Carboxyalkyl- and Carboxyphenylcobaloximes. Substituent Effect of Chelated Cobalt[1,2]

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Abstract: *m*- and *p*-carboxyphenylcobaloximes and their methyl esters have been synthesized and characterized. The pK_as for carboxyl proton dissociation of the carboxyphenylcobaloximes and the rate constants for base-catalyzed hydrolysis of their methyl esters have been measured and compared to those of other substituted methyl benzoates. The aquocobaloxime moiety is thus found to be a moderately electron-donating Hammett substituent which becomes more electron donating upon ionization of its axial water ligand. Application of the Taft dual substituent parameter equation to the base-catalyzed hydrolysis of nine substituted methyl benzoates has allowed the calculation of inductive and resonance substituent parameters for both the aquo- and hydroxocobaloxime moieties. These results show that in this system the substituent effect of the cobaloxime moieties is almost completely inductive ($\sigma_I = -0.30, -0.48$ for the aquo and hydroxo complexes, respectively), with only a minor resonance component ($\sigma_{R(BA)} = -0.05, -0.07$, respectively). The p$K_a$s of the aquo and pyridine complexes of carboxymethyl- and carboxyethylcobaloxime have also been determined. In this system, the apparent inductive effect of the cobaloxime moiety is found to be highly dependent upon the number of methylene groups between the cobalt atom and the carboxyl function. These results imply that the acidities of carboxymethyl cobalt complexes are significantly lowered by $\sigma \rightarrow \pi$ conjugation.

Introduction

Coenzyme B_{12} (5′-deoxyadenosylcobalamin) is well known to be involved in the enzymatic catalysis of a series of intriguing 1,2-intramolecular rearrangements in which an electronegative group and a hydrogen atom on adjacent carbons exchange places.[3] In the past 12 or so years a large number of proposals for the mechanism(s) of these reactions have been put forward, frequently on the basis of organocobalt model chemistry.[4-21] With a few notable exceptions,[4,5,12,20] most of the suggested mechanisms envision the formation of organocobalt intermediates in which a substrate carbon atom becomes bonded to cobalamin cobalt. Consequently, it is of interest to determine the steric and inductive effects of chelated cobalt centers on bound organic groups in organocobalt complexes. There is very little relevant data available in the literature. Johnson and co-workers[22] studied the halogenation of the phenyl ring of benzylcobaloximes and concluded that the phenyl substituent $-CH_2Co(D_2H_2)py$ was more electron donating than $-CH_3$ but less so than $-OCH_3$. Hill and co-workers[23] studied the ^{19}F NMR shifts of *m*- and *p*-$FC_6H_4Co(III)\{(DO)(DOH)pn\}X^2$, for a variety of X, and concluded from the values of the meta and para ^{19}F chemical shifts that the cobalt center acted as both a σ and π donor to the aromatic ring in this system. Finally, the pK_as of carboxyalkylcobalt complexes have been reported to be 7.2 for carboxymethylcobalamin,[24,25] 7.14 for carboxymethyl(pyridine)cobaloxime,[26] and 5.70 for carboxyethyl(pyridine)cobaloxime.[26] These observations are particularly interesting in that they suggest that under certain circumstances chelated cobalt centers may behave as if they were extremely electron donating.

The present report details our attempts to quantitate the inductive and resonance substituent effects of dimethylglyoximato chelated cobalt centers by consideration of the acidities of carboxymethyl-, carboxyethyl-, and carboxyphenylcobaloximes, as well as the rates of base-catalyzed hydrolysis of the methyl esters of carboxyphenylcobaloximes.

Experimental Section

Materials. Alkyl and aryl halides, dimethylglyoxime, cobaltous chloride, cobaltous acetate, sodium borohydride, sodium and potassium hydroxide, methanol, buffer components, and inorganic salts and acids were obtained in the highest purity commercially available and used without further purification.

Substituted methyl benzoates were recrystallized from aqueous methanol. Pyridine was dried over type 4A molecular sieve, redistilled under argon, and stored in the dark, over type 4A molecular sieve under argon. Glass distilled deionized water was used throughout.

***m*-$CH_3OOCC_6H_4Co(D_2H_2)py$.** Cobaltous chloride hexahydrate (4.76 g, 0.02 mol) and 4.65 g of dimethylglyoxime (0.04 mol) were stirred in 75 mL of methanol under argon for 30 min. NaOH (1.60 g) and 1.60 g of pyridine were added, and stirring was continued for 30 min. For reduction to Co(I), 0.80 g of NaOH was added followed by 0.107 g of $NaBH_4$ in methanol. After the reaction mixture had turned green, 8.60 g (0.04 mol) of methyl *m*-bromobenzoate in methanol was added, and the reaction mixture was warmed to 55–60 °C. After 60 min the reaction mixture had turned brown, and it was rereduced with 0.11 g of $NaBH_4$. Sixty minutes later it was reduced again with 0.11 g of $NaBH_4$. After stirring for 60 min more, the reaction mixture was filtered and evaporated to 100 mL, and 100 mL of water was added. Cooling in ice produced a crop of yellow crystals, and subsequent evaporation of solvent produced three more crops of yellow crystals (total wt 5.70 g) which were considerably contaminated with unreacted methyl *m*-bromobenzoate.

The crude product was dissolved in methylene chloride and applied to a 3 × 35 cm column of silica gel (in methylene chloride) and eluted with 500 mL of methylene chloride to remove methyl *m*-bromobenzoate. The desired product was eluted with acetone, the acetone fraction was concentrated to 25 mL, and then 50 mL of water was added to precipitate the product which was dried in vacuo over P_2O_5 to yield 0.74 g (7.4%) of *m*-$CH_3OOCC_6H_4Co(D_2H_2)py$: C, H, N;[27] NMR ($CDCl_3$–methanol-$d_4$) δ_{Me_4Si} 2.03 (s, 12 H), 3.87 (s, 3.1 H), 6.70–9.03 (m, 8.8 H).

***m*-$CH_3OOCC_6H_4Co(D_2H_2)HOH$.** *m*-$CH_3OOCC_6H_4Co(D_2H_2)$-HOH (0.74 g, 1.47 mmol) was dissolved in 150 mL of methanol with warming; 75 mL of water and 1.33 g of Bio-Rad AG 50W-X8 ion exchange resin (H^+ form, 6.8 mequiv) were added, and the mixture was stirred for 16 h in the dark. The mixture was filtered twice, and the supernatant was evaporated to 30 mL, cooled in ice, and filtered to produce 0.65 g of yellow powder which was washed with cold water and dried in vacuo over P_2O_5: yield 72%; C, H, N; NMR ($CDCl_3$–methanol-d_4) δ_{Me_4Si} 2.15 (s, 12 H), 3.84 (s, 3.1 H), 6.72–7.82 (m, 4.3 H).

***m*-$HOOCC_6H_4Co(D_2H_2)HOH$.** *m*-$CH_3OOCC_6H_4Co(D_2H_2)HOH$ (0.15 g) was dissolved in 50 mL of methanol; 40 mL of water and 10 mL of 5.0 N KOH was added, and the solution was stirred for 3 h. The pH was then adjusted to 2.26 with HCl, and the solution was evaporated to 40 mL, cooled in ice, and filtered to yield 0.11 g of orange powder: yield 76%; C, H, N; NMR ($CDCl_3$–methanol-d_4) δ_{Me_4Si} 2.13 (s, 12 H), 6.70–7.75 (m, 4.4 H).

The para isomers of the above compounds were synthesized in a strictly analogous manner.

***p*-$CH_3OOCC_6H_4Co(D_2H_2)py$.** Yield 10%; C, H, N; NMR ($CDCl_3$) δ_{Me_4Si} 2.03 (s, 12 H), 3.82 (s, 2.9 H), 7.17–8.87 (m, 9.0 H).

***p*-$CH_3OOCC_6H_4Co(D_2H_2)HOH$.** Yield 75%; C, H, N; NMR

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($CDCl_3$-methanol-d_4) δ_{Me_4Si} 2.15 (s, 12 H), 3.81 (s, 3.1 H), 7.10–7.60 (m, 4.2 H).

***p*-$HOOCC_6H_4Co(D_2H_2)HOH$.** Yield 93%; C, H, N; NMR ($CDCl_3$-methanol-d_4) δ_{Me_4Si} 2.13 (s, 12 H), 7.11–7.68 (m, 4.2 H).

$HOOCCH_2Co(D_2H_2)HOH$ was synthesized from its methyl ester as described by Schrauzer and Windgassen.[26]

$HOOCCH_2CH_2Co(D_2H_2)HOH$ was synthesized directly from β-bromopropionic acid by the method of Crumbliss and Gaus.[28]

Methods. All work with the organocobaloximes was performed in dim light and solutions were covered with aluminum foil whenever possible. Glass distilled deionized water was used throughout, and ionic strength was maintained at 1.0 M with KCl.

UV and visible spectra were recorded on a Cary 14 recording spectrophotometer. Absorbance measurements were made on a Cary 14 or Gilford Model 250 spectrophotometer. pH measurements were made with a Radiometer PHM 64 pH meter as described previously,[29,30] with samples, standards, electrodes, and rinse water incubated at the measurement temperature.

Equilibrium Measurements. Pyridine was titrated potentiometrically at 25.0 ± 0.1 °C at 0.02 M concentration.

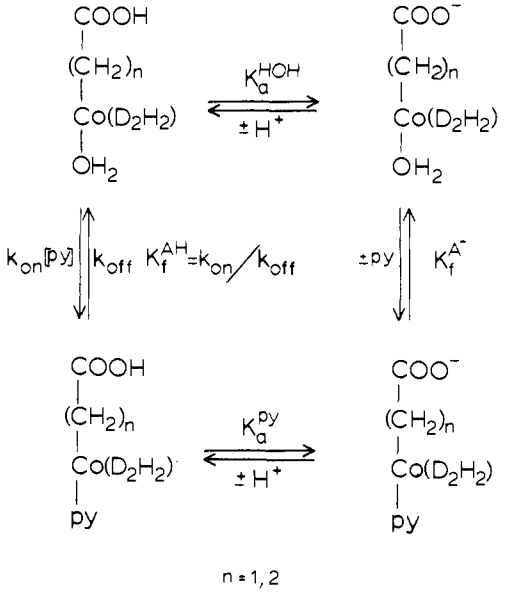
Values for the proton dissociation constants for the carboxyphenyl- and carboxyalkyl(aquo)cobaloximes were obtained by spectrophotometric titration with the data being collected and analyzed as has been described.[29,30] Binding constants for pyridine to the carboxylate species of the carboxyalkylcobaloximes ($K_f^{A^-}$, Scheme I) were obtained spectrophotometrically[29,30] at pH 8.93 for $^-OOCCH_2Co(D_2H_2)HOH$, and at pH 8.43 for $^-OOCCH_2CH_2Co(D_2H_2)HOH$. Apparent binding constants, $K_f^{AH'}$ (Scheme I), for pyridine to the neutral carboxyalkylcobaloximes were determined spectrophotometrically at pH 4.24 for $HOOCCH_2Co(D_2H_2)HOH$ and pH 2.79 for $HOOCCH_2CH_2Co(D_2H_2)HOH$. In both experiments the pyridine is partly protonated, and the equilibrium constants with respect to free base pyridine (K_f^{AH}, Scheme I) were calculated from $K_f^{AH} = K_f^{AH'}/\alpha_{py}$, where α_{py} is the fraction of pyridine as the free base (unprotonated) species. An additional value for K_f^{AH} was calculated from the measured values of k_{on} and k_{off} (Scheme I, see below) for each of the carboxyalkylcobaloximes, and these were averaged with the spectrophotometric values. Values for the proton dissociation constant for the carboxyl group of the carboxyalkyl(pyridine)cobaloximes (K_a^{py}, Scheme I) were calculated from

$$K_a^{py} = K_a^{HOH}K_f^{A^-}/K_f^{AH} \quad (1)$$

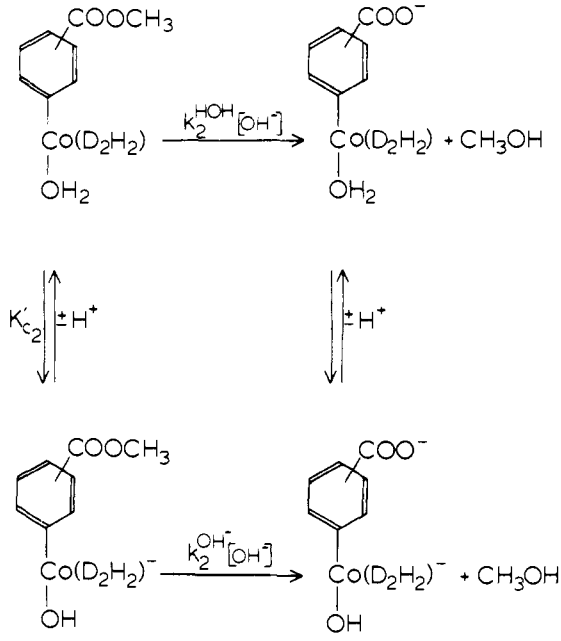
based on the cyclic nature of the equilibria in Scheme I.

Values for the apparent proton dissociation constants for axial water proton dissociation (pK_{c_2}, Scheme II, below) for *m*- and *p*-$CH_3OOCC_6H_4Co(D_2H_2)HOH$ were determined spectrophotometrically as has been described.[29,30] It was always possible to obtain such spectrophotometric measurements rapidly enough to avoid significant hydrolysis of those esters. (See below.)

Scheme I



Scheme II



Kinetic Measurements. Pseudo-first-order rate constants, k_{obsd}, for the ligation of pyridine (in at least tenfold excess over cobaloxime) to the neutral carboxyalkylcobaloximes were obtained spectrophotometrically as described previously,[29,30] at pH 4.16 for $HOOCCH_2Co(D_2H_2)HOH$ using a Gilford 250 spectrophotometer, and at pH 2.89 for $HOOCCH_2CH_2Co(D_2H_2]HOH$ using a stopped-flow apparatus. Second-order rate constants, k'_{on}, at the particular pH, were determined from the slopes of least-squares fits of the data to

$$k_{obsd} = k'_{on}[py]_{tot} + k_{off} \quad (2)$$

where $[py]_{tot}$ is the total concentration of pyridine distributed over both ionization states. The intercept was used as a value of k_{off} for $HOOCCH_2CH_2Co(D_2H_2)py$. Values of k_{on}, the second-order ligation rate constant with respect to free base pyridine, were calculated from $k_{on} = k'_{on}/\alpha_{py}$. The pyridine dissociation rate constant, k_{off}, for $HOOCCH_2(D_2H)HOH$ was determined spectrophotometrically by pH-jumping solutions of preformed carboxyalkyl(pyridine)cobaloximes as has been described.[29,30]

First-order rate constants, k_{obsd}, for base-catalyzed hydrolysis of substituted methyl benzoates at a given pH (maintained by phosphate buffers, or KOH concentration) were determined from the time dependence of the UV absorbance of the methyl benzoate at the appropriate wavelength (230–255 nm). For methylbenzoates without cobalt substituents, second-order rate constants, k_2, were obtained from the slopes of least-squares fits of the first-order rate constants to

$$k_{obsd} = k_2 a_{OH^-} \quad (3)$$

where a_{OH^-} was calculated from the measured pH and K_w (10^{-14} at 25.0 °C). Data for each methyl benzoate were collected over at least two orders of magnitude of a_{OH^-} for use in eq 3.

Results

Values for the proton dissociation constants of the two carboxyalkylcobaloximes (pK_a^{HOH} in Scheme I) at five temperatures are listed in Table I and plotted in Figure 1 as $\ln K_a^{HOH}$ vs. $1/T$ to yield values for the enthalpy and entropy of ionization (Table I).

The pK'_a of pyridinium ion was found to be 5.56 ± 0.01. Values for the binding constants for pyridine to the neutral and anionic species of the carboxyalkylcobaloximes (Scheme I) are given in Table II along with the calculated values of pK_a^{py} (Scheme I). It can be seen that substitution of pyridine for water in the axial position causes an increase of 0.24 units in the carboxyl pK_a of carboxymethylcobaloxime and an increase of 0.15 units in that of carboxyethylcobaloxime.

Values of pK'_a for carboxyl dissociation of the carboxy-

Table I. Temperature Dependence of pK_a^{HOH} for $HOOCCH_2Co(D_2H_2)HOH$ and $HOOCCH_2CH_2Co(D_2H_2)HOH$, Ionic Strength 1.0 M

Compd	Temp, °C	pK_a^{HOH}	ΔH,[a] kcal/mol	ΔS,[b] eu
$HOOCCH_2Co(D_2H_2)HOH$	5.1 ± 0.1	6.40 ± 0.01	1.75 ± 0.09	−23.0 ± 0.3
	15.1 ± 0.1	6.35 ± 0.01		
	25.0 ± 0.1	6.30 ± 0.01		
	35.0 ± 0.2	6.26 ± 0.01		
	45.0 ± 0.1	6.23 ± 0.01		
$HOOCCH_2CH_2Co(D_2H_2)HOH$	5.1 ± 0.1	4.97 ± 0.01	1.49 ± 0.05	−17.4 ± 0.2
	15.0 ± 0.1	4.93 ± 0.02		
	25.0 ± 0.1	4.89 ± 0.02		
	35.1 ± 0.1	4.85 ± 0.02		
	45.1 ± 0.1	4.83 ± 0.02		

[a] Calculated from the slope of a plot of ln K_a^{HOH} vs. $1/T$ (Figure 1). [b] Calculated from the intercept of a plot of ln K_a^{HOH} vs. $1/T$ (Figure 1).

Table II. Equilibria and Kinetics for Pyridine Binding to the Carboxyalkylcobaloximes, 25.0 °C, Ionic Strength 1.0 M

Compd		$HOOCCH_2Co(D_2H_2)HOH$	$HOOCCH_2CH_2Co(D_2H_2)HOH$
	pH	4.16 ± 0.01	2.89 ± 0.06
k_{on}, $M^{-1}\,s^{-1}$	α_{py}[a]	3.83 ± 0.12 × 10^{-2}	2.13 ± 0.30 × 10^{-3}
	k'_{on}, $M^{-1}\,s^{-1}$	2.16 ± 0.04 × 10^{-2}	1.54 ± 0.09
	k_{on},[b] $M^{-1}\,s^{-1}$	5.64 ± 0.21 × 10^{-1}	7.23 ± 1.10 × 10^{2}
k_{off}, s^{-1}		9.19 ± 0.22 × 10^{-5} [c]	4.12 ± 0.24 × 10^{-1} [d]
	pH	4.24 ± 0.01	2.79 ± 0.02
	α_{py}[a]	4.57 ± 0.14 × 10^{-2}	1.70 ± 0.09 × 10^{-3}
K_f^{AH}, M^{-1}	$K_f^{AH'}$, M^{-1} [e]	2.98 ± 0.12 × 10^{2}	2.80 ± 0.23
	K_f^{AH}, M^{-1} [f]	6.51 ± 0.33 × 10^{3}	1.65 ± 0.16 × 10^{3}
	K_f^{AH}, M^{-1} [g]	6.14 ± 0.27 × 10^{3}	1.75 ± 0.29 × 10^{3}
	K_f^{AH}, M^{-1} [h]	6.33 ± 0.21 × 10^{3}	1.70 ± 0.17 × 10^{3}
$K_f^{A^-}$,[e] M^{-1}		3.65 ± 0.19 × 10^{3}	1.20 ± 0.07 × 10^{3}
pK_a^{pyi}		6.54 ± 0.03	5.04 ± 0.05

[a] Calculated by $\alpha_{py} = K'_a/(K'_a + [H^+])$ using $pK'_a = 5.56 \pm 0.01$ for pyridine. [b] Calculated by $k_{on} = k'_{on}/\alpha_{py}$. [c] Average of six determinations. [d] From the intercept of a plot of k_{obsd} vs. $[py]_{tot}$, eq 2. [e] Spectrophotometric determination. [f] Calculated by $K_f^{AH} = K_f^{AH'}/\alpha_{py}$. [g] Calculated by $K_f^{AH} = k_{on}/k_{off}$. [h] Average of the two values from *f* and *g*. [i] Calculated from eq 1.

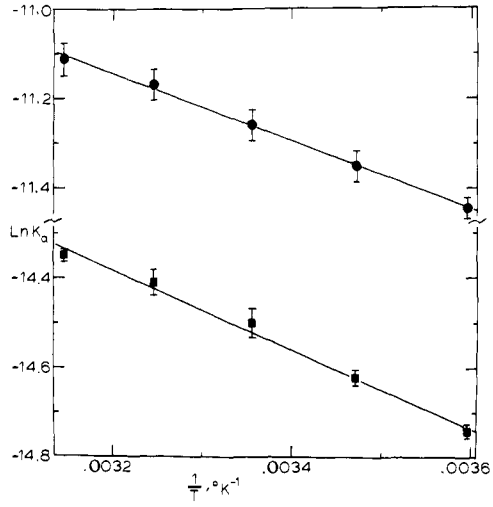


Figure 1. Dependence of ln K_a for carboxyl proton dissociation on the reciprocal of absolute temperature. $HOOCCH_2Co(D_2H_2)HOH$ (●), slope = −751 ± 24 K, intercept = −8.74 ± 0.08; $HOOCCH_2CH_2CO(D_2H_2)$-HOH (■), slope = −882 ± 47 K, intercept = −11.6 ± 0.2. Error bars represent ± one standard deviation.

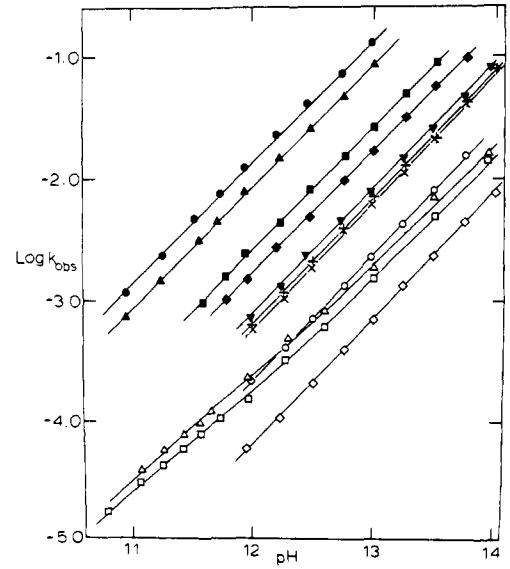


Figure 2. Dependence of k_{obsd} for methyl benzoate hydrolysis on pH, ionic strength 1.0 M, 25.0 °C. *p*-NO_2- (●), *m*-NO_2- (▲), *m*-Br- (■), *p*-Br- (♦), H- (▼), *m*-CH_3- (×), *m*-NH_2- (+), *p*-CH_3O- (○), *m*-cobaloxime- (△), *p*-cobaloxime- (□), *p*-NH_2- (◇). Solid lines are calculated from eq 3 or 4 (see text), and the values of k_2 in Table III.

phenylcobaloximes were 4.24 ± 0.04 for the para isomer and 4.15 ± 0.06 (average of two determinations) for the meta isomer. Owing to the poor solubility of these compounds and the small changes of extinction attendant upon ionization (especially for the meta isomer), these values are felt to be too unreliable to draw any quantitative conclusions regarding the substituent effect of the cobalt center.

pH-rate profiles for base-catalyzed hydrolysis of substituted methyl benzoates are shown in Figure 2. Varying phosphate buffer concentration over the range of 0.015–0.20 M at two different pH's had no effect on the observed rate constants for

Table III. Kinetics of Base-Catalyzed Hydrolysis of Substituted Methyl Benzoates, 25.0 °C, Ionic Strength 1.0 M

Substituent	σ_p[a]	σ_m[a]	σ_I[b]	$\sigma_{R(BA)}$[b]	k_2^p, M^{-1} s^{-1}	k_2^m, M^{-1} s^{-1}
H	0	0	0	0	$9.07 \pm 0.09 \times 10^{-2}$	$9.07 \pm 0.09 \times 10^{-2}$
NH_2	−0.660	−0.161	0.12	−0.82	$8.03 \pm 0.08 \times 10^{-3}$	$7.72 \pm 0.15 \times 10^{-2}$
Br	0.232	0.391	0.44	−0.19	$1.75 \pm 0.02 \times 10^{-1}$	$2.74 \pm 0.01 \times 10^{-1}$
NO_2	0.778	0.710	0.65	0.15	1.28 ± 0.03	$8.45 \pm 0.03 \times 10^{-1}$
CH_3O	−0.268		0.27	−0.61	$2.77 \pm 0.04 \times 10^{-2}$	
CH_3		−0.069	−0.04	−0.11		$7.28 \pm 0.16 \times 10^{-2}$
$Co(D_2H_2)HOH$	−0.313[c]	−0.269[c]	−0.30[d]	−0.05[d]	$2.97 \pm 0.11 \times 10^{-2}$ [e]	$3.45 \pm 0.12 \times 10^{-2}$ [e]
$Co(D_2H_2)OH^-$	−0.508[c]	−0.441[c]	−0.48[d]	−0.07[d]	$1.54 \pm 0.04 \times 10^{-2}$ [e]	$1.93 \pm 0.06 \times 10^{-2}$ [e]

[a] Taken from ref 31. [b] Taken from ref 32. [c] Calculated from k_2 and eq 5; see text. [d] Calculated from k_2 and eq 7; see text. [e] From least-squares fits of k_{obsd} to eq 4; see text.

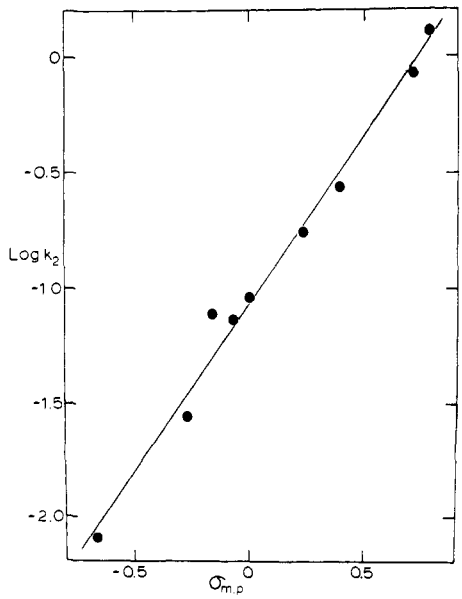


Figure 3. Dependence of log k_2 for substituted methyl benzoate saponification on the Hammett substituent constants, σ_m or σ_p. Slope = 1.463 ± 0.070, intercept = −1.069 ± 0.032.

hydrolysis of either the *m*- or *p*-cobaloxime substituted compounds. Inspection of Figure 2 shows that the first-order rate constants for base-catalyzed hydrolysis of the *m*- and *p*-cobaloxime substituted methyl benzoates are not first order in hydroxide ion as is consistent with the known ionization of axial water (pK'_{c2}, Scheme II) in the alkyl(aquo)cobaloximes.[29,30] Application of Scheme II leads directly to the rate law

$$k_{obsd} = K_w(K'_{c_2}k_2^{OH^-} + k_2^{HOH}[H^+])/(K'_{c_2}[H^+] + [H^+]^2) \quad (4)$$

where the constants are defined in Scheme II. Using the spectrophotometrically determined values of pK'_{c_2} (11.41 ± 0.01 for *p*-$CH_3OOCC_6H_4Co(D_2H_2)HOH$ and 11.75 ± 0.06 for the meta isomer) and $K_w = 10^{-14}$, the kinetic data for the cobaloxime substituted methyl benzoates were fit to eq 4 by the method of least squares to obtain the values for the second-order rate constants for the aquo- and hydroxocobaloxime substituted compounds which are listed in Table III, along with the values for the other substituted methyl benzoates.

Figure 3 shows a standard Hammett plot of the data for methyl benzoate hydrolysis. A least-squares fit of the data in Table III to

$$\log k_2 = \rho\sigma + \log k_2^0 \quad (5)$$

($n = 9, f^{33} = 0.073$) provided values for ρ (1.463 ± 0.070) and $\log k_2^0$ (−1.069 ± 0.032).[35] The solid line in Figure 3 and the values for σ_m and σ_p for the aquo- and hydroxocobaloxime substituents listed in Table III were calculated from these values and eq 5. As can be seen in Table III, both the aquo- and hydroxocobaloxime moieties behave as moderately electron-donating Hammett substituents and show relatively similar values for σ in both the meta and para positions. Substitution of hydroxide for water in the axial position causes a significant increase in the apparent electron-donating ability of the cobaloxime moiety.

Discussion

Synthesis of Arylcobaloximes. As seen above, arylcobaloximes are accessible in low yield via reaction of cobaloximes (I) with aryl bromides. These results are similar to those of Tucker,[36] who found that aryl-Co(BAE)[2] and aryl-Co(SALEN)[2] complexes could be obtained from aryl halides and the appropriate Co(I) complex in low yields. Tucker has postulated a mechanism involving halogen abstraction by the Co(I) chelate followed by coupling of the resultant aryl radical and Co(II) complex,[36] which is consistent with his finding of arene by-products in the final reaction mixtures. While no attempt was made to delineate the mechanism of this reaction in the present study, the steric requirements of the octahedral cobalt complexes would seem to make a nucleophilic aromatic substitution mechanism[37] unlikely.

These results show that Grignard-incompatible aryl-cobalt complexes are obtainable via reductive arylation, albeit in low yield. It must, however, be pointed out that the Grignard route[38] is always to be preferred when the desired aryl group is Grignard compatible since this synthesis, despite the inconvenience of the reverse Grignard addition, proceeds with very high yields.

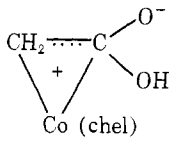
Several attempts were also made to synthesize aryl cobaloximes via the reaction of cobaloximes (II) with arylhydrazines in the presence of O_2 as described by Goedken et al.[39] Although arylcobaloximes are formed in these systems, the yields are not appreciably better than those described herein, and since the workup is more difficult and the starting materials less readily available, the reductive arylation route is to be preferred.

Carboxyalkylcobalt Complexes. As seen in Tables I and II, the carboxyalkylcobaloximes behave as relatively weak carboxylic acids, characterized by low enthalpies of ionization but very large, entropies of ionization as is typical of carboxylic acids.[40,41] Correlation of the pK_a values of 24 substituted acetic acids[42,43] with the Taft σ^* parameter[44] according to

$$pK_a = \rho^*\sigma^* + pK_a^0 \quad (6)$$

(using the method of least squares, $f = 0.078$[33]) provides values of $\rho^* = -0.689 \pm 0.017$ and $pK_a^0 = 4.81 \pm 0.03$. Using these values, eq 6, the values of pK_a for the carboxymethylcobaloximes (Tables I and II), and the value of pK_a for carboxymethylcobalamin (7.2[24,25]), we can calculate apparent values of σ^* for -$Co(D_2H_2)HOH$ (−2.16), -$Co(D_2H_2)py$ (−2.51), and -Co-cobalamin (−3.6). Similarly, correlation of the pK_a values of 24 substituted propionic acids[43] with σ^*[44,46] via eq

6 (f = 0.157[33]) provides values of σ^* = −0.237 ± 0.014 and pK_a^0 = 4.81 ± 0.02 from which we calculate σ^* = −0.34 for -Co(D_2H_2)HOH and σ^* = −0.97 for -Co(D_2H_2)py. Clearly, the *apparent* inductive effect of the cobaloxime moiety is very highly dependent upon the number of methylene groups between the cobalt atom and the carboxyl function. It is just as clear that the extremely low acidity of the carboxymethylcobalt complexes cannot be due solely to an inductive electronic effect.[48] The extremely low acidity of carboxymethylcobalamin has been attributed to hydrogen bonding between the carboxyl group and one of the acetamide side chains of the corrin ring.[24] Extension of this explanation to the carboxymethylcobaloximes[26] would seem to require restriction of at least one solvent molecule to bridge the hydrogen bond between the carboxyl group and an equatorial oxime function. In either case, this would seem to be a somewhat contrived explanation of what appears to be an observation of the well-known β effect of alkyl-transition metal complexes.[49] Hence, the weak acidity of the carboxymethylcobalt complexes, like that of the carboxymethylmanganese and -iron complexes of Green and coworkers,[50] should probably be attributed to the occurrence of significant $\sigma \rightarrow \pi$ conjugation (or vertical stabilization)[51] in these complexes, which can be viewed as indicative of significant contributions of the resonance form I to the structure of



I

these acids. This explanation is consistent with the observation of Hogenkamp et al.[52] of severely restricted rotation about the C-Co bond of carboxymethylcobalamin and has been used by Johnson and co-workers[53] to explain the very low acidity of the conjugate acids of 2,3- and 4-pyridiniomethylpentacyanocobaltate(III) ions.[53] Further investigations of this interesting and potentially biochemically important effect are in progress.

The Cobaloxime Moiety as an Aromatic Substituent. As seen in Table III, the -Co(D_2H_2)HOH moiety behaves as a moderately electron-donating Hammett substituent in both the meta and para positions which becomes significantly more donating in both positions upon ionization of the axial water ligand. The relative similarity of substituent effect in the meta and para positions is also indicated by the similar pK_a' of the m- and p-HOOCC$_6$H$_4$Co(D_2H_2)HOH complexes. Such similarity of substituent effect in the meta and para positions is indicative of a small resonance contribution to the substituent effect. Exner[54] has shown that for a wide variety of substituents for which no resonance interaction with the benzene ring is expected, the ratio of σ_p to σ_m (derived from the pK_as of the substituted benzoic acids) is 1.14. From Table III, we calculate σ_p/σ_m = 1.16 for -Co(D_2H_2)HOH and 1.15 for -Co(D_2H_2)-OH^-, again implying little resonance interaction of the cobalt center with the benzene ring. This question is amenable to quantitation using the dual substituent parameter equation of Ehrenson et al.[32]

$$\log (k/k^0) = \sigma_I\rho_I^i + \sigma_R\rho_R^i \qquad (7)$$

where k and k^0 represent the reactivity (or other correlatable property) of the substituted and unsubstituted aromatic derivatives, respectively, σ_I and σ_R are inductive and delocalization parameters of the substituent, and ρ_I and ρ_R represent the susceptibility of the reaction center to inductive and resonance effects, respectively (the superscript i refers to the position of the substituent). Using the values of σ_I and $\sigma_{R(BA)}$[55] listed by Ehrenson et al.[32] (and given in Table III), we have fit

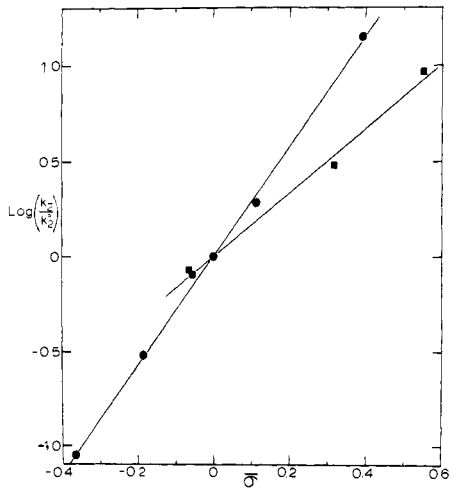


Figure 4. Derived two-dimensional plots of the dual substituent parameter analysis of the kinetics of substituted methyl benzoate saponification using eq 8-11. (●), para-substituted methyl benzoates, $\bar{\rho}$ = 2.880, f = 0.032; (■), meta-substituted methyl benzoates, $\bar{\rho}$ = 1.674, f = 0.068.

our data for methyl benzoate saponification (excluding the cobalt substituents) to eq 7 using the method of least squares to obtain the values ρ_I^p = 1.391, ρ_R^p = 1.489 (n = 5, f = 0.032[33]), and ρ_I^m = 1.363 and ρ_R^m = 0.311 (n = 5, f = 0.068[33]).[56] These correlations can be visualized using the graphical procedure of Wells et al.[57] in which eq 7 is recast as

$$\log (k/k^0) = \bar{\sigma}\bar{\rho} \qquad (8)$$

where

$$\bar{\rho} = \rho_I + \rho_R \qquad (9)$$

$$\lambda = \rho_R/\rho_I \qquad (10)$$

and

$$\bar{\sigma} = (\sigma_I + \lambda\sigma_R)/(1 + |\lambda|) \qquad (11)$$

Such plots are shown in Figure 4 for the para-((●), $\bar{\rho}$ = 2.880), and meta-((■), $\bar{\rho}$ = 1.674) substituted methyl benzoates. Using the four values of ρ thus obtained, eq 7, and the values of k_2 for the cobalt substituted methyl benzoates (Table III), we can calculate the values of σ_I and $\sigma_{R(BA)}$ for the -Co(D_2H_2)HOH and -Co(D_2H_2)OH^- substituents which are listed in Table III. From these values we can see that while both the aquo- and hydroxocobaloxime moieties behave as only moderately electron-donating Hammett substituents, the effect is almost completely inductive for both of these cobalt centers (i.e., $\sigma_{R(BA)}$ is very small). The values of −0.30 and −0.48 for σ_I for Co(D_2H_2)HOH and Co(D_2H_2)OH^-, respectively, make these centers the most inductively electron-donating substituents known.[58]

It is of interest to compare these results to those of Hill et al.,[23] who studied the ^{19}F NMR shifts of m- and p-FC$_6$H$_4$Co(III)[(DO)(DOH)pn]X, for X = -CH$_3$, p-FC$_6$H$_4$, OCN (or NCO), I, Br, and SCN (or NCS) in CH_2Cl_2 and Me_2SO, and concluded that there is extensive resonance interaction of the cobalt center with the covalently bound aryl group. These results may also be quantitated via eq 7 using as a basis set the ^{19}F NMR shifts of substituted fluorobenzenes in Me_2SO reported by Taft and co-workers.[59] Correlation of these shifts with $\sigma_{R(BA)}$ provides the values ρ_I^p = −10.28 and ρ_R^p = −22.78 (n = 9, f = 0.200) and ρ_I^m = −5.118 and ρ_R^m = −0.544 (n = 9, f = 0.197) from which we can calculate for the Co[(DO)(DOH)pn]X center values of σ_I ranging from −0.57 to −0.06 (for X = CH$_3$- and X = SCN(NCS), respectively),

and $\sigma_{R(BA)}$ ranging from −0.24 to −0.38 (for the same X).[60] It is clear that the resonance contribution to the substituent effect is much larger here than in our cobaloxime substituted methyl benzoates. This indicates that either the axial ligand, the equatorial ligand, or both, have a pronounced effect on the ability of the cobalt center to interact via π delocalization with a covalently bound aryl group, or alternatively, that the extent of such resonance interaction from chelated cobalt substituents is very strongly dependent on the nature of the reaction (or detection) center. These interesting questions are currently under investigation.

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(2) Abbreviations: RCo(D_2H_2)L-substituted organo(ligand)bis(dimethylglyoximato)cobalt = organo(ligand)cobaloxime; RCo{(DO)(DOH)pn}X = organo(ligand)diacetylmonoximeiminodiacetylmonoximatoiminopropane-1,3-cobalt; py = pyridine; BAE = *N,N'*-ethylenebis(acetylacetoneiminato)ligand; SALEN = *N,N'*-ethylenebis(salicylideneiminato)ligand.

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