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Reductive Defluorination of (Trifluoromethyl)cobamides[1]

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The ^{19}F NMR spectrum of base-on β-(difluoromethyl)cobalamin, previously reported as a broad singlet or as a doublet, has now been shown to be a severely collapsed AB quartet of doublets. Similarly, the α-fluorines of a variety of perfluoroethylcobamides and of the diastereomers of difluoromethyl heptamethylcobyrinate also display AB patterns. When (trifluoromethyl)cobamides are treated with zinc reductants in a variety of media, or subjected to controlled-potential reduction in buffered aqueous media at potentials between −1.0 and −1.2 V, the (trifluoromethyl)cobamide disappears with simultaneous appearance of the appropriate (difluoromethyl)cobamide and the dealkylated cobamide. Under all of these conditions, the rates of disappearance of the starting material and the rates of appearance of the defluorinated and dealkylated products are identical. However, controlled-potential reduction in DMF/1-propanol resulted only in dealkylation. Dealkylation in these systems is shown to result from reduction of the (trifluoromethyl)cobamides, as the (difluoromethyl)cobamides are indefinitely stable to reductive dealkylation by any of these reducing agents. Similar defluorination and dealkylation of (trifluoromethyl)cobamides occur with borohydride, but the defluorination yields are lower. When (trifluoromethyl)cobalamins are treated with zinc in 10% acetic acid-*d*, the (difluoromethyl)cobalamin products contain a single, nonexchangeable deuterium atom in the difluoromethyl ligand as demonstrated by ^{19}F, ^{1}H, and ^{2}H NMR spectroscopy. However, reduction with $NaBH_4$ in D_2O yields the nondeuterated derivatives, while reduction with $NaBD_4$ in H_2O yields the deuterated derivatives. Controlled-potential coulometry experiments show that the net defluorination of β-(trifluoromethyl)cobalamin results from the consumption of two electrons. These results are consistent with an ECE mechanism for reductive defluorination of (trifluoromethyl)cobamides by zinc reductants and by controlled-potential reduction, but the defluorination of these complexes by borohydride must occur by an entirely different mechanism.

Introduction

Reductive dehalogenation of α-(haloalkyl)cobalt complexes was first described by Ricroch et al.[2,3] for α-(haloalkyl)cobaloximes and (trifluoromethyl)cobaloximes. In the latter case, treatment of $CF_3Co(D_2H_2)L$[1] with $NaBH_4$ was reported to yield $CH_3Co(D_2H_2)L$ via (difluoromethyl)- and (fluoromethyl)cobaloxime intermediates, indicating that a stepwise defluorination can occur.[4] We have previously reported[9,10] that reductive alkylation of cobalt corrins with CF_3I leads to mixtures of (trifluoromethyl)- and (difluoromethyl)cobamides,[11] although (fluoromethyl)- and methylcobamides are not observed. As is the case with other alkylating agents,[10,13] reductive alkylation of cobalamin or cobinamide with CF_3I leads to mixtures of β-alkylcobamides (i.e., with the organic ligand in the "upper" axial ligand position) and α-alkylcobamides (with the organic ligand in the "lower" axial ligand position). Such reductive alkylations thus lead to complicated mixtures of products, but separation, purification, and characterization of the α- and β-CF_3- and α- and β-CF_2HCbl's[1] and the α- and β-CF_3- and α- and β-CF_2HCbi's[1] have been acheived.[10] We now report the results of a study of the direct defluorination of CF_3Cba's[1] by chemical reductants and by controlled-potential reduction.

Reductive dehalogenation of $CFCl_3$, CF_2Cl_2, and CF_3Cl to CO (and, in the case of $CFCl_3$, to intermediate halomethanes) by titanium(III) catalyzed by corrinoids was recently reported by Hogenkamp et al.[12] These authors proposed mechanisms in which reductive dealkylation of initially formed (halomethyl)cobamides leads to products via free dihalocarbenes. Our earlier observations of apparent defluorination of CF_3Cba's by zinc and borohydride reductants[9,10] have consequently prompted us to examine the possibility that reductive defluorination of CF_3Cba's is involved in the reductive dehalogenation of CF_3Cl catalyzed by cobamides.

Experimental Section

CF_3- and CF_2HCba's were synthesized from H_2OCbl or factor B[14] (prepared by the method of Renz[15]) using CF_3I as previously described.[10] For preparations of β-CF_3Cbl, the yield of this complex was maximized by the following modification. H_2OCbl (100 mg, 0.074 mmol) in methanol (20 mL) was purged with argon for 1 h. Zinc wool (100 mg, freshened briefly with dilute HCl) was added, and the reduction was allowed to occur for 30 min. Gaseous CF_3I was introduced into the system by slow bubbling while the reaction mixture was stirred for 40 min at room temperature. β-CF_3Cbl was purified by preparative HPLC as described previously[10] (yield, 55%). The CF_3CF_2Cba's were prepared similarly using CF_3CF_2I. Heptamethyl dicyanocobyrinate and its alkylated derivatives were prepared by the method of Murakami et al.[16]

Analytical HPLC was performed with a 4.6 × 250 mm Beckman C8 Ultrasphere column as described previously.[10,13,17] UV-visible spectra were recorded on a Cary 219 recording spectrophotometer, and all cobamides were quantitated by conversion to their dicyano derivatives ($\epsilon_{368} = 3.04 \times 10^4\ M^{-1}\ cm^{-1}$)[18] by aerobic photolysis in excess cyanide. The binding constant for pyridine and β-CF_2HCbi was determined by spectrophotometric titration at 540 nm.[19] NMR spectra were obtained on a GE QE 300 or Bruker AMX 300 NMR spectrometer using as references external fluorobenzene (^{19}F), external TSP (^{1}H), and natural-abundance solvent (H_2O) deuterium (^{2}H, $\delta = 4.67$ ppm). pH values were measured on a Radiometer PHM 84 pH meter equipped with a Radiometer type C combined electrode. Electrochemical experiments were conducted with a Bioanalytical Systems CV-27 voltammograph using a

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(1) Abbreviations: $RCo(D_2H_2)L$, alkyl(ligand)cobaloxime = alkyl(ligand)bis(dimethylglyoximato)cobalt(III); Cba, cobamide; H_2OCbl, aquocobalamin; β-RCbl, β-alkylcobalamin; α-RCbl, α-alkylcobalamin; $(H_2O)_2Cbi$, diaquocobinamide; β-RCbi, β-alkylcobinamide; α-RCbi, α-alkylcobinamide; Me_7Cby, heptamethyl cobyrinate; β-RMe_7Cby, heptamethyl β-alkylcobyrinate; α-RMe_7Cby, heptamethyl α-alkylcobyrinate; CAPS, 3-(cyclohexylamino)propanesulfonic acid.

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Table I. NMR Spectroscopic Data for (Fluoroalkyl)cobamides

R	cobamide	solvent	T, °C	$\delta_{^{19}F}$, ppm[a]	$\Delta\delta_{^{19}F}$, ppm[b]	$^2J_{FF}$, Hz	$^2J_{HF}$, Hz
CF_2H	α-Cbi	10% D_2O[c]	25	23.63, 26.62	2.99	156.5	53.6
	β-Cbi	10% D_2O[c]	25	24.96, 26.99	2.03	149.1	54.0
		10% D_2O/0.5 M py[d]	25	20.25, 22.02	1.77	172.2	53.5
	α-Cbl	10% D_2O[c]	25	23.13, 26.40	3.27	155.3	48.0
		DMSO-d_6	25	24.42, 26.86	2.44	158.4	53.0
		DMSO-d_6	110	26.69, 28.56	1.87	154.0	54.1
	β-Cbl, base-on	10% D_2O[c,e]	25	18.36, 18.55	0.19	181.3	54.1
		DMSO-d_6	25	17.52, 18.10	0.58	182.3	56.4
		DMSO-d_6	75	18.59, 19.26	0.67	177.0	53.8
	β-Cbl, base-off	1.0 M HCl[c,f]	25	25.40, 27.17	1.77	148.4	53.5
CF_3CF_2	α-Cbi	10% D_2O	25	27.85, 30.80, 35.23 (s)	2.95	208.0	
	β-Cbi	10% D_2O	25	21.84, 23.24, 32.33 (s)	1.40	183.2	
	α-Cbl	10% D_2O	25	27.55, 31.01, 35.39 (s)	3.46	204.9	
	β-Cbl, base-on	10% D_2O	25	15.94, 16.37, 32.82 (s)	0.43	244.0	
		DMSO-d_6	25	15.93, 16.17, 32.21 (s)	0.24	231.4	
	β-Cbl, base-off	1.0 M HCl[f]	25	22.00, 23.36, 32.35 (s)	1.36	231.4	
CF_2H	α-Me_7Cby[g]	C_6D_6	25	23.48, 26.28	2.80	161.6	53.2
	β-Me_7Cby[g]	C_6D_6	25	23.16, 24.56	1.40	160.0	54.0
CF_2D	α-Cbl[h]	10% D_2O	25	22.34, 25.62[i]	3.28	162.7	
	β-Cbl, base-on[j]	10% D_2O	25	17.74 (s)[k]			
	β-Cbl, base-off[j]	1.0 M HCl[f]	25	24.73, 26.71[i]	1.98	147.2	

[a] AB quartet of doublets, unless otherwise indicated. Chemical shifts relative to external C_6H_5F. [b] $\Delta\delta_{^{19}F} = \delta_{^{19}F_A} - \delta_{^{19}F_B}$. [c] Reference 10. [d] In this solvent, the complex is 91% α-(py)-β-(CF_2H)Cbi (K_{assn} = 21.3 M^{-1}). [e] ^1H NMR: CF_2H, 5.08 ppm (t, $^2J_{HF}$ = 53.1 Hz). [f] Locked to D_2O in a concentric insert. [g] Tentatively assigned on the basis of ^{19}F chemical shift and $\Delta\delta_{^{19}F}$. [h] ^2H NMR: CF_2D, 4.62 ppm (s). [i] AB quartet; D–F coupling not resolved. [j] ^2H NMR: CF_2D, 5.04 ppm (s). [k] Incipient F–F coupling not resolved.

Ag/AgCl (satd), KCl (satd) reference electrode. Reduction potentials are reported as the cathodic peak potentials from cyclic voltammetry in 0.05 M CAPS[1] buffer, 0.5 M KCl, using a 200 mV s^{-1} sweep rate and a hanging mercury drop electrode. Controlled-potential reduction and coulometery experiments were performed with the same equipment in 0.05 M aqueous phosphate buffer, 0.5 M KCl, in 0.05 M aqueous CAPS buffer, 0.5 M KCl, or in DMF/1-propanol (50% v/v), 0.2 M tetrabutylammonium iodide, using a mercury pool electrode.

Reductive defluorination reactions were monitored by analytical HPLC. Samples were taken at appropriate time intervals and immediately frozen in a dry ice/acetone bath. Reaction products were quantitated using the averaged values of chromatogram integrations obtained by UV detection at 254 and 350 nm, correcting for differences in molar absorptivities as described previously.[10]

Results

NMR Spectra of (Fluoroalkyl)cobamides. We have previously reported[10] that while the ^{19}F NMR spectra of base-off β-CF_2HCbl, α-CF_2HCbl, and both α- and β-CF_2HCbi display an AB quartet of doublets as expected for these diastereotopic fluorines, the spectrum of base-on β-CF_2HCbl appears as an anomalous doublet (Table I). Hogenkamp et al.[12] have also recently reported a doublet ^{19}F spectrum for base-on β-CF_2HCbl. As the anomalous spectrum appears for the only compound without a trans axial water ligand, the spectrum of the complex of β-CF_2HCbi with pyridine as an axial ligand (i.e., α-(py)-β-(CF_2H)-Cbi) was obtained in a solution of β-CF_2HCbi in 0.5 M pyridine (K_{assn} = 21.3 M^{-1}, 91% complexed in 0.5 M pyridine). This spectrum was an AB quartet of doublets (Table I) with a slightly smaller difference in fluorine chemical shifts ($\Delta\delta_{^{19}F}$ = 1.77 ppm) than that of β-CF_2HCbi($\Delta\delta_{^{19}F}$ = 2.03 ppm). Interestingly, the ^{19}F spectrum of β-CF_2HCbl in DMSO-d_6 was a partially collapsed AB quartet of doublets with $\Delta\delta_{^{19}F}$ = 0.58 ppm despite the fact that it remained base-on in this solvent, as determined spectrophotometrically. The difference in fluorine chemical shift increased with temperature (Table I, $\Delta\delta_{^{19}F}$ = 0.67 ppm at 75 °C). Strangely, α-CF_2HCbl had a smaller difference in ^{19}F chemical shift in DMSO-d_6 (2.44 ppm) than in 10% D_2O (3.27 ppm) and the $\Delta\delta_{^{19}F}$ decreased with increasing temperature (Table I). For comparison, the ^{19}F spectra of α- and β-CF_3CF_2Cbl and α- and β-CF_3CF_2Cbi were also observed (Table I). For all of these compounds the CF_2 resonance was an AB quartet (the vicinal ^{19}F–^{19}F coupling being unresolved) although the difference in geminal ^{19}F chemical shifts for base-on β-CF_3CF_2Cbl was quite small ($\Delta\delta_{^{19}F}$ = 0.43 ppm) and decreased in DMSO-d_6 ($\Delta\delta_{^{19}F}$ = 0.24 ppm). The CF_3 resonances occurred as singlets at 32.3–35.2 ppm. For both the CF_2H- and CF_3CF_2 series of compounds, the value of $\Delta\delta_{^{19}F}$ decreased in the order α-Cbl > α-Cbi > β-Cbi ~ base-off β-Cbl > base-on β-Cbl. Reductive alkylation of heptamethyl dicyanocobyrinate (i.e., $(CN)_2Me_7$Cby[1]) with CF_3I also produced a pair of diastereomeric CF_2H complexes. While these were not separated and further characterized, each generated a ^{19}F spectrum which was an AB quartet of doublets, tentatively assigned on the basis of chemical shift and $\Delta\delta_{^{19}F}$ values (Table I).

The diastereomeric, deuterated derivatives, α- and β-CF_2DCbl, were also prepared (vide infra). The ^{19}F spectrum of base-on CF_2DCbl was a broad ($\Delta\nu_{1/2}$ ~ 23 Hz) non-Gaussian singlet, indicating the existence of the unresolvable[20] D–F coupling. The ^{19}F spectra of both base-off β-CF_2DCbl and α-CF_2DCbl were AB quartets (Table I). Finally, examination of the ^{19}F spectrum of a concentrated sample of base-on β-CF_2HCbl in D_2O, for which over 36 000 transients were collected, revealed that it is indeed a severely collapsed AB quartet of doublets in which the fluorine chemical shifts differ by only 0.19 ppm (Table I), easily giving the appearance of a doublet in spectra with lesser signal-to-noise ratios.

Comparison of the ^1H NMR spectra of β-CF_2HCbl and β-CF_2DCbl permits location of the CF_2H proton resonance which appears as a triplet at 5.08 ppm ($^2J_{HF}$ = 53.1 Hz). Similarly, the ^2H resonance of β-CF_2DCbl appeared as a broad singlet at 5.04 ppm, the anticipated D–F coupling (ca. 8 Hz)[20] being unresolvable.

Reductive Defluorination of CF_3Cba's. When any of the four CF_3Cba's is treated with Zn/20% H_3PO_4, Zn/10% CH_3COOH, or Zn/10% NH_4Cl or is electrochemically reduced in aqueous solution at potentials of −1.0 to −1.2 V under anaerobic conditions, the starting CF_3Cba gradually disappears with simultaneous appearance of the analogous CF_2HCba and (after aerobic sampling) the dealkylation product, H_2OCbl or $(H_2O)_2$Cbi. An example of such a reaction is shown in Figure 1 for the controlled-potential reduction of β-CF_3Cbl at −1.20 V in aqueous solution. For the zinc reductants, the yields of CF_2HCba's were ~30%, while controlled-potential reduction in aqueous solution gave 47% defluorination and 53% dealkylation. A similar reaction occurred when the CF_3Cba's were treated with $NaBH_4$ in aqueous solution, but the reaction was faster and the yields of CF_2HCba's were lower. However, when β-CF_3Cbl was electrochemically reduced at −1.20 V in DMF/1-propanol (50% v/v) with 0.2 M tetrabutylammonium iodide as supporting electrolyte, dealkylation

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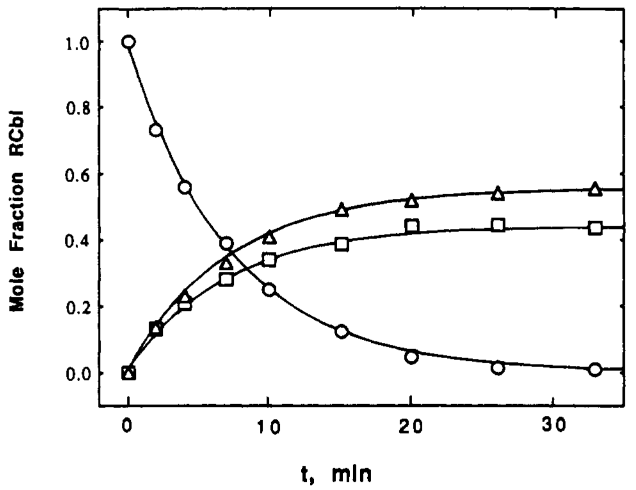

Figure 1. Time-dependence of the controlled-potential reduction of β-CF_3Cbl, 1.0 × 10^{-3} M, in 0.05 M CAPS, pH 9.50, 0.5 M KCl, at −1.20 V: (○) β-CF_3Cbl; (□) β-CF_2HCbl; (△) H_2OCbl. The solid lines were calculated from the appropriate first-order rate expressions and the rate constants in Table II.

Table II. Apparent First-Order Rate Constants for the Reductive Defluorination and Dealkylation of CF_3Cba's by Zinc and by Controlled-Potential Reduction[a]

RCba	conditions	10^3k_{obs}, s^{-1} [b]		
		CF_3Cba	CF_2HCba	H_2OCba
β-CF_3Cbl	Zn/NH_4Br[c]	1.85	1.70	1.93
	Zn/H_3PO_4[d]	6.26	6.30	6.24
	−1.20 V[e]	2.30	2.42	2.33
	−1.05 V[f]	0.308	0.337	0.322
α-CF_3Cbl	Zn/NH_4Br[c]	3.17	2.67	2.83
	Zn/H_3PO_4[d]	1.83	2.00	1.83
β-CF_3Cbi	Zn/NH_4Br[c]	6.64	6.25	7.43
	Zn/H_3PO_4[d]	6.35	6.67	5.76
α-CF_3Cbi	Zn/NH_4Br[c]	2.27	2.28	2.22
	Zn/H_3PO_4[d]	4.83	4.67	4.35

[a] 0 °C, except as noted. [b] From the slopes of plots of ln ($[RCba]_t$/$[RCba]_\infty$) vs time. Uncertainties estimated to be ±10%. Correlation coefficients (r^2) ranged from 0.972 to 0.999. [c] 10% NH_4Br, pH 4.8. [d] 20% H_3PO_4, pH 1.0. [e] Controlled-potential reduction in 0.05 M CAPS buffer, pH 9.5, 0.5 M KCl, 25 °C. [f] Controlled-potential reduction in 0.05 M phosphate buffer, pH 6.5, 0.5 M KCl, 25 °C.

occurred, but no β-CF_2HCbl was formed.

The time dependences for the disappearance of the starting CF_3Cba and for appearance of both of the products were strictly first-order, and apparent first-order rate constants were obtained from the slopes of semilogarithmic plots (Table II). The rates of dealkylation and defluorination were strongly dependent on the applied potential in controlled-potential reductions. Unlike many RCba's,[10,13,21-26] the CF_2HCba's proved to be indefinitely stable to reduction by zinc reductants and by BH_4^- and to controlled-potential reduction at potentials as low as −1.20 V. Hence, all of the dealkylation product (H_2OCbl or $(H_2O)_2Cbi$) comes from the reductive dealkylation of the CF_3Cba. Most importantly, the measured rate constants, which undoubtedly reflect only the rate of an initial reduction step, are identical for the disappearance of CF_3Cba and the appearance of both products for any given compound under any given condition. This effectively demonstrates that the disappearance of the CF_3Cba's, the formation of the CF_2HCba product, and the net dealkylation are all rate-limited by the same process, i.e., an initial reduction step.

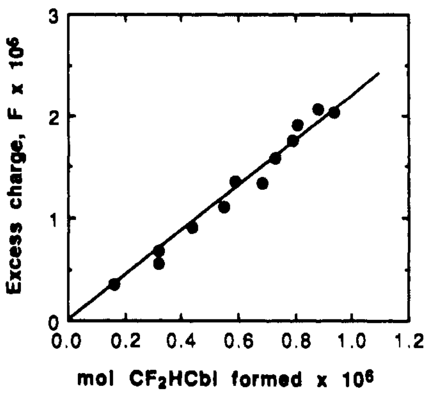

Figure 2. Plot of the excess charge (in faradays) consumed upon reductive defluorination of 2.0 × 10^{-6} mol of β-CF_3Cbl (in 6.0 mL of 0.05 M phosphate buffer, pH 6.50, 0.5 M KCl) to β-CF_2HCbl at −1.00 V, after correction for the charge consumed by dealkylation (see text), vs moles of β-CF_2HCbl formed. The solid line is a least-squares fit (with intercept 0.0); slope = 2.2 ± 0.2.

When the reduction of β- or α-CF_3Cbl was carried out in Zn/10% acetic acid-*d*/D_2O or by controlled-potential reduction in D_2O, the defluorinated product contained a single nonexchangeable deuterium atom in the organic ligand as demonstrated by ^{19}F, ^1H, and ^2H NMR spectroscopy (Table I). Similarly, synthesis of (trifluoromethyl)- and (difluoromethyl)cobalamins from CF_3I and H_2OCbl in Zn/10% acetic acid-*d*/D_2O produced diastereomeric CF_3Cbl's and CF_2DCbl's. In contrast, reductive defluorination of β-CF_3Cbl with $NaBH_4$ in D_2O yielded CF_2HCbl's; i.e., no deuterium from the solvent was incorporated into the organic ligand. Conversely, reduction of the CF_3Cbl's with $NaBD_4$ in H_2O did result in formation of CF_2DCbl's. These results are in direct contrast to those of Ricroch et al.[2] on the reductive dehalogenation of α-(haloalkyl)cobaloximes.

Attempts to observe reductive dehalogenation using two additional water-soluble reductants failed. Formate, known to effectively reduce H_2OCbl,[21,27] had no effect on β-CF_3Cbi at 0.5 M over 24 h at pH 5.5. In contrast, when 6 mM β-CF_3Cbl was treated with 0.06 M Ti(III) (conditions similar to those reported by Hogenkamp et al.[12] for the cobamide-catalyzed dehalogenation of halomethanes by Ti(III)), a slow dealkylation of β-CF_3Cbl was observed ($t_{1/2} > 2$ h), but no β-CF_2HCbl could be detected.

Electrochemistry. Cyclic voltammagrams of the CF_3Cba's and CF_2HCba's displayed the typical, irreversible reduction wave previously observed by others for a wide variety of RCbl's and RMe_7Cby's.[22-26,28,29] Values of the cathodic peak potentials, E_{pc}, were −1.26 and −1.68 V for β-CF_3Cbl and β-CF_2HCbl, respectively. The former value is reasonably close to that (−1.00 V vs SCE) previously reported by Zhou et al.[26] for CF_3Cbl[29] generated in situ in 0.1 M tetrabutylammonium perchlorate in DMF. Surprisingly, the E_{pc} value for β-CF_2HCbl is quite negative and similar to values previously observed by others[22-24,28] for simple alkylcobalamins without electron-withdrawing substituents on the α-carbon of the organic ligand. Similar, irreversible reduction waves were also observed for the other CF_3Cba's and CF_2HCba's, and the E_{pc} values were as follows: α-CF_3Cbl, −0.96 V; α-CF_2HCbl, −1.4 V; β-CF_3Cbi, −0.90 V; β-CF_2HCbi, −1.33 V; α-CF_3Cbi, −0.63 V; α-CF_2HCbi, −1.35 V. Presumably, the more negative reduction potentials for the CF_2HCba's are responsible for the stability of these compounds with respect to reductive dealkylation.

In order to attempt to determine the net number of electrons involved in the reductive defluorination of the CF_3Cba's to

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(29) The configuration of the RCbl's generated in situ in the work reported by Zhou et al.[26] is unknown, but these complexes should most likely be nearly pure β-RCbl's under the conditions utilized.[21] The RMe_7Cby's similarly generated in situ are most likely mixtures of the α- and β-diastereomers.

CF$_2$HCba's, controlled-potential coulometry experiments were performed on β-CF$_3$Cbl using a mercury pool electrode. Assuming that the reductive dealkylation of β-CF$_3$Cbl consumes a single electron (vide infra), the total charge consumed could be corrected for the amount of charge consumed in dealkylation of β-CF$_3$Cbl at various times during the reduction by careful quantitation of the components of the reaction mixture. The excess charge above that consumed in the dealkylation thus reflects the charge consumed upon net defluorination of β-CF$_3$Cbl to β-CF$_2$HCbl. In Figure 2, this excess charge, in faradays, is plotted against the number of moles of β-CF$_2$HCbl formed. The slope of this plot is 2.2, indicating that two electrons are consumed per molecule of β-CF$_3$Cbl defluorinated to β-CF$_2$HCbl.

Discussion

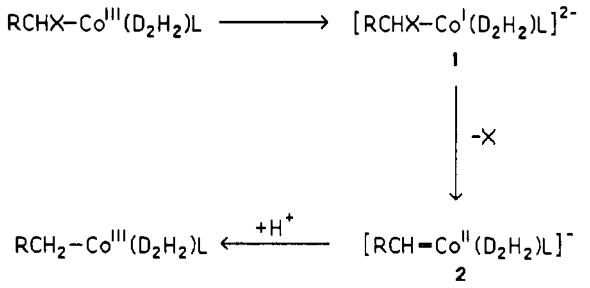
Penley et al.[30] originally described the synthesis and ^{19}F NMR spectra of several (fluoromethyl)cobalamins,[31] including CF$_2$HCbl. These authors reported the ^{19}F resonance of CF$_2$HCbl as a broad singlet at 18.95 ppm[32] and the CF$_2$H proton resonance as a singlet at ca. 0.2 ppm, on the basis of the fact that this resonance was missing from the proton spectrum of CF$_3$Cbl. However, the ^{19}F NMR resonance CF$_2$HCbl[31] was recently reported as a doublet by Hogenkamp et al.,[12] and our comparison of the proton NMR spectra of β-CF$_2$HCbl and β-CF$_2$DCbl permits the unequivocal assignment of the CF$_2$H proton resonance to a triplet at 5.08 ppm ($^2J_{HF}$ = 53.1 Hz). Toscano et al.[8] similarly reported the CF$_2$H proton resonance of CF$_2$HCo(D$_2$H$_2$)py (in CDCl$_3$) to be a triplet at 5.95 ppm ($^2J_{HF}$ = 53.0 Hz).

The "doublet" ^{19}F resonance of base-on β-CF$_2$HCbl has now been found to be a severely collapsed AB quartet of doublets in which the chemical shifts of the diastereotopic fluorines differ by less than 0.2 ppm. This small diastereotopic chemical shift difference is quite surprising, since, in the only two base-on β-RCbl's with diastereotopic α-methylene groups for which complete ^{1}H NMR assingments are known, β-(5′-deoxyadenosyl)cobalamin,[33] and β-(adeninylpropyl)cobalamin,[34] the chemical shift differences for the diastereotopic α-methylene protons are 0.98 and 0.66 ppm, respectively. Nonetheless, this small difference in the CF$_2$H fluorine chemical shifts is responsible for the previous reports[9,10,12] that base-on β-CF$_2$HCbl displays a doublet fluorine NMR spectrum.

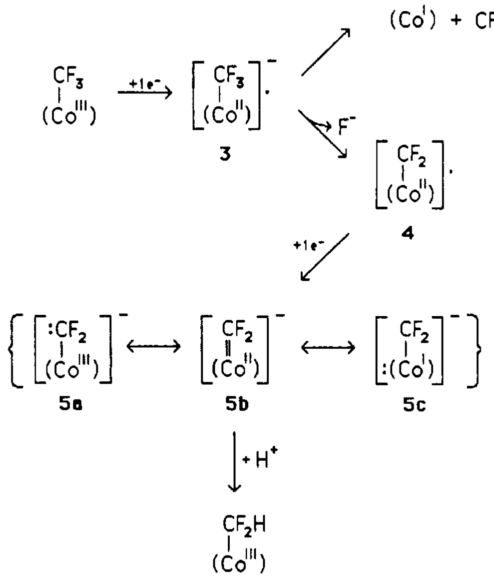
The kinetic experiments described above surely measure the rate of an initial reduction step, rather than the rate of any chemical step. The rate of reduction in these heterogeneous systems will obviously depend on such variables as the surface area of the reductant, agitation, etc. As no attempt was made to study the dependence of these rates on these variables, the data in Table II should not be used to compare the rates of reduction of the various CF$_3$Cba's. The important observation is that, under all conditions studied, the rates of formation of the Co–C bond cleavage product and of CF$_2$HCba are identical. This indicates that both of these chemical steps are rate-limited by the initial reduction step under these conditions.

Reduction potentials for RCba's have been previously observed by many others[22-26,28,35] for a wide variety of alkylcobalamins and heptamethyl alkylcobyrinates. Reported values for these reduction potentials range from −0.60 to −1.60 V under various conditions. These reduction potentials have been assigned to a one-electron reduction leading to a RCba$^{\bullet-}$ radical anion which subsequently undergoes carbon–cobalt bond cleavage to yield an organic radical and the appropriate cobalt(I) species.[22-26,28] This mode of Co–C bond cleavage has been directly observed for CH$_3$Cbl in the spectroelectrochemical experiments of Rubinson et al.[22] In addition, Zhou et al.,[26] who observed cathodic peak potentials for the reduction of 26 RCbl's[29] generated in situ during single-scan voltammetry of HOCbl in the presence of alkyl halides (including CF$_3$I), have effectively argued that these peak potentials very closely approximate the redox potentials for the RCo^{II}/R$^\bullet$ + Co^I couple based on thermodynamic cycles and measured values for the Co^{II}/Co^I redox potential and the bond dissociation energies of RCo^{III} species. In our studies, sampling of the anaerobic reaction mixtures for HPLC analysis results in air oxidation of the cobalt(I) homolysis product, leading to the observed dealkylation products (i.e., H$_2$OCbl or (H$_2$O)$_2$Cbi). The rate constants for Co–C bond cleavage of CH$_3$Cbl$^{\bullet-}$ and CH$_3$Cbi$^{\bullet-}$ in DMF/1-propanol are reported[24] to be 1200 and 2.7 s^{-1}, respectively, at −30 °C. However, in aqueous media, Kim and Birke[23] reported a rate constant of 0.37 s^{-1} for the homolysis of base-off CH$_3$Cbl$^{\bullet-}$ at 25 °C. This difference presumably reflects the poor competition of solvent cage escape with rapid CH$_3$$^\bullet$ + Co(I) recombination in water due to the lack of abstractable hydrogens in aqueous solution.

Scheme I



Scheme II



Ricroch et al.[2] originally proposed an initial two-electron reduction (Scheme I) for the reductive dehalogenation of α-(haloalkyl)cobaloximes by BH$_4^-$, leading to the dianion **1**. Following elimination of the halide, a proposed cobalt(II) anion (**2**) was thought to be protonated at the α-carbon in hydroxylic media to result in the dehalogenated product.[36] However, it is very unlikely that such a mechanism can be operating in the case of the reductive defluorination of CF$_3$Cba's. The potentials for the reduction of the RCba$^{\bullet-}$ radical anions are unknown but must surely be considerably more negative than the one-electron-reduction potentials of the RCba's (−0.60 to −1.60 V). Given the mild reducing conditions employed here (zinc reductants or controlled-potential reduction at −1.0 to −1.2 V), it seems extremely unlikely that the initial event is a two-electron reduction. Since our controlled-

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(30) Penley, M. W.; Brown, D. G.; Wood, J. M. *Biochemistry* **1970**, *9*, 4302.

(31) These compounds were probably β-RCbl's under the synthesis conditions reported.

(32) Relative to C$_6$H$_5$F, but originally measured relative to CFCl$_3$.[30]

(33) Summers, M. F.; Marzilli, L. G.; Bax, A. *J. Am. Chem. Soc.* **1986**, *108*, 4285.

(34) Pagano, T. G.; Marzilli, L. G.; Flocco, M. M.; Tsai, C.; Carrell, H. L.; Glusker, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 531.

(35) Hogenkamp, H. P. C.; Holmes, S. *Biochemistry* **1970**, *9*, 1886.

(36) An alternative mechanism in which H$^-$ directly attacked the halide leading to **2** could not be ruled out.[2]

potential coulometry experiments show that a total of two electrons are consumed in the net defluorination of CF_3Cba's, we propose the ECE mechanism shown in Scheme II.[37] Here, the anticipated one-electron reduction leads to the radical anion **3**, which partitions between carbon–cobalt bond cleavage and elimination of fluorine to form the radical intermediate **4**. The latter then undergoes an additional one-electron reduction to form the anion **5**, the analogue of species **2** (Scheme I) proposed as the intermediate in the reductive dehalogenation of α-(haloalkyl)cobaloximes by Ricroch et al.[2] This species may be described as the cobalt(II)–difluorocarbenoid species **5b** or the equivalent valence-bond structures **5a** and **5c**. As in the case of the cobaloximes, protonation of this species leads to the difluorocobamide.

Evidence for the partitioning of the radical anion **3** between carbon–cobalt bond homolysis and defluorination comes from the observation that controlled-potential reduction of β-CF_3Cbl in DMF/1-propanol yields dealkylation only: no β-CF_2HCbl could be detected. In this solvent, which provides ample abstractable hydrogen atoms, the dealkylation of $CH_3Cbl^{\bullet-}$ and $CH_3Cbi^{\bullet-}$ is known to be extremely rapid,[24] while, in water, carbon–cobalt bond cleavage of base-off $CH_3Cbl^{\bullet-}$ is reported[23] to occur at a rate comparable to those observed here for defluorination of the CF_3Cba's. Direct evidence that solvent is the source of the CF_2H proton comes from the observation of formation of the CF_2DCbl's in deuterated media. Surprisingly, the opposite result was obtained when β-CF_3Cbl was defluorinated by borohydride, β-CF_2DCbl being obtained with $NaBD_4/H_2O$, while β-CF_2HCbl was the product in $NaBH_4/D_2O$. This indicates that reductive defluorination of CF_3Cba's with BH_4^- occurs by a different mechanism than that operative with zinc reductants and controlled-potential reduction. As this result is also opposite to that of Ricroch et al.[2] for the reductive dehalogenation of α-(haloalkyl)cobaloximes by BH_4^-, the mechanism of reductive dehalogenation of α-(haloalkyl)cobaloximes by BH_4^- is also different from that of CF_3Cba defluorination by BH_4^-. Our observations suggest that the latter reaction may result from the direct attack of a hydride ion on the α-carbon of the CF_3Cba.

While β-CF_3Cbl was found to be slowly dealkylated ($t_{1/2} > 2$ h) by Ti(III), no defluorination was observed under conditions similar to those employed by Hogenkamp et al.[12] for the reductive dehalogenation of CF_3Cl by Ti(III) catalyzed by cobamides. This observation supports the conclusion of these workers that the cobamide-catalyzed dehalogenation of CF_3Cl by Ti(III) occurs by reductive dealkylation of CF_3Cba's followed by further reaction of $CF_3^{\bullet}$ and not by defluorination of CF_3Cba's.

In sum, reductive defluorination of CF_3Cba's by zinc reductants and controlled-potential reduction appear to occur by the ECE mechanism of Scheme II, but by a different mechanism when $NaBH_4^-$ is the reductant. Several interesting differences in the behavior of cobaloximes and cobamides in this regard have been revealed. Thus, (trifluoromethyl)cobaloximes are stable to reduction by zinc[5] but defluorinated by borohydride,[3,8] presumably by a mechanism in which the CF_2H proton comes from solvent.[3] In contrast, (trifluoromethyl)cobamides are defluorinated by zinc (and controlled-potential reduction), apparently by the ECE mechanism of Scheme II, in which the CF_2H proton comes from solvent, but are defluorinated by borohydride by a different mechanism in which the CF_2H proton comes from the reductant.

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[37] A reviewer has pointed out that the current data do not eliminate the possibility that the dealkylation step is heterolytic, i.e., $[CF_3\text{–}Co^{II}]^{\bullet-} \rightarrow Co^{II} + CF_3^-$. However, the complete suppression of defluorination in DMF/1-propanol suggests the homolysis mechanism depicted in Scheme II. See also the arguments of Zhou et al.[26]

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Non-Metal Redox Kinetics: Iodine Monobromide Reaction with Iodide Ion and the Hydrolysis of IBr

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The dissociation equilibrium constant for IBr_2^-, $K_1 = (3.5 \pm 0.6) \times 10^{-3}$ M at 25.0 °C and $\mu = 1.0$ M, is determined. Pulsed-accelerated-flow (PAF) methods are used to measure the very rapid reactions when solutions of IBr_2^-/Br^- are mixed with excess I^- in 1.0 M H^+ at 25.0 °C. The proposed mechanism is as follows:

$$IBr_2^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} IBr(aq) + Br^-$$

$$IBr(aq) + I^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} I_2Br^-$$

$$I_2Br^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} I_2(aq) + Br^-$$

$$I_2(aq) + I^- \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} I_3^-$$

Reactant concentrations are adjusted so that I_2Br^- formation is the rate-determining step; k_2 is $(2.0 \pm 0.3) \times 10^9\ M^{-1}\ s^{-1}$ and k_{-2} is $800 \pm 300\ s^{-1}$ (from studies under reversible conditions). The k_2 rate constant is intermediate between values of the rate constants for I^- with ICl(aq) and I^- with I_2(aq). The equilibrium constant for the hydrolysis of IBr(aq) is $(2.4 \pm 0.4) \times 10^{-7}\ M^2$ at 25.0 °C, $\mu = 0.5$ M, for $IBr(aq) + H_2O \rightleftharpoons HOI + Br^- + H^+$. PAF methods are used to study the reactions of IBr_2^-/Br^- solutions with bases. The hydrolysis of IBr(aq) is extremely rapid; $k_{hydr} = k_{H_2O} + k_{OH}[OH^-] + k_B[B]$, where $k_{H_2O} = (8 \pm 3) \times 10^5\ s^{-1}$, $k_{OH} = (6.0 \pm 0.4) \times 10^9\ M^{-1}\ s^{-1}$, and $k_B = (3.5 \pm 0.2) \times 10^9\ M^{-1}\ s^{-1}$ for $B = CO_3^{2-}$ or PO_4^{3-}. Two IBr(aq) species are proposed to be in rapid equilibrium: H_2OIBr (50%) and IBr (50%), where the less hydrated IBr species reacts with PO_4^{3-} and CO_3^{2-} at the diffusion limit.

Introduction

Hydrolysis reactions of diatomic interhalogen compounds of iodine, bromine, and chlorine are extremely rapid compared to reactions of the halogens themselves.[1,2] The rate constant for the hydrolysis of ICl(aq)[1] is $2.4 \times 10^6\ s^{-1}$ compared to values of

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[1] Wang, Y. L.; Nagy, J. C.; Margerum, D. W. *J. Am. Chem. Soc.* **1989**, *111*, 7838–7844.

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