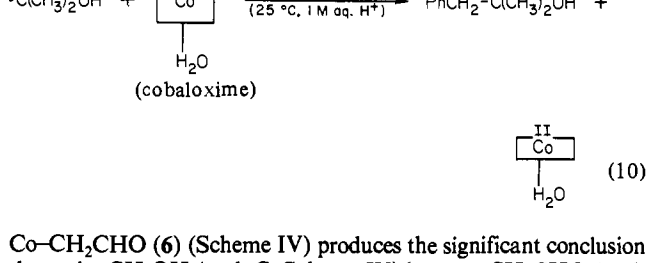
The above studies show that Co–CH_2CHO (**6**) is consumed by an intermediate produced under the reaction conditions, but that the intermediate or intermediates that consume **6** are either directly diverted by, or come after, the intermediates affected by 1,5,6-trimethylbenzimidazole and nitroxide. Recent work by Espenson[25a] shows that α-hydroxy radicals undergo a very rapid,

(22) (a) Zimmerman, A. H.; Reed, K. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 7203. (b) Huyser, E. S.; Feller, D.; Borden, W. T.; Davidson, E. R. *Ibid.* **1982**, *104*, 2956. (c) Reference 20b. It should be noted that the Co–CH_2CHO product is supported by UV-visible evidence only.

(23) (a) The rate of H· abstraction from CH_3OH is from ref 4g. Ingold, K. U. In "Free Radicals"; Kochi, J., Ed.; Wiley: New York, 1973; Vol. 1, p 76. (b) For 2·CH_2CHO → $(-CH_2CHO)_2$ see ref 4e. (c) Assuming $[Co(II)\cdot] \simeq [Co(II)\cdot]_{av} = ([Co(II)\cdot]_i + [Co(II)\cdot]_f/2 \simeq [Co(II)\cdot]_f/2$, then $[CH_3CHO]/[\mathbf{6}] = (k[CH_3OH][\cdot CH_2CHO])/(k'[Co(II)\cdot][\cdot CH_2CHO])$ and $[CH_3CHO]/[(CH_2CHO)_2] = (k[CH_3OH][\cdot CH_2CHO])/k'[\cdot CH_2CHO]^2$. Given that $[CH_3CHO]/[Co–CH_2CHO] > (95 \pm 4)/5$, and $[CH_3OH]/[Co(II)]_{av} = 4 \times 10^3$, one can estimate $k'_{(est)} < 10^7\ M^{-1}\ s^{-1}$.

(24) (a) Lerner, D. A.; Bonneau, R.; Gianotti, C. *J. Photochem.*, **1979**, *11*, 73. (b) Endicott, J. F.; Ferraudi, G. J. *J. Am. Chem. Soc.* **1977**, *99*, 243.

$k \sim 10^7\ M^{-1}\ s^{-1}$, S_H2 reaction[25] with $PhCH_2$–Co complexes (eq 10). A detailed consideration of the possible routes that consume



(10)

Co–CH_2CHO (**6**) (Scheme IV) produces the significant conclusion that only ·CH_2OH (path C, Scheme IV) but not ·CH_2CHO (path B) or $ROCH_2CHOH$ or its Co–$CH(OH)CH_2OR$ form (**7**, **8**, path A) can be consuming the formylmethyl complex **6**, since only path C gives CH_3CHO and *both* $CH_3OCO_2^-$ and $CH_3OCO_2CH_3$. The formylmethyl complex appeared to be the ideal trap for ·CH_2OH, so that identification of the expected $HOCH_2$–CH_2CHO would provide unequivocal evidence for ·CH_2OH and all the radical chemistry leading to its formation. Following this lead, the β-hydroxypropionaldehyde and expected dehydration product, acrolein, were searched for by ^1H NMR, IR, and UV spectroscopy. Our inability to detect these reactive species was consistent with control experiments showing authentic acrolein to be unstable and undetectable under the reaction conditions employed. In order to generate more stable radical trapping products, the methanolysis of **3** was performed in the presence of 1.0 equiv of other cobalt(III) complexes, $RCo(C_2(DO)(DOH)_{pn})X$ (R = $PhCH_2$–, CH_2=$CHCH_2$–). Unfortunately, no S_H2-like decomposition to generate Co(II) and organic products ($PhCH_2CH_2OH$, CH_2=$CHCH_2CH_2OH$) was observed in these cases.

Since the use of $PhCH_2OH$ as a solvent for the deprotection of **3** had previously yielded the PhĊHOH-derived product, PhCHO, trapping of the PhCHOH radical with **6** was attempted. The base-catalyzed deprotection of **3** in the presence of 2 equiv of **6** in $PhCH_2OH$ resulted in no net decomposition of the formylmethyl complex. This result is not altogether unexpected, given that alkylcobaloximes that react in an apparent S_H2 reaction with ·$C(CH_3)_2OH$ fail to react with benzyl radicals.[25a]

Additional Attempted ·CH_2CHO Radical Trapping and Other Experiments. Throughout the course of these studies, several types of additional experiments were tried with the hope of detecting a ·CH_2CHO radical. Added $Co^{II}[C_2(DO)(DOH)_{pn}]X$, ca. 4.5 equiv, which is the maximum amount soluble in MeOH, had no effect on the methanolysis products. Although Co–CH_2CHO should form if enough Co(II) were added, we now know Co–CH_2CHO (**6**) is unstable under the reaction conditions and therefore that stable **6** is not expected.

A CH_3CHO yield experiment was run in CD_3OH with the thought that the k_H/k_D isotope effect of D· abstraction from CD_3OH vs. H· abstraction from CH_3OH would cause a decrease in the CH_3CHO yield and an increase in the other pathways and products (Scheme III). No isotope effect on the CH_3CHO yield was observed, however, results that are still consistent with a ·CH_2CHO intermediate but do require that the CH_3CHO pathway be at least 10 times faster than the other possible reactions (Scheme III), even in CD_3OH.

(25) (a) McHatton, R. C.; Espenson, J. H.; Bakač, A. *Ibid.* **1982**, *104*, 3531. (b) Espenson, J. H.; Shveima, J. S. *Ibid.* **1973**, *95*, 4468. (c) Cooksey, C. J.; Dodd, D.; Johnson, M. P.; Lockman, B. L. *J. Chem. Soc., Dalton Trans.* **1978**, 1814. (d) Crease, A. E.; Johnson, M. D. *J. Am. Chem. Soc.* **1978**, *100*, 8013. (e) Gupta, B. D.; Funabiki, T.; Johnson, M. D. *Ibid.* **1976**, *98*, 6697. (f) Bury, A.; Cooksey, C. J.; Funabiki, T.; Gupta, B. D.; Johnson, M. D. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1050. (g) Funabiki, T.; Gupta, B. D.; Johnson, M. D. *J. Chem. Soc., Chem. Commun.* **1977**, 653. (h) Crease, A. E.; Gupta, B. D.; Johnson, M. D.; Bialkowska, E.; Duong, K. N. V.; Gaudemer, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2611. (i) Ashcroft, M. R.; Bury, A.; Cooksey, C. J.; Davies, A. G.; Gupta, B. D.; Johnson, M. D.; Morris, H. *J. Organomet. Chem.* **1980**, *195*, 89. (j) Bougeard, P.; Bury, A.; Cooksey, C. J.; Johnson, M. D. *J. Am. Chem. Soc.* **1982**, *104*, 5230.

Discussion

Since much of the preliminary discussion was provided in the last section, only the key findings and any additional discussion that is required is presented in the section that follows.

The Initial Reaction of 3 with CH_3O^-: Formation of the T_d Intermediate. Several lines of evidence require that the initial reaction of **3** with CH_3O^- occurs at the carbonyl carbon in **3** (site 7, Figure 1) as expected, and not at the other conceivable sites (1–6, Figure 1). The major evidence includes the lack of Co–R bond cleavage upon CH_3O^-/CH_3OH treatment in cobalt alkyls lacking a carbonate, the observed products, especially $CH_3OC(O)OCH_3$ formation (eq 5), the independence of the kinetics upon axial 1,5,6-trimethylbenzimidazole under conditions from 0 to >98% of base-on **3**, and the similar values, within experimental error, of the statistically corrected[26] methanolysis rate for simple ethylene carbonate $\overline{CH_2O(C{=}O)OCH_2}$, $k_2(obsd')/2 = 6 \pm 2\ M^{-1}\ s^{-1}$ (30 ± 2 °C),[26] and the value for the carbonate model compound **3**, $k_2(obsd) = 3.3 \pm 0.8\ M^{-1}\ s^{-1}$ (25 ± 1 °C). These results are consistent only with CH_3O^- attack at the carbonyl carbon, as discussed in the last section. It is interesting to note that both carbonates undergo facile methanolyses, approximately 10^2–10^3 faster than simple esters.[27] Since no long-lived intermediates accumulate, the subsequent chemistry must be faster than the $k_2(obsd)\cdot[CH_3O^-] \approx 1\ s^{-1}$, suggesting the subsequent chemistry is kinetically competent to model diol dehydratase, which turns over at ca. 12 times/s.

Following formation of the tetrahedral intermediate, nearly statistical, 50 ± 10%, opening of the carbonate in essentially a $B_{AC}2$ (base-catalyzed, acyl-oxygen cleavage, bimolecular) mechanism[28] is required to explain the eventual formation of 50 ± 10% of $CH_3OCO_2CH_3$ and $CH_3OCO_2^-$. A proposed outline of this well-known alcoholysis chemistry has already been provided in the first part of Scheme I, where the anionic, conjugate bases of **7a** and **8a** are omitted for clarity, although they must be formed initially prior to their rapid protonation to yield **7a** and **8a**.

The Co–$CH(OH)CH_2OR$ (R = H, –$COCH_3$) α-Hydroxy Complexes, Their Co–C Bond Homolyses, and Subsequent Reactions. It is the α-hydroxy complexes **7a** and **8a** (Scheme I) and especially their subsequent chemistry that is of greatest interest toward establishing a chemical precedent for diol dehydratase. Although we have not directly detected **7a** or **8a**, the BDE > 0 (and probably[29] 15 kcal/mol ≳ BDE ≫ 0 kcal/mol) expected for

(26) (a) While both faces of simple ethylene carbonate, $k_2(obsd') = 11 \pm 4\ m^{-1}\ s^{-1}$, are available for CH_3O^- attack, the ORTEP plot[1] and molecular models of **3** show that the macrocyclic ligand effectively shields one face of the carbonate in **3**, $k_2(obsd) = 3.3 \pm 0.8\ M^{-1}\ s^{-1}$, so that $k_2(obsd')$ divided by a statistical factor of 2, $k_2(obsd')/2 = 6 \pm 2\ M^{-1}\ s^{-1}$, provides a better comparison to $k_2(obsd) = 3.3 \pm 0.8\ M^{-1}\ s^{-1}$. This comparison will be even closer when the temperature difference of the two measurements and other factors[26b] are taken into account. A case in point is the observed,[26c] uncorrected rate constants for substituted ethylene carbonates, $\overline{RCHCR'R''OC(O)O}$: R = R′ = R″ = H, k_{rel} (52 °C) = 1.00; R = CH_3, R′ = R″ = H, k_{rel} (52 °C) = 0.46; R = R′ = CH_3, R″ = H, k_{rel} (52 °C) = 0.29; R = R′ = R″ = CH_3, k_{rel} (52 °C) = 0.15. (b) We note that $k_2(obsd')$ is obtained from $-d(\nu_{CO})/dt$ (= $-dA/dt$ for this

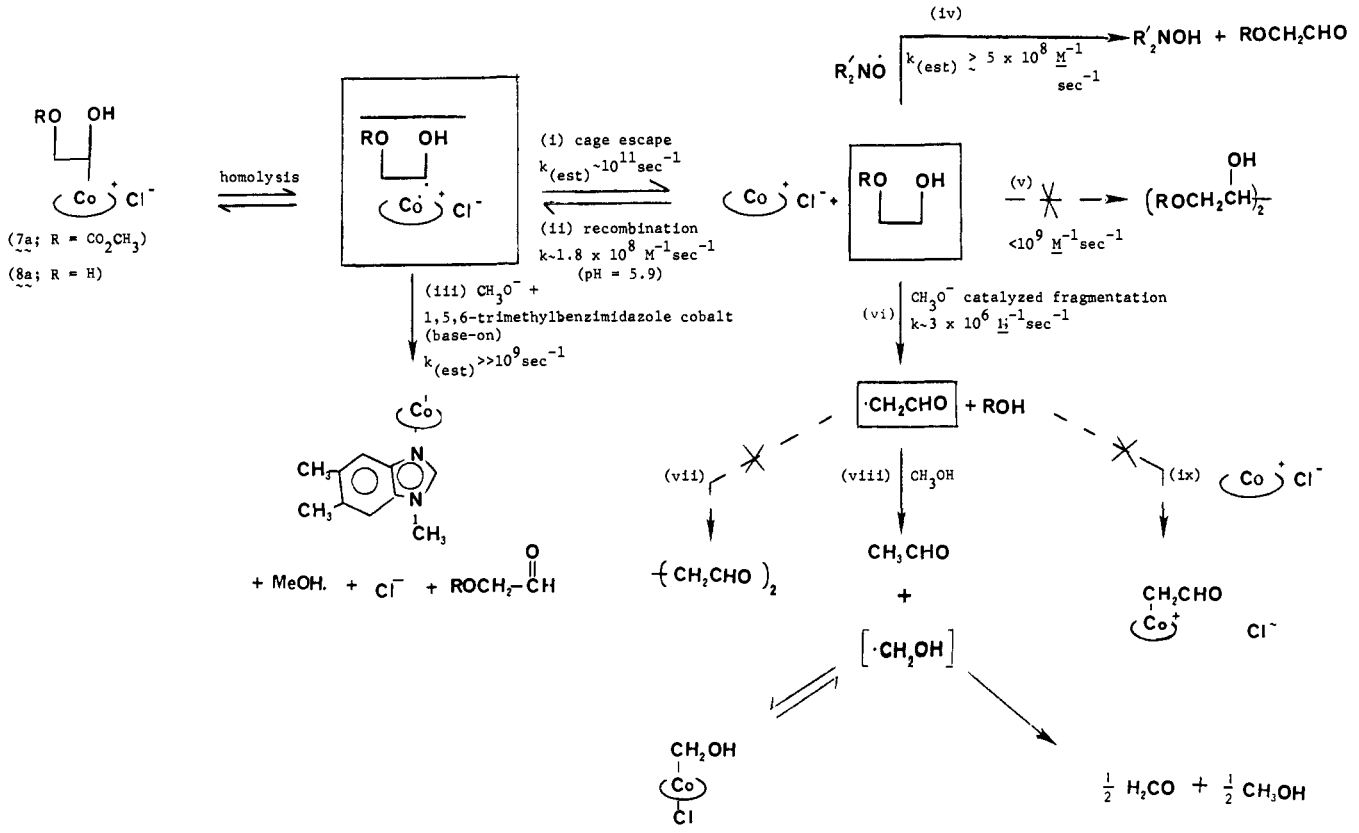
$$A \xrightarrow{k_1} B \xrightarrow{\sim k_1} C$$

system, while $d[Co(II)]/dt = d(C)/dt$. If one assumes $k_1 = k_2$, then it can be shown, analogously to similar treatments,[26d] that $d(C)/dt = (-d(A)/dt)kt$. (c) Katzhendler, J.; Poles, L. A.; Sarel, S. *Isr. J. Chem.* **1972**, *10*, 111. (d) Capellos, C.; Bielski, B. H. J. "Kinetic Systems"; Wiley-Interscience: New York, 1972; Chapter 9.

(27) (a) For $CH_3OCO_2CH_3 + HO^- \rightarrow CH_3OCO_2^-$ in 80% CH_3OH, $k_2(obsd) = 4 \times 10^{-3}\ M^{-1}\ s^{-1}$ (25 °C). Kirby, A. J. In "Comprehensive Chemical Kinetics"; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1972; Vol. 10, pp 168–176. (b) For p-$MeOC_6H_4CO_2{}^*CH_3 + CH_3O^- \rightarrow p$-$MeOC_6H_4CO_2CH_3 + {}^*CH_3O^-$, $k_{obsd} = 1.1 \times 10^{-2}\ M^{-1}\ s^{-1}$ (30 °C). Jones, L. B.; Sloane, T. M. *Tetrahedron Lett.* **1966**, 831.

(28) (a) Ingold, C. K. "Structure and Mechanism in Organic Chemistry", 2nd ed.; Cornell University Press: Ithaca, NY, 1969; p 1131. (b) Lowry, T. H., Richrdson, K. S. "Mechanism and Theory in Organic Chemistry", 2nd ed.; Harper and Row: New York, 1981; p 651. (c) The aminolysis of carbonate diesters has attracted recent attention: Fife, T. H.; Hutchins, J. E. C. *J. Am. Chem. Soc.* **1981**, *103*, 4194 and references therein.

Scheme V



these complexes strongly suggests that they will have at least transient existence at 25 °C. Meyerstein's work,[8] supporting the formation of such α-hydroxy complexes with B_{12} (pH 5.9), and the fact that isolable, transition-metal α-hydroxy compounds do exist, provides additional support for **7a** and **8a** as do other arguments.[30]

Although the exact Co–C BDE and lifetimes of **7a** and **8a** are of interest, the observation of the Co(II) product, which lacks a Co–C bond, starting from **3** and the T_d intermediate containing such a bond, leads to the inescapable conclusion that such Co–C bonds are weak. More important to the present study, then, are the two possible ways of explaining the nitroxide trapping (eq 5) and 1,5,6-trimethylbenzimidazole (eq 8) experiments, either via the direct reaction of the nitroxide and the axial base with the α-hydroxy complexes **7a** and **8a** or by the participation of the α-hydroxy radicals $HOCH_2\dot{C}HOH$ and $CH_3OCO_2CH_2\dot{C}HOH$.

At this point it is useful to jump ahead somewhat to consider the major evidence, other than the nitroxide and 1,5,6-trimethylbenzimidazole results, supporting the presence of radical intermediates. We know that (a) Co(II) is formed, which implies that $\cdot CH(OH)CH_2OR$ (R = H, $-COCH_3$) are formed, (b) that just a few equivalents of radical traps such as galvanoxyl or duroquinone greatly decrease the CH_3CHO yield, (c) that the radical-derived product PhCHO is formed when $PhCH_2OH$ is used in the place of CH_3OH as a solvent, and (d) that a solvent-derived $\cdot CH_2OH$ radical is implicated as the species that consumes added Co–CH_2CHO (**6**) to produce 1 equiv of Co(II) in a reaction that is stopped by added nitroxide or 1,5,6-trimethylbenzimidazole. Overall, we see no way to explain the products CH_3CHO, Co(II), $CH_3OCO_2^-$, and $CH_3OCO_2CH_3$ (but no Co–CH_2CHO (**6**)) and the Co–CH_2CHO results other than via the very well precedented, CH_3O^- catalyzed, radical fragmentation reactions[4] of $CH_3OCO_2CH_2\dot{C}HOH$ and $HOCH_2\dot{C}HOH$ *out of the radical cage* where Co(II)·, and thus Co–CH_2CHO formation, are less available.

With the evidence for radical intermediates in hand, it is reasonably easy to see that the nitroxide (eq 5) and 1,5,6-trimethylbenzimidazole results (eq 8) are most readily interpreted in terms of, and offer additional support for, the $CH_3OCO_2CH_2\dot{C}HOH$ and $HOCH_2\dot{C}HOH$ radicals. The important literature precedents were provided earlier in eq 7 and 9.

The observed effect of added nitroxide (**9**, eq 5) is just that expected on the basis of eq 7, $ROCH_2\dot{C}HOH + R_2'N\text{–}O\cdot$ (**9**) → $ROCH_2CHO + R_2'N\text{–}OH$, then $ROCH_2CHO + CH_3O^-/CH_3OH \rightarrow HOCH_2CHO + ROCH_3$ (R = H, $-CO_2CH_3$), this sequence fully accounting for the lack of CH_3CHO and $CH_3OCO_2^-$ and the 100% rather than 50% yield of $CH_3OCO_2CH_3$. We cannot rule out the possibility of *some* direct oxidation of the α-hydroxy cobalt complexes **7a** and **8a** (Scheme V) by the nitroxide, but note that this chemistry would have to occur competitively with the ca. $k = 4\text{–}6 \times 10^8$ M^{-1} s^{-1} (eq 7) rate of the nitroxide α-hydroxy radical chemistry, and no precedent exists other than the ca. 10^9 slower, somewhat related reaction shown back in eq 6.

The observed 1,5,6-trimethylbenzimidazole effect (eq 8) is fully consistent with, and also required by, the *caged* α-hydroxy radical + $BzCo^{II}\cdot$ intermediates that are proposed in Scheme V and the precedent shown in eq 9. Cyclic voltammetry studies demonstrated that 1,5,6-trimethylbenzimidazole addition decreased the Co(II)/Co(I) reduction couple by 170 mV in *CH_3OH*, and it was

(29) (a) Organotransition-metal complexes with Co–C BDE ≥20 kcal/mol are known to be stable and isolable at 25 °C.[6] Using (i) the reasonable estimate[29b] of an Arrenhius *A* factor of 10^{12}–10^{14} s^{-1} and (ii) the observed methanolysis rate of **3**, $k_{obsd} = 3.3$ M^{-1} s^{-1} (25 °C) as a lower limit on $k_{(homolysis)}$ of the Co–CH(OH)R intermediates (since no buildup of intermediates is observed), a crude estimate of Co–CH(OH)R BDE ≲15 kcal/mol results. (b) Benson, S. W. "Thermochemical Kinetics"; 2nd ed.; Wiley-Interscience: New York, 1976; Chapter 3.

(30) A third argument for the α-hydroxy complexes **7a** and **8a** is that statistical opening of the T_d intermediate to 50% each of $CH_3OCO_2CH_2CH(O^-)$–Co and $^-OCH_2CH(OCO_2CH_3)$–Co with their intact Co–C bonds (and thus relatively similar energies) seems more reasonable than direct opening to 50% each of the homolysis product, $CH_3OCO_2CH_2\dot{C}HO^-$ + Co·, and the Co–C bonded product, $^-OCH_2CH(OCO_2CH_3)$–Co (which would seem to be of rather different energies). This argument is weakened, however, by the likelihood that there is less product than reactant control of the transition state for ring opening. The ring-opening reaction releases ca. 6 kcal/mol of strain energy and is, therefore, probably exothermic, with the transition state more closely resembling the starting material (the T_d intermediate).

previously noted that Meyerstein sees the same reaction from base-on B_{12} (the production of Co(I) $B_{12(s)}$ and, presumably, $HOCH_2CHO$). As noted earlier, a fuller understanding of the axial base effect is presently not available, however, and will require further studies.

The Nonparticipation by the Formylmethyl Complex Co–CH_2CHO (6). The Co–CH_2CHO (**6**) experiments demonstrated that **6** added to the methanolysis of **3** did not yield CH_3CHO, a result that unequivocally rules out the often cited, but unverified, Co(III) π-complex mechanism (Scheme II) in the present work, as well as any other cobalt-participation mechanism that would produce Co–CH_2CHO (**6**). It appears that the Co–CH(OH)R bond homolysis is simply faster than the unproven OH-migration, Co(III) π-complex mechanism (Scheme II). To the extent that the cage chemistry, Co· + ·CH_2CHO → Co–CH_2CHO, occurs faster than cage escape, our results also argue against any other conceivable cobalt participation mechanism that would produce caged Co· + ·CH_2CHO, such as the Co(I) and Co(III) routes, Scheme II (routes that were also disfavored on the basis of other data). There is also our unexpected result from the last section, the relatively slow rate constant, k'(est) $<10^7$ M^{-1} s^{-1}, for the combination of freely diffusing Co(II)· + ·CH_2CHO. This tentative result requires verification, possibly using flash photolysis of Co–CH_2CHO (**6**), and studies probing the importance of the axial ligands. Meyerstein's most recent pulse radiolysis study[8] provided spectral evidence for Co·($B_{12(r)}$) + ·CH_2CHO → Co–CH_2CHO, although no absolute rate constant was reported.

The Proposed Mechanism. A scheme that is consistent with all the available data is shown in Scheme V. An important question is whether or not the proposed mechanism is quantitatively consistent with the absolute rate constants available directly, or as estimates, for many of the individual, or closely related, reactions. The rate constants are presented in Scheme V and their sources are provided in the footnote.[31] Obvious questions include: should base-catalyzed rearrangement, $ROCH_2\dot{C}HOH$ + MeO^- → RO^- + MeOH + ·CH_2CHO, occur exclusively over dimer formation, $ROCH_2CH(OH)$–$CH(OH)CH_2OR$, and should 1 equiv of nitroxide essentially completely inhibit the above radical fragmentation reaction by oxidizing the radical?

Following homolysis (Scheme V), cage escape (step i k(est)[31b] ~ 10^{11} s^{-1}) will occur faster than the fragmentation reaction of the $ROCH_2\dot{C}HO^-$ radical-anion ($k \sim 3 \times 10^6$ M^{-1} s^{-1}, step vi).[4i,e] Little α-hydroxy radical dimer (step v) is expected since k(est)[4e] $<10^9$ M^{-1} s^{-1} for the combination of two anionic, deprotonated radicals ($ROCH_2\dot{C}HO^-$) and since k (step vi) = 3×10^6 s^{-1} $\gg$ k (step v) ~ (10^9 M^{-1} s^{-1})[$ROCH_2\dot{C}HO^-$]^2 at radical concentrations [$ROCH_2\dot{C}HO^-$] $\ll 5 \times 10^{-2}$ M, a condition probably satisfied by many powers of 10. When 1×10^{-2} M (1 equiv) nitroxide (**9**) was added, the nitroxide oxidative-trapping reaction (step iv $k >$ (5×10^8 M^{-1} s^{-1}·[1×10^{-2}]) = $k > 5 \times 10^6$ s^{-1}) should effectively compete with the fragmentation reaction (step vi $k \sim 3 \times 10^6$ s^{-1}), which it does. The deprotonated, anionic, and thus more reducing[32] $ROCH_2\dot{C}HO^-$ should have a faster electron transfer rate according to Marcus theory[33] than the protonated $ROCH_2\dot{C}HOH$, where k(est) ~ 5×10^8 M^{-1} s^{-1} was measured, providing further support for k(step iv) $\gg$ k(step vi).

The anticipated fate of the ·CH_2CHO radical was previously discussed in connection with Scheme III as was the unexpected conclusion that k (step ix) $\ll 10^9$ M^{-1} s^{-1}. It is not known for certain whether or not the reduction to Co(I) in the presence of axial base comes from the caged radical pair as shown, step iii, or directly from **7a** and **8a**. There is little difference between the two in many ways, however, as each involves Co–C bond breaking and an electron transfer to cobalt, the two possibilities differ only in the timing of these steps. The proposed mechanism does an excellent job of accounting for the observed chemistry while also accommodating a large body of relevant literature data. It is unlikely that this mechanism is correct in every detail,[34] however, and it still must survive the test of time.

Summary and Conclusions

In summary, the major conclusions of the present model study of the cobalt-participation question in diol dehydratase are summarized below. We note that several of the conclusions are based on the observed reactions (products) and, therefore, are independent of any mechanistic uncertainties.

(1) No evidence was obtained that requires or supports cobalt participation in the present study, even when the cobalt–carbon bond was preformed, thereby inviting such participation.

(2) A direct probe of the often cited, but unverified, Co(III) π-complex mechanism was provided by the first preparation of the postulated intermediates containing both α- and β-hydroxyl groups Co–CH(OH)CH_2OH. *The π-complex mechanism was ruled out* by the lack of Co–CH_2CHO formation, this often cited mechanism failing the test of kinetic competence, the α-OH group and the weak Co–C bond governing the chemistry and not the β-OH group. The independent preparation[1] of the Co–CH_2CHO complex **6** via Co(III) π-complex chemistry is significant in that it demonstrates that both pathways are available in the B_{12} model system employed.

(3) Base-on cobalt participation was not only unnecessary, it proved to be a hindrance, inducing a side reaction to Co(I) and $HOCH_2CHO$, thereby inhibiting the CH_3CHO-producing reaction.

(4) The present studies, especially the effect of base-on cobalt participation, are consistent with the observations made by Meyerstein using coenzyme B_{12}. We note that a critical evaluation and electrochemical testing of the known B_{12} models were performed[26] as a foundation for the present studies. The Co[C_2-(DO)$(DOH)_{pn}$] model used herein is an especially close mimic of the B_{12} Co(II)/Co(I) reduction potential whereas the cobaloxime Co(II)–Co(I) $E_{1/2}$ is ca. 0.5 V more negative, for example.[26] Even with this precaution, the present studies compared with the more recent B_{12} electrochemistry[19b] of Savéant and co-workers have uncovered important differences in the $B_{12(r)}/B_{12(s)}$ and Co(II)/Co(I) Co[C_2(DO)$(DOH)_{pn}$] axial ligation effects.[19a] The extension of the carbonate protecting group approach to B_{12} is

(31) (a) The sources of the estimated or observed rate constants are as follows: step i,[31b,c] k(est) ~ 10^{11} s^{-1}; step ii,[8] k(est) ~ 1.8×10^8 M^{-1} s^{-1} at pH 5.9 for B_{12}; step iii,[16a] $k = 4 \pm 2 \times 10^9$ M^{-1} s^{-1} for a *bimolecular* reaction between these two radicals; step iv,[12] k(est) ~ 5×10^8 M^{-1} s^{-1} (pH 3–5, 25 °C; probably faster at basic pH where $ROCH_2\dot{C}HO^-$ is present); step v,[4e] k(est) < 10^9 M^{-1} s^{-1}; step vi,[4i,4e] $k \sim 3 \times 10^6$ M^{-1} s^{-1}. The estimate rate constants for steps vii, viii, and ix were provided[23] and discussed earlier in the text. (b) Koenig, T. In "Organic Free Radicals"; Pryor, W. A., Ed.; American Chemical Society: Washington, DC, 1978; ACS Symp. Ser. No. 69, Chapter 9.; Koenig, T. In "Free Radicals"; Kochi, J., Ed.; Wiley: New York, 1973; Vol. 1. (c) Kaptein, R. *Adv. Free Radical Chem.* **1975**, *5*, 319.

(32) Lilie, J.; Beck, G.; Henglein, A. *Ber. Bunsenges.* Phys. *Chem.*, **1971**, *75*, 458.

(33) Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155.

(34) (a) One important point, which we have no evidence for or against, is the possible involvement by ·$CH_2CH(OH)(OCH_3)$ and/or ·$CH_2CH(OH)_2$ in eq 2. Under the reaction conditions, the final product is in fact[1] CH_3CH-$(OH)(OCH_3)$, and whether or not ·CH_2CHO + CH_3OH ⇌ $CH_2CH(O$-$H)(OCH_3)$, then ·$CH_2CH(OH)(OCH_3)$ + CH_3OH → $CH_3CH(OH)(OCH_3)$ + ·CH_2OH or just simple, well-known CH_3CHO + CH_3OH ⇌ $CH_3CH(O$-$H)(OCH_3)$ occurs is not known. Due to the resonance energy of ·CH_2CHO ↔ CH_2=CHO· (which, although somewhat controversial, is small but >0)[34b] and the fact that $CH_3CHO + H_2O \rightleftharpoons CH_3CH(OH)_2$, $K_{eq} \approx 1$ at 20 °C (≡ $K'_{eq}[H_2O] = [CH_3CH(OH)_2]/[CH_3CHO]$),[34c,d] it seems rather likely that ·CH_2CHO + CH_3OH ⇌ ·$CH_2CH(OH)(OCH_3)$ has a $K_{eq} \ll 1$ (although ·$CH_2CH(OH)(OCH_3)$ should react faster with CH_3OH).[35] While the data in the present manuscript rule out the π-complex mechanism and Co–$CH_2CH(OH)(OR)$ (R = H, CH_3) ⇌ Co–CH_2CHO formation, it does not rule out an unprecedented,[34e] $HOCH_2\dot{C}HOH$ → ·$CH_2CH(OH)_2$, radical rearrangement, although all the experimental[4] and theoretical[21c] evidence suggests $HOCH_2\dot{C}HOH$ → H_2O + ·CH_2CHO is the preferred pathway. (See the recent work cited in ref 21e, however.) It is interesting to note that the question of such 1,2 migrations vs. a fragmentation-readdition mechanism is a pervasive ambiguity in the free-radical literature.[34f] Through the synthesis and study of ^{18}O-labeled **3**, Co–$\overline{CHO(C{=}O)}$*OCH_2, the possibility of · CH_2CH(*OH)(OH) formation could be addressed. (b) See ref 22a and ref 27 and 28 therein. (c) March, J. "Advances in Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977; p 804. (d) Schmitz, E.; Eichhorn, I. In "The Chemistry of the Ether Linkage"; Patai, S., Ed.; Wiley-Interscience: New York, 1967; p 312. (e) see the discussion, p 800 of ref 4d. (f) Freidlina, R. Kh.; Terent'ev, A. B. "Advances in Free Radical Chemistry"; Williams, G. H., Ed.; Heyden: London, 1982; Vol. 6, Chapter 1.

needed and is in progress, as are collaborative pulse radiolysis studies.[35]

A remaining question is whether the basic pH ≈ 10–12 conditions used herein more closely approximate those at the active site of diol dehydratase, optimum pH 6–10, or whether the computationally, but not experimentally, suggested proposal of protonation H_2O^+–CH_2–$\dot{C}H(OH)$ to induce $-OH_2^+$ migration is correct.[21] While there is no evidence, to our knowledge, for such a Brønsted acid site approaching $pK_a \approx -3$ within diol dehydratase, we have suggested[36] that *both* an acidic and basic site may be available in the protein, acid···(H)$OCH_2\dot{C}HO$–H···base, and additional discussion is presented elsewhere.[36] We also refer the interested reader to Golding's excellent treatment[21a] of previous model studies of diol dehydratase, including the protonation, $-OH_2^+$ migration mechanism.[21e]

Finally, there is the remaining question of the relevance, if any, of the present, or any other, model studies to diol dehydratase where the elegant stereochemical studies of Arigoni[37] require some type of *gem*-diol intermediate, for example. We have shown elsewhere how we believe it is possible to summarize the present model results, all the known α-hydroxy radical chemistry, and the stereochemical and other studies of diol dehydratase into a unified mechanism we prefer to call the "bound radical mechanism".[36]

Experimental Section

(A) General. (i) Methods of Handling Air-Sensitive Compounds. All manipulations involving air-sensitive materials were performed as described in the preceding manuscript.[1]

(Ii) Equipment. NMR, IR, UV–visible, and gas chromatographic analyses were performed as described in the preceding manuscript.[1]

Electrochemical experiments were performed on a Princeton Applied Research Model 173 potentiostat in conjunction with a Model 175 Universal programmer. For the scan rate of 0.10 V/s, voltammograms were recorded on a Hewlett–Packard Model 7045A X-Y recorder. For the scan rates of 5 V/s, a Tektronix Model 502A oscilloscope equipped with a type C-5A camera was used. The potential vs. SCE was evaluated by using an internal ferrocene standard. A three-electrode cell was used with a platinum bead working, platinum wire auxillary, and silver wire or saturated calomel reference electrode.

(iii) Materials. All solvents used in this study were purified as previosuly described.[1] Other chemicals prepared or purified by previously described methods include ethylene carbonate, dimethyl carbonate, bromotrichloromethane, methyl carbonate anion, $(n\text{-}C_4H_9)_4NI$, $PhCH_2OH$, 1,5,6-trimethylbenzimidazole, ethylene glycol, **3**, **6**, $Co^{II}[C_2(DO)(DOH)_{pn}]X$,[1] $(CO)Co[C_2(DO)(DOH)_{pn}]$, and $RCo^{III}[C_2(DO)(DOH)_{pn}]X$ (R = X = I; R = $PhCH_2$, X = I; R = $n\text{-}C_4H_9$, X = Br).[2a] Glycoaldehyde (Aldrich), nitrous oxide (Matheson), CD_3OD (KOR), and CD_3OH (KOR) were used without further purification. Acrolein (Aldrich) was distilled into methanol immediately prior to use. Allyl bromide (Aldrich) was distilled prior to use. The nitroxide Tempone (**9**) (Aldrich) was purified by recrystallization from petroleum ether to give a constant melting point of 38–39 °C (lit.[38] 39 °C). *N*-Hydroxy-2,2,6,6-tetramethylpiperidone (**10**) was prepared by hydrogenation (Pd/C, 1 atm of H_2, MeOH, 1.5 h) of the yellow nitroxide (**9**). The colorless solution was filtered (under N_2) to remove the Pd/C, the MeOH was removed via rotoevaporation, and a white solid formed on standing (ν_{CO} (MeOH) = 1709 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.22 (s, 12 H), 2.21 (s, 4 H), 3.49 (s, 1 H)).

(iv) Preparation of Other Co(III) Complexes. $ICo[C_2(DO)(DOH)_{pn}]PF_6$ was prepared by the action of $AgPF_6$ on $ICo[C_2(DO)(DOH)_{pn}]I$. To a solution of 50 mg of $ICo[C_2(DO)(DOH)_{pn}]I$ in 20 mL of CH_3OH was added 22 mg (1.0 equiv) of $AgPF_6$, and the resultant precipitate of AgI removed by filtration through glass wool. Removal of solvent by rotary evaporation gave the desired product.

$(CH_2{=}CHCH_2{-})Co[C_2(DO)(DOH)_{pn}]Br$ was prepared by the oxidative addition of allyl bromide to Co(I). In the drybox, 0.5 g (1 mmol) of $(OC)Co[C_2(DO)(DOH)_{pn}]Br$ and 0.65 mL (8 mmol) of allyl bromide were combined in 25 mL of benzene. The reaction mixture was protected from light and stirred at 30 °C for 5 min. The resultant red solution was evaporated to give a red solid: ^1H NMR ($CDCl_3$, Me_4Si) δ 1.01 (t, 6 H), 1.51 (m, 2 H), 2.31 (s, 6 H), 2.75 (q, 4 H), 3.82 (m, 6 H), 4.58 (m, 2 H), 5.0 (m, 1 H). Persistent impurities at δ 0.03 (q) and 2.06 (s) were present. The allylcobalt complex decomposed on all chromatography supports tried, and upon gentle heating, and was therefore used as a crude (ca. 90% pure) material.

(B) Kinetic Studies. (i) Methanolysis of Ethylene Carbonate. The rate of methanolysis of ethylene carbonate was measured by following the disappearance of the carbonyl stretching frequency (ν_{CO} = 1805 cm^{-1}) in the IR spectrum. A stock solution of 2×10^{-2} M ethylene carbonate in methanol was treated with the standard 0.91 M KOH/methanol mixture, the solution was transferred to a (0.1-mm pathlength) CaF_2 solution cell, and the disappearance of the carbonate was monitored at 30 ± 2 °C. Over the methoxide concentration range examined, 0.9–1.8 $\times 10^{-3}$ M (0.45–0.90 equiv, five points), first-order plots were obtained, and a second-order rate constant of 11 ± 4 M^{-1} s^{-1} was obtained by dividing the pseudo-first-order rate constants by methoxide concentration.

(ii) Methanolysis of 3. Methanol solutions of **3** for kinetic runs were prepared in the drybox, quantitatively transferred to septum-capped cells, and protected from light. Methanolic base solutions were transferred to 2-dram vials, septum capped, and removed with the visible cells from the drybox. For each kinetic run, a starting spectrum was taken and 5 min was allowed for temperature equilibration. Base catalyst was transferred by microliter syringe to the cells, which were given one hard shake and returned to the cell holder. At the moment the base was injected into the cell, a digital clock was started to monitor the reaction time. Growth of burgundy-red cobalt(II) (λ_{max} 520 nm (ϵ_{max} 3.6×10^3 M^{-1} cm^{-1})) product was followed vs. time.

Initial kinetic runs were taken at [**3**] = [MeO^-] = $(2.16\text{–}5.57) \times 10^{-4}$ M in a rectangular (1-cm pathlength) cell. The observed data suffered from irreproductibility and often did not give straight kinetic plots, presumably due to small amounts of light or oxygen, and were discarded.

The kinetic runs reported herein were performed at higher concentrations in a cylindrical (0.1-mm pathlength) cell at 22.5 ± 1 °C, were reproducible, and gave liner first-order plots over at least 90–95% of the reaction for the concentrations tested, [**3**] = $0.57\text{–}1.3 \times 10^{-2}$ M, [MeO^-] = $0.84\text{–}1.8 \times 10^{-2}$ M (Table I). The observed second-order rate constant of 2.7 ± 0.5 M^{-1} s^{-1} (22.5 °C) was obtained from 12 separate kinetic experiments by dividing the pseudo-first-order rate constant by the methoxide concentration. The kinetics were repeated at 25 ± 1 °C over the concentrations [**3**] = $0.93\text{–}1.86 \times 10^{-2}$ M, [MeO^-] = $0.47\text{–}2.33 \times 10^{-2}$ M. The observed second-order rate constant of 3.3 ± 0.8 M^{-1} s^{-1} (25 °C) was determined from 15 separate kinetic experiments.

(iii) Effect of 1,5,6-Trimethylbenzimidazole on the Observed Methanolysis Kinetics. Kinetic runs at 22.5 °C ([**3**] = 1.54×10^{-2} M, [MeO^-] = 1.17×10^{-2} M, [Bz] = 1.54×10^{-2} M) and 25 °C ([**3**] = [MeO^-] = 9.30×10^{-3} M, [Bz] = $0.93\text{–}1.2 \times 10^{-2}$ M) gave second-order rate constants in the above manner that were identical within experimental error with those obtained in the absence of axial base (Table I, entries 9, 24, and 25).

Under conditions of excess 1,5,6-trimethylbenzimidazole, the observed product was Co(I). The growth of Co(I) (λ_{max} 680 nm) vs. time at 25 °C was recorded for [**3**] = 1.5×10^{-2} M, [MeO^-] = 1.3×10^{-2} M, and [Bz] = 3.08×10^{-1} M (20.5 equiv). The observed second-order rate constant (calculated in the above manner) of 2.1 M^{-1} s^{-1} was within the range of observed rate constants in the absence of axial base.

(iv) Effect of N_2O on the Observed Kinetics. A 1.24×10^{-2} M solution of **3** in methanol was bubbled for 5 min with N_2O before addition of methoxide ([MeO^-] = 1.1×10^{-2}). Following the growth of Co(II), the observed second-order rate constant of 2.70 M^{-1} s^{-1} at 22.5 °C was obtained, similar to those obtained in the absence of N_2O.

(v) Effect of Nitroxide on the Observed Kinetics. The effects of the nitroxide (**9**) on the methanolysis kinetics of **3** were examined at 22.5 °C ([**3**] = 1.30×10^{-2} M, [MeO^-] = 1.11×10^{-2} M, [**9**] = 1.30×10^{-2} M; [**3**] = 1.24×10^{-2} M, [MeO^-] = 1.11×10^{-2} M, [**9**] = 1.24×10^{-2} M; [**3**] = 8.90×10^{-3} M, [MeO^-] = 1.32×10^{-2} M, [**9**] = 8.90×10^{-3} M), and at 25 °C ([**3**] = 9.30×10^{-3} = [MeO^-] = [**9**]). The kinetics were identical within experimental error with those without nitroxide (Table I, entries 6–8, 26).

(vi) Effect of I^- on the Observed Kinetics. The methanolysis kinetics were performed in the presence of excess $(n\text{-}Bu)_4N^+I^-$ at 22.5 °C. The observed second-order rate constants of 4.09 and 1.72 M^{-1} s^{-1} ([**3**] = 1.33×10^{-2} M, [MeO^-] = 9.3×10^{-3} M, [I^-] = 1.33 M; [**3**] = 2.00×10^{-2} M, [MeO^-] = 9.3×10^{-3} M, [I^-] = 2.0 M) demonstrate no major effect of added I^- upon the observed kinetics.

(C) Control with R–$Co[C_2(DO)(DOH)_{pn}]X$ and MeO^-. A solution of 5.0 mg of $(n\text{-}C_4H_9)Co[C_2(DO)(DOH)_{pn}]Br$ in 1.0 mL of CD_3OD was treated with 1 equiv of 0.5 M NaOD/CD_3OD. Over 1 h, no loss of the cobalt(III)alkyl (λ_{max} 475 nm) and only a decrease in the δ 2.5 (–N=C(CH_3)) signal (presumably due to deuterium exchange) were observed.

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No cobalt(II) was produced in this reaction.

(D) **Methanolysis of 3 in the Presence of Nitroxide.** A solution of 5.0 mg of **3** and 2.0 mg of the nitroxide (**9**) in 1.0 mL of CD_3OD was treated with 1.0 equiv of 0.50 M $NaOD/CD_3OD$. After 2 min the products were analyzed by IR, visible, and GC and included 90 ± 10% Co(II) (λ_{max} 520 nm), 100 ± 10% $CH_3OCO_2CH_3$ (ν_{CO} = 1755 cm^{-1}), N-hydroxy-2,2,6,6-tetramethylpiperidone (ν_{CO} = 1709 cm^{-1}) in a 70% isolated yield (following air-free chromatography (Al_2O_3/THF) in the drybox) in comparison to authentic material, and no (<5%) CH_3CHO and $CH_3OCO_2^-$. Air oxidation of the cobalt(II) products followed by examination of the ^1H NMR spectrum provided no additional useful information.

The above reaction was repeated with the modification that the solution was neutralized with 1 μL of concentrated HCl. The ^1H NMR spectrum of the resulting products included 26 ± 5% $HOCH_2CHO$ (as its CD_3OD hemiacetal), δ 3.44 (d, 2 H), 4.32 (t, 1 H).

In a control experiment, the base sensitivity of the observed glycoaldehyde product was tested. Glycoaldehyde (5 mg) was dissolved in CD_3OD (1.0 mL) and the ^1H NMR spectrum was taken before and after addition of 1 equiv of $NaOD/CD_3OD$. It was observed that if 1 μL of concentrated HCl was added 2 min after treatment with base, 40 ± 5% of the starting glycoaldehyde remained. Using this correction factor, the observed glycoaldehyde yield in the **3** + **9** methanolysis can be placed at about 65%.

Methanolysis of **3** with 0.5 and 1.5 equiv of methoxide in the presence of 1.05 equiv of **9** and with 3.0 equiv of **9** resulted in similar products to those reported above, where the corrected glycoaldehyde yields never exceeded 65%.

In two additional control experiments, the effect of **9** on acetaldehyde and the effect of **3** on the ESR spectrum of **9** were determined. To 1.0 mL of a standard 1.1 × 10^{-2} M solution of CH_3CHO/CH_3OH was added 2.0 mg of **9** and 1.0 equiv of MeO^-. After 2 min, 60 ± 10% CH_3CHO remained (GC). The ESR spectrum of **9** (4.0 mg/4.0 mL, 5.9 × 10^{-3} M) with and without 2.5 mg (0.24 equiv) of **3** was examined. Both samples gave identical three-line spectra, g = 2.0076, a_n = 12.5 G.

(E) **Methanolysis of 3 in the Presence of 1,5,6-Trimethylbenzimidazole.** To 1.0-mL aliquots of a 1.1 × 10^{-2} M solution of **3** in methanol were added 0, 0.25, 0.4, 0.8, 1.0, 1.6, 3.9, 7.0, 10, 12, 17, and 25 equiv of 1,5,6-trimethylbenzimidazole (Bz). Methoxide (1.0 equiv) was added, and after 2 min at room temperature the products were analyzed by GC, IR, and visible spectroscopy. The results of these experiments were as follows: (0 equiv of Bz) 0% Co(I), 100% Co(II), 61% CH_3CHO, 50% $CH_3OCO_2CH_3$, and 50% $CH_3OCO_2^-$; (0.25 equiv of Bz) 42% CH_3CHO, 53% $CH_3OCO_2CH_3$, and 47% $CH_3OCO_2^-$; (0.4 equiv of Bz) 14% Co(I) and 86% Co(II); (0.8 equiv of Bz) 29% Co(I) and 71% Co(II); (1.0 equiv of Bz) 36% CH_3CHO, 57% $CH_3OCO_2CH_3$, and 43% $CH_3OCO_2^-$; (1.6 equiv of Bz) 47% Co(I) and 53% Co(II); (3.9 equiv of Bz) 54% Co(I), 46% Co(II), 23% CH_3CHO, 71% $CH_3OCO_2CH_3$, and 29% $CH_3OCO_2^-$; (7 equiv of Bz) 65% Co(I) and 35% Co(II); (10 equiv of Bz) 10% CH_3CHO; (12 equiv of Bz) 90% $CH_3OCO_2CH_3$ and 10% $CH_3OCO_2^-$; (17 equiv of Bz) 81% Co(I), 19% Co(II), and 60% CH_3CHO; and (25 equiv of Bz) 89% Co(I), 11% Co(II), <5% CH_3CHO, 100% $CH_3OCO_2CH_3$, and 0% $CH_3OCO_2^-$.

Control experiments for the acetaldehyde yields were performed by treating 1.0-mL aliquots of standard 1.1 × 10^{-2} M acetaldehyde in methanol with varying amounts of Bz and 1.0 equiv of methoxide. The observed yields (equiv of Bz) were the following: 80 ± 5% (0 equiv), 70 ± 5% (5 equiv), 60 ± 5% (10 equiv), and 45 ± 10% (25 equiv).

The search for glycoaldehyde in the above reaction was performed at 1.1–2.2 × 10^{-2} M **3** in CD_3OD, using both pyridine and 1,5,6-trimethylbenzimidazole as the axial base. The 360-MHz ^1H NMR experiments demonstrated that even using the acid-quench technique developed for the detection of glycoaldehyde (vide ante), glycoaldehyde decomposed too fast in the presence of 10–25 equiv of axial base and 1 equiv of methoxide to be detected. Therefore, in both the methanolysis reactions and in control experiments with 1.1 × 10^{-2} M $HOCH_2CHO/CD_3OD$ + 25 equiv of axial base, no glycoaldehyde survived the reaction conditions.

The possibility of acetic acid or acetate being produced as a product was ruled out by adding these substances to the reaction mixtures and comparing ^1H NMR spectra before and after. A significant point is that there is no other molecule of the formula $C_2H_4O_2$ other than glycoaldehyde that is a reasonable product in the above methanolyses. As with acetic acid, ethylene glycol was also ruled out as a major product (<5%) in these reactions.

(F) **Tests for Co(I) and Co(III) Pathways. (i) N_2O Trapping Experiments.** The literature indicates that Co(I) but not Co(II) is oxidized by N_2O. To test this, a solution of Co(I) was prepared. A solution of 5 mg of $Co[C_2(DO)(DOH)_{pn}]I_2$ in 1.0 mL of methanol was treated with 2 mg of $NaBH_4$. The resultant blue solution of cobalt(I) was bubbled for 30 s with N_2O and rapidly turned yellow. An end absorption (ca. 300 nm) was the only discernible peak in the visible spectrum of the yellow product solution.

To a 1.1 × 10^{-2} M solution of **3** in methanol was added 1 equiv of base. After 2 min the burgundy red solution of cobalt(II) was bubbled for 30 s with N_2O, and the products were analyzed. The N_2O did not affect any of the observed products.

A solution of 5 mg of **3**/1.0 mL of CH_3OH was bubbled with N_2O for 30 s and then 1.0 equiv of MeO^- was added. After 2 min the products were analyzed by GC and visible and IR spectroscopy, and the products included 55 ± 10% CH_3CHO, 50 ± 10% $CH_3OCO_2CH_3$, 50 ± 10% $CH_3OCO_2^-$, and 100 ± 5% $Co^{II}[C_2(DO)(DOH)_{pn}]Cl$.

(ii) **The Effect of Added Co(III).** To a solution of 5 mg of **3**/1.0 mL of CH_3OH were added $Co[C_2(DO)(DOH)_{pn}]I(PF_6)$ (11 mg, 1.6 equiv) and then 1.0 equiv of MeO^-. The observed products were 60% CH_3CHO, 50% $CH_3OCO_2CH_3$, 50% $CH_3OCO_2^-$, and 100% Co(II), i.e., unchanged by the presence of Co(III).

(G) **Additional Experiments with $(OHCCH_2)Co[C_2(DO)(DOH)_{pn}]I$ (6). (i) Methanolysis of 3 in the Presence of 6.** A solution of 5 mg of **3** and 5 mg (0.9 equiv) of **6** in 1.0 mL of CH_3OH was treated with 12 μL (1.0 equiv) of the standard KOH/CH_3OH base solution. After 2 min the products were determined to be 180 ± 10% Co(II) (based on **3**), 50% $CH_3OCO_2CH_3$, 50% $CH_3OCO_2^-$, and 60% CH_3CHO, but no formylmethyl complex (ν_{CO} = 1650 cm^{-1}, λ_{max} 392 nm, ^1H NMR δ 8.97, 1.56).

The above experiment was repeated with 10 mg of **6** (1.8 equiv), and the observed products included 180 ± 10% Co(II) (based on **3**), 50% $CH_3OCO_2CH_3$, 50% $CH_3OCO_2^-$, 60% CH_3CHO, and 80 ± 10% of the formylmethyl complex (ν_{CO} = 1650 cm^{-1}, λ_{max} 392 nm, ^1H NMR δ 8.97, 1.56).

(ii) **Methanolysis of 3 in the Presence of 6 and Nitroxide.** A solution of 5 mg of **3**, 5 mg of **6**, and 2 mg of the nitroxide **9** in 1.0 mL of CH_3OH was treated with 1.0 equiv of the standard methoxide solution. After 2 min the products included 80 ± 10% Co(II) (λ_{max} 520 nm), 50 ± 20% (70 ± 30% when corrected for expected decomposition) of the formylmethyl complex **6** (ν_{CO} = 1650 cm^{-1}, λ_{max} 392 nm, ^1H NMR δ 8.97, 1.56), 100% $CH_3OCO_2CH_3$ (ν_{CO} = 1755 cm^{-1}), and no detectable (<5%) CH_3CHO or $CH_3OCO_2^-$.

(iii) **Methanolysis of 3 in the Presence of 6 and 1,5,6-Trimethylbenzimidazole.** A solution of 5 mg of **3**, 5 mg of **6**, and 45 mg (25 equiv) of 1,5,6-trimethylbenzimidazole in 1.0 mL of CH_3OH was treated with 1.0 equiv of the standard methoxide solution. After 2 min the observed products included 80 ± 10% Co(I) (λ_{max} 680, 580 nm), 20 ± 5% Co(II) (λ_{max} 520), 100 ± 10% $CH_3OCO_2CH_3$ (ν_{CO} = 1755 cm^{-1}), no (<5%) CH_3CHO or $CH_3OCO_2^-$, and 80 ± 5% of the formylmethyl complex (ν_{CO} = 1630 cm^{-1}). The IR shift from 1650 cm^{-1} to 1630 cm^{-1} for the formylmethyl complex in the presence of the axial base was confirmed by adding 45 mg of 1,5,6-trimethylbenzimidazole to a solution of 5 mg of **3**/1.0 mL of CH_3OH.

(iv) **Electrochemistry of the Co(II)/Co(I) Couple.** In order to better understand the axial base effect on the methanolysis of **3**, the electrochemistry of the reduction of Co(II) to Co(I) was studied by cyclic voltammetry with and without 1,5,6-trimethylbenzimidazole.

In a three-electrode cell (platinum bead working, platinum wire auxiliary, and silver wire pseudo reference electrode) in the drybox was placed 5.0 mL of an electrolyte solution (330 mg $(n\text{-}C_4H_9)_4N^+PF_6^-$/10.0 mL of CH_3OH). To this solution was added 2.0 mg of $Co^{II}[C_2(DO)(DOH)_{pn}]Br$ to give a 1.0 × 10^{-3} M solution. The cyclic voltammogram of this solution was then obtained by scanning 0 to −1.2 V. Next, 50 mg (30 equiv) of 1,5,6-trimethylbenzimidazole was added, and the cyclic voltammogram was retaken. Ferrocene was then added as an internal standard and its reversible oxidation wave obtained $E_{1/2}$ = +0.56 V (Ag wire). This cyclic voltammogram was repeated outside of the drybox with the identical solution, measuring the ferrocene/ferrocinium couple vs. the saturated calomel electrode, $E_{1/2}$ = +0.35 V (SCE). Using this internal standard, the reduction potentials without axial base (−0.86 V (SCE), ip_a/ip_c = 0.73, ΔE_p = 64 ± 2 mV) and with added trimethylbenzimidazole (−0.69 V (SCE), ip_a/ip_c = 0.87, ΔE_p = 66 ± 2 mV) were obtained.

(H) **Attempted Trapping of Solvent-Derived Radicals with Cobalt(III) Alkyls. (i) Search for $HOCH_2CH_2CHO$ and $CH_2{=}CHCHO$.** A solution of 5 mg of **3**, 10 mg of **6** and 1.0 mL of CH_3OH was treated with 1.0 equiv of standard methoxide solution and the products were analyzed by IR and UV spectroscopy. No acrolein (ν_{CO} = 1695 cm^{-1}, λ_{max} 210, 315 nm) was detected in this reaction.

In a control experiment, a 1 × 10^{-2} M solution of acrolein/methanol was prepared by distilling 7 μL of acrolein into 10 mL of CH_3OH. To 1.0 mL of this solution was added 12 μL (1.0 equiv) of the standard methoxide solution, and the reaction mixture was examined by IR and UV after 2 min. No acrolein was detected in these controls.

A solution of 5 mg of **3**, 5 mg of **6** and 1.0 mL of CD_3OD was treated with 1.0 equiv of standard methoxide solution. After 2 min, the co-

balt(II) product was oxidized to Co(III) with 10 μL of $BrCCl_3$, and the ^1H NMR spectrum was taken. No peaks assigned as β-hydroxypropionaldehyde or the expected dehydration product, acrolein, were obtained.

(ii) **Attempted Use of Cobalt Alkyls as Traps.** A solution of 5 mg of **3** and 5 mg of $(PHCH_2)Co[C_2(DO)(DOH)_{pn}]I$ in 1.0 mL of CH_3OH was treated with 1.0 equiv of standard methoxide solution. After 2 min the products included 100% Co(II) (based on **3**), 50% $CH_3OCO_2CH_3$, 50% $CH_3OCO_2^-$, and 60% CH_3CHO. Oxidation of the Co(II) with 10 μL of $BrCCl_3$ and ^1H NMR analysis showed ca. 100% of the Co(III)-benzyl complex to be intact (δ 2.5 (s, 2 H, $PhCH_2$-CO), 6.6-7.3 (m, 5 H, $PhCH_2$-CO)).

A solution of 5 mg of **3** and 5 mg of $(CH_2{=}CHCH_2)Co[C_2(DO)(DOH)_{pn}]Br$ (ca. 90% pure) in 1.0 mL of CH_3CHO was treated with 1.0 equiv of standard methoxide solution. After 2 min the products included 100% Co(II), 60% CH_3CHO, 50% $CH_3OCO_2CH_3$, and 50% $CH_3OCO_2^-$. Upon $BrCCl_3$ oxidation and workup, the allyl complex had decomposed (the δ 4.58, 5.00 peaks were absent).

(iiii) **Use of $PhCH_2OH$ as a Solvent. Attempted $PhCHOH$ Trapping by Co-CH_2CHO.** With the hope of generating the more stable trapping product, PhCH=CHCHO, benzyl alcohol was used as the solvent. A solution of 5 mg of **3** and 10 mg of **6** in 1.0 mL of $PhCH_2OH$ (purified by the described procedure[1]) was treated with 1.0 equiv of standard base. After 30 min, the observed products included 80% Co(II) and ca. 180% **6**; i.e., the formylmethyl complex did not react with the $PhCHOH$ generated under the reaction conditions. This result is consistent with Espenson's observations[25a] that $\cdot C(CH_3)_2OH$, but not $PhCH_2\cdot$, show apparent S_H2 reactions with RCo complexes (R = $PhCH_2$- in Espenson's case).

(I) **Search for $\cdot CH_2CHO$.** The intermediacy of the proposed $\cdot CH_2CHO$ radical was probed by the attempted trapping by Co(II) and by the use of deuterated solvent.

(i) **Co(II) Trapping.** A solution of 5 mg of **3** and 20 mg (4.5 equiv, the limit of solubility) of $Co^{II}[C_2(DO)(DOH)_{pn}]Br$ in 1.0 mL of CH_3OH was treated with 1 equiv of standard methoxide solution, and the products were analyzed by GC, IR, and visible spectroscopy. Aside from the large amount of Co(II), the products were unaffected by the Co(II): 50% $CH_3OCO_2CH_3$, 50% $CH_3OCO_2^-$, and a normal, ~60% CH_3CHO.

(ii) **Solvent Isotope Effect.** Solutions of 5 mg of **3** in 1.0 mL CH_3OH, CD_3OH, and CD_3OD were all treated with 1.0 equiv of the appropriate solvent conjugate bases, and the products were analyzed by GC, IR, and visible spectroscopy. Identical product yields of 60% CH_3CHO, 50% $CH_3OCO_2^-$, 50% $CH_3OCO_2CH_3$, and 100% Co(II) were obtained (or their deuterated analogues).

(J) **Methanolysis of 3 in the Presence of Both Nitroxide and 1,5,6-Trimethylbenzimidazole.** In order to try to determine the relative order of the nitroxide and axial base effects on the methanolysis of **3**, i.e., whether they affect the same or different intermediates, the deprotection was run in the presence of both reagents.

A solution of 5 mg of **3**, 1 mg (1 equiv) of the nitroxide **9**, and 45 mg (25 equiv) of 1,5,6-trimethylbenzimidazole in 1.0 mL of CH_3OH was treated with 12 μL (1 equiv) of the standard methoxide solution. The observed reaction products included 90% Co(II) (λ_{max} 520 nm), ca. 100% *N*-hydroxy-2,2,6,6-tetramethylpiperidone (ν_{CO} = 1709 cm^{-1}), 100% $CH_3OCO_2CH_3$ (ν_{CO} = 1755 cm^{-1}), and no (<5%) CH_3CHO.

In a control experiment a solution of 5 mg of **3** and 45 mg of 1,5,6-trimethylbenzimidazole in 1.0 mL of CH_3OH was treated with 1.0 equiv of standard base. After 2 min the resultant blue Co(I) solution was treated with 1 mg of the nitroxide **9**, which gave rise to an immediate reaction producing 100% Co(II), λ_{max} 520 nm. This control shows that it is impossible to tell whether Co(I) or Co(II) is first produced in this experiment, and therefore, whether or not the axial base effect precedes the nitroxide trapping effect in the methanolysis reaction.

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Registry No. 3, 75504-42-6; **6**, 87728-42-5; **9**, 2896-70-0; **10**, 3637-11-4; $ICo[C_2(DO)(DOH)_{pn}]PF_6$, 87728-35-6; $ICo[C_2(DO)(DOH)_{pn}]I$, 75962-04-8; $(CH_2{=}CHCH_2^-)Co[C_2(DO)(DOH)_{pn}]Br$, 87728-48-1; $(OC)Co[C_2(DO)(DOH)_{pn}]Br$, 87728-49-2; $AgPF_6$, 26042-63-7; allyl bromide, 106-95-6; ethylene carbonate, 96-49-1; diol dehydratase, 9026-90-8.

On the Structure and Stability of 1,3-Dilithiopropanes and Other α,ω-Dilithioalkanes. The Importance of LiH Complexes as Structural Alternatives and Reaction Intermediates

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Abstract: A doubly lithium bridged struture (**3**) is found by ab initio theory (3-21G basis set) to be the lowest-energy geometry of 1,3-dilithiopropane. This form exhibits considerable thermodynamic stability, e.g., opening to an extended conformation (**6**) is endothermic by 24.6 kcal/mol and disproportionation with propane into 2 mol of *n*-propyllithium is calculated to require 19.4 kcal/mol. Doubly bridged structures like **3** are the intramolecular equivalent of organolithium dimers, and the stabilization energy of **3** is about half that for methyllithium dimerization. On the other hand, elimination of LiH from 1,3-dilithiopropane (**3**) is more favorable than from primary alkyllithiums, in agreement with experimental observations. Conversion of **3** to an allyllithium-LiH complex, **8** (a possible elimination intermediate), is exothermic by 29.0 kcal/mol whereas the ethylene-LiH complex (**13**) is 7.2 kcal/mol less stable then ethyllithium. The corresponding vinyllithium-LiH complex (**15**) is 29.8 kcal/mol more stable than the most favorable 1,2-dilithioethane geometry (**14**). While the second lithiations of ethane and of propane are favorable thermodynamically, both 1,2-dilithioethane and 1,3-dilithiopropane are unstable toward conversion to LiH complexes. When such eliminations are blocked structurally or the carbanionic sites substituted by stabilizing groups, vicinal and 1,3-dilithio derivatives can be expected. Truncated basis sets were employed to investigate the role of lithium p and valence orbitals in bonding. While electrostatic interactions (ion triplets) are most important, some multicenter covalent character is also indicated. MNDO structures for the dimers of the α,ω-dilithioalkanes indicate opened tetrahedral arrangements. Unlike the lower homologues, the doubly bridged form (**20**) of 1,4-dilithiobutane is indicated to be stable thermodynamically toward elimination to a 3-butenyllithium-LiH complex (**22**). This explains why the higher α,ω-dilithioalkanes are more readily accessible as synthetic reagents.

In their classical study of the lithiation of α,ω-dibromoalkanes, West and Rochow[1] were able to prepare 1,4-dilithiobutane and higher α,ω-dilithioalkanes but not 1,2-dilithioethane or 1,3-dilithiopropane. While 1,2-dilithioethane is still unknown,[2] Seetz,

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