Alkylation and Arylation of Mercury(II) and Thallium(III) by Organocobalt Compounds

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Abstract: Kinetic measurements are reported for a series of reactions of organobis(dimethylglyoximato)cobalt(III) complexes with mercury(II) perchlorate in aqueous perchloric acid solution, $RCo(DH)_2(H_2O) + Hg^{2+} + H_2O \rightarrow RHg^+ + Co(DH)_2(H_2O)_2^+$, where DH_2 is dimethylglyoxime and R is an alkyl, benzyl, or aryl group. The reactions obey the second-order rate law, $-d[RCo(DH)_2(H_2O)]/dt = k[Hg^{2+}][RCo(DH)_2(H_2O)]$. At 25° and an ionic strength of 1.0 M (adjusted with $NaClO_4$), the values of k for the alkyl compounds range from 54 for R = CH_3 to $9.4 \times 10^{-2}\ M^{-1}\ sec^{-1}$ for R = $n\text{-}C_3H_7$; for the benzyl compounds, from 6.5×10^{-3} for R = $p\text{-}NO_2C_6H_4CH_2$ to $1.1 \times 10^{-1}\ M^{-1}\ sec^{-1}$ for R = $p\text{-}CH_3OC_6H_4CH_2$ (corresponding to $\rho = -1.18$); and for the aryl compounds, from 2.5×10^2 for $p\text{-}FC_6H_4$ to $3.0 \times 10^4\ M^{-1}\ sec^{-1}$ for $p\text{-}CH_3OC_6H_4$ (corresponding to $\rho = -6.3$). The results are interpreted in terms of bimolecular electrophilic displacement mechanisms. A few kinetic measurements are also reported for the corresponding reactions with Tl^{3+} to form RTl^{2+}.

The alkylation of mercury(II) by organocobalt compounds was first described by Halpern and Maher[1] who reported, in 1964, that $CH_3Co(CN)_5{}^{3-}$ reacts with $HgCl_2$ in aqueous solution to form CH_3HgCl. Such reactions and their analogs, *e.g.*, the corresponding alkylations of thallium(III), have subsequently received considerable attention on the part of several workers,[2-8] especially following the demonstration by Wood, Kennedy, and Rosen in 1968 that methylcobalamin (the methylcobalt derivative of vitamin B_{12}) was capable of effecting the synthesis of both monomethylmercury and dimethylmercury in enzymatic as well as nonenzymatic systems.[2] Interest in these reactions has been heightened by their probable biosynthetic role in the conversion of inorganic mercury to highly toxic methylmercury compounds in lake and river sediments under environmental conditions.[2,9]

Following several earlier fragmentary studies on the alkylation of other mercury(II) salts by various organocobalt compounds,[3-6] we undertook a comprehensive study of the kinetics of the alkylation, benzylation, and arylation of mercury(II) perchlorate by organobis(dimethylglyoximato)cobalt(III) complexes, $RCo(DH)_2(H_2O)$, in aqueous perchloric acid solution (eq 1).

$$RCo(DH)_2(H_2O) + Hg^{2+} + H_2O \xrightarrow{k_1} RHg^+ + Co(DH)_2(H_2O)_2{}^+ \qquad (1)$$

While this study was in progress a communication by Adin and Espenson[7] appeared which described essentially similar measurements on the same *alkylation* reactions. The principal additional contributions described in this paper are the extensions of these studies to the corresponding benzylation and arylation reactions, including the determination of the influence of ring substituents on the rates. A few measurements also are reported on the related alkylations and arylations of thallium(III) by organocobalt compounds (eq 2).

$$RCo(DH)_2(H_2O) + Tl^{3+} + H_2O \xrightarrow{k_2} RTl^{2+} + Co(DH)_2(H_2O)_2{}^+ \qquad \text{(2(}$$

Experimental Section

Materials. All the organocobalt compounds were prepared and isolated in pure form as the pyridinato complexes, $RCo(DH)_2(C_5H_5N)$. The alkyl and benzyl compounds were prepared according to the procedure of Schrauzer and Windgassen,[10] by the reactions of $Co^I(DH)_2(C_5H_5N)^-$ (generated *in situ* by reduction of $Co^{II}(DH)_2(C_5H_5N)$ with sodium borohydride) with the corresponding alkyl or benzyl halides.

Anal. Calcd for $CH_3Co(DH)_2(C_5H_5N)$: C, 43.87; H, 5.78; N, 18.27. Found: C, 43.89; H, 5.78; N, 18.18. Calcd for $C_2H_5Co(DH)_2(C_5H_5N)$: C, 45.34; H, 6.09; N, 17.63. Found: C, 45.43; H, 6.07; N, 17.65. Calcd for $n\text{-}C_3H_7Co(DH)_2(C_5H_5N)$: C, 46.70; H, 6.37; N, 17.02. Found: C, 46.44; H, 5.96; N, 16.90. Calcd for $CF_3CH_2Co(DH)_2(C_5H_5N)$: C, 39.92; H, 4.69; N, 15.52; F, 12.63. Found: C, 39.69; H, 4.64; N, 15.71; F, 12.67. Calcd for $(CH_3)_2CHCo(DH)_2(C_5H_5N)$: C, 46.70; H, 6.37; N, 17.02. Found: C, 46.56; H, 6.29; N, 16.90. Calcd for $C_6H_5CH_2Co(DH)_2(C_5H_5N)$: C, 52.29; H, 5.70; N, 15.24. Found: C, 52.08; H, 5.75; N, 15.19. Calcd for $p\text{-}CH_3C_6H_4\text{-}CH_2Co(DH)_2(C_5H_5N)$: C, 53.35; H, 5.97; N, 14.82. Found: C, 53.03; H, 6.03; N, 14.64. Calcd for $p\text{-}CH_3OC_6H_4CH_2Co\text{-}(DH)_2(C_5H_5N)$: C, 51.60; H, 5.77; N, 14.33. Found: C, 51.53; H, 5.65; N, 14.16. Calcd for $p\text{-}FC_6H_4CH_2Co(DH)_2\text{-}(C_5H_5N)$: C, 50.36; H, 5.51; N, 14.69. Found: C, 50.13; H, 5.37; N, 14.54. Calcd for $p\text{-}NO_2C_6H_4CH_2Co(DH)_2(C_5H_5N)$: C, 47.63; H, 5.00; N, 16.66. Found: C, 47.04; H, 4.89; N, 16.33.

The aryl cobalt compounds were prepared by reactions of the corresponding aryl Grignard reagents with $Co(DH)_2(C_5H_5N)Cl$ according to the method of Schrauzer[11] and isolated in pure form.

Anal. Calcd for $C_6H_5Co(DH)_2(C_5H_5N) \cdot CH_2Cl_2$: C, 46.24; H, 4.89; N, 13.72. Found: C, 46.28; H, 4.94; N, 13.70 (presence of one CH_2Cl_2 molecule of crystallization confirmed by nmr). Calcd for $p\text{-}CH_3C_6H_4Co(DH)_2(C_5H_5N)$: C, 52.20; H, 5.66; N, 15.20. Found: C, 52.38; H, 5.80; N, 15.25. Calcd for $p\text{-}FC_6H_4Co(DH)_2(C_5H_5N)$: C, 49.25; H, 5.00; N, 15.11. Found: C, 48.75; H, 4.90; N, 14.84. Calcd for $p\text{-}CH_3OC_6H_4Co(DH)_2\text{-}(C_5H_5N)$: C, 50.53; H, 5.51; N, 14.73. Found: C, 49.81; H, 5.34; N,13.94.

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(9) S. Jensen and A. Jernelöv, *Nature (London)*, **223**, 753 (1969).

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

Solutions of mercury(II) perchlorate were prepared by dissolving reagent grade mercuric oxide (Baker) in aqueous perchloric acid. Solutions of thallium(III) perchlorate were prepared by dissolving thallium(III) hydroxide (which had been precipitated with ammonia and thoroughly washed with distilled water) in aqueous perchloric acid. Sodium perchlorate was prepared by neutralizing reagent grade perchloric acid with sodium carbonate and recrystallizing the precipitated salt. Distilled water was used in the preparation of all solutions.

Stoichiometry and Products. The stoichiometries of the reactions (*i.e.*, the molar ratio of organocobalt compounds and Hg^{2+} or Tl^{3+} that reacted with each other) were determined for representative systems by spectral titration of a *ca.* 10^{-3} *M* solution of the organocobalt compound with a standard solution of mercury(II) or thallium(III) perchlorate, following the absorbance decrease in the region of the absorbance maximum of the organocobalt compound (*ca.* 450 nm).

The following procedure was used to isolate and characterize the products of representative reactions. Equivalent amounts (*ca.* 0.03 *M*) of the organocobalt compound and of mercury(II) perchlorate were allowed to react in 0.1 *M* aqueous $HClO_4$. Following completion of the reactions (confirmed spectrophotometrically), 2 equiv of sodium chloride were added and the solutions cooled to 0° to precipitate the organomercurial products as the white chlorides, RHgCl, which were washed with water, dried *in vacuo*, and characterized by their melting point and nmr spectra. The filtrate, following separation of the organomercury chloride, was concentrated by evaporation and passed through a Dowex 50 W-X8 cation-exchange column which retained the $Co(DH)_2(H_2O)_2^+$ product. The latter was eluted with 0.2 *M* $HClO_4$ and the eluent solution concentrated by evaporation, followed by addition of ethanol, and cooling to precipitate pure $[Co(DH)_2(H_2O)_2]ClO_4$ which was characterized spectrally and by elemental analysis.

Kinetic Measurements. The kinetics of the reactions were determined by monitoring the decrease in absorbance of the organocobalt compounds, usually in the region of 450 nm where the latter characteristically exhibit strong absorption (for example, $CH_3Co(DH)_2(OH_2)$: λ_{max} 442 nm, ϵ_{max} 1.3×10^3) and the products, *i.e.*, $Co(DH)_2(H_2O)_2^+$ and RHg^+ (or RTl^{2+}), are virtually transparent. The rates of reactions with half-lives shorter than about 10 sec were measured with a Durrum-Gibson stopped flow spectrophotometer, while those of slower reactions were measured in a Cary 14 spectrophotometer. In each case the reaction chamber was thermostated at 25.0 ± 0.2°.

Results and Discussion

Stoichiometry and Products. While it was convenient, from the synthetic standpoint, to prepare and isolate the organocobalt compounds as the pyridinato complexes, dissociation of the pyridine ligand according to eq 3 was virtually complete under the reaction conditions (≥ 0.2 *M* $HClO_4$), so the species actually present in solution was effectively the organoaquo complex, *i.e.*, $RCo(DH)_2(H_2O)$. This was confirmed spectrophotometrically and is also supported by the excellent agreement between our own kinetic results and the results of the measurements of Adin and Espenson[7] on the corresponding reactions of Hg^{2+} with several of the actual alkyl aquo complexes, $RCo(DH)_2(H_2O)$ (R = CH_3, C_2H_5, *n*-C_3H_7).

$$RCo(DH)_2(C_5H_5N) + H_3O^+ \rightleftharpoons RCo(DH)_2(H_2O) + C_5H_5NH^+ \quad (3)$$

In agreement with the results already reported by Adin and Espenson[7] for Hg^{2+}, spectral titrations (such as those depicted in Figure 1) of several representative organocobalt compounds with Hg^{2+} or Tl^{3+} yielded end points close to Hg^{2+} (or Tl^{3+}):$RCo(DH)_2(H_2O)$ = 1:1 in accord with the stoichiometries of eq 1 and 2. Further confirmation of the stoichiometry was provided (i) by the actual isolation in yields exceeding 90% of several representative organomercurial products as the corresponding pure chlorides, RHgCl (*e.g.*, for R = CH_3, $C_6H_5CH_2$, and C_6H_5) and (ii) by quantitative matching of the final solution spectra with the known spectrum of the product ion, $Co(DH)_2(H_2O)_2^+$.

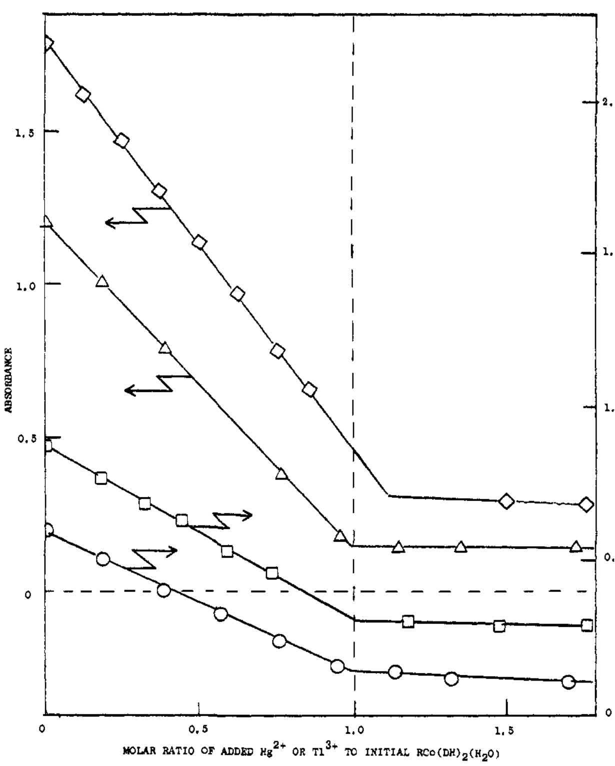
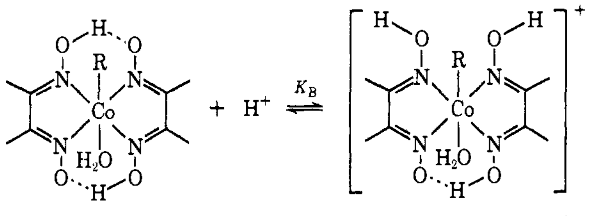


Figure 1. Spectral titrations at 440 nm of $RCo(DH)_2(H_2O)$ complexes with Hg^{2+} and Tl^{3+}: △, 9.54×10^{-4} *M* $CH_3Co(DH)_2(H_2O)$ with Hg^{2+}; ○, 1.15×10^{-3} *M* $C_6H_5CH_2Co(DH)_2(H_2O)$ with Hg^{2+}; □, 1.37×10^{-3} *M* $C_6H_5Co(DH)_2(H_2O)$ with Tl^{3+}; ◇, 1.59×10^{-3} *M* $CH_3Co(DH)_2(H_2O)$ with Tl^{3+} (1.0 *M* H^+).

Kinetics of Alkylation and Arylation of Mercury(II). The kinetic behavior of these reactions has been described by Adin and Espenson.[7] Because of the limited solubility of the organocobalt compounds at higher pH's, it was necessary to perform the kinetic measurements in fairly acidic solutions containing at least 0.2 *M* H^+ (as $HClO_4$). Under these conditions considerable protonation of $RCo(DH)_2(H_2O)$, according to eq 4 and 5, occurs. This protonation can be detected spectrophotometrically and through its influence upon the kinetics of the reactions with Hg^{2+}.



$RCo(DH)_2(H_2O)$ $\quad$ $RCo(DH_2)(DH)(H_2O)^+$ $\quad$ (4)

$$[RCo(DH_2)(DH)(H_2O)^+]/[RCo(DH)_2(H_2O)][H^+] = K_B \quad (5)$$

As demonstrated by Adin and Espenson[7] for the alkyl compounds, the kinetic behavior of the reactions could be accommodated by the assumption that only $RCo(DH)_2(H_2O)$ (and *not* $RCo(DH_2)(DH)(H_2O)^+$) reacts with Hg^{2+}. The rate law, accordingly, assumes

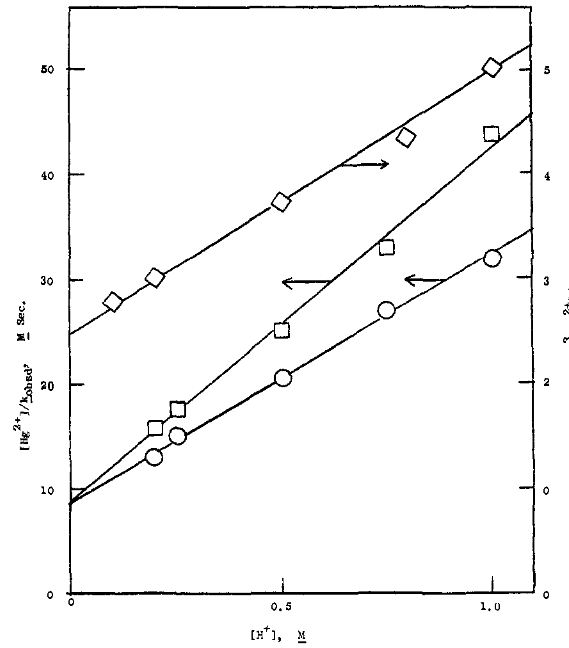


Figure 2. Representative plots of $[Hg^{2+}]/[k_{obsd}]$ *vs.* $[H^+]$ according to eq 8. ○, R = p-$CH_3OC_6H_4CH_2$; □, R = C_2H_5; ◇, R = C_6H_5.

the form of eq 6, where $[RCo]_{total}$ = $[RCo(DH)_2(H_2O)]$ + $[RCo(DH_2)(DH)(H_2O)^+]$.

$$-d[RCo]_{total}/dt = k_1[RCo(DH)_2(H_2O)][Hg^{2+}] \quad (6)$$

$$= \frac{k_1[RCo]_{total}[Hg^{2+}]}{(1 + K_B[H^+])} \quad (7)$$

The kinetic experiments typically encompassed the initial composition ranges 1×10^{-4}–5×10^{-4} M RCo_{total}, 2.5×10^{-3}–2×10^{-1} M Hg^{2+}, and 0.2–1.0 M H^+. The ionic strength was maintained at 1.0 M with $NaClO_4$. All kinetic measurements were made at 25.0 ± 0.2°. Hg^{2+} was always in sufficient excess over RCo_{total} that the observed kinetics were pseudo first order in accord with eq 8.

$$-d \ln [CoR]_{total}/dt = k_{obsd} = \frac{k_1[Hg^{2+}]}{1 + K_B[H^+]} \quad (8)$$

Pseudo-first-order rate plots (ln $[CoR]_{total}$ *vs.* t), which were always linear over at least four half-lives, yielded values of k_{obsd}. Values of k_1 and K_B were derived, through eq 8, from the slopes and intercepts of linear plots of $[Hg^{2+}]/[k_{obsd}]$ *vs.* $[H^+]$, such as those depicted in Figure 2. This kinetic behavior, which had already been demonstrated by Adin and Espenson[7] for the alkylcobalt complexes, was found to apply also to the benzyl and arylcobalt complexes of the present study. Confirmation of the first-order dependence in the Hg^{2+} concentration was provided by plots such as those depicted by Figure 3. All the values of k_1 and K_B, determined in this way, are listed in Table I.

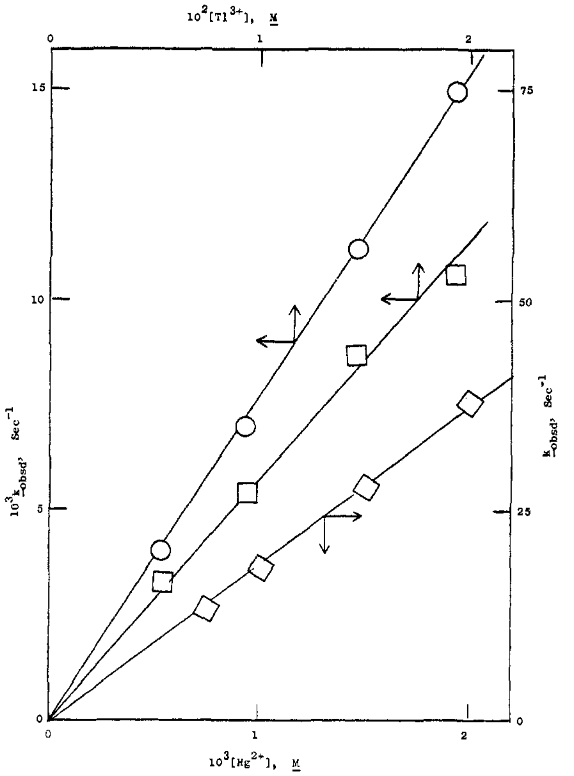


Figure 3. Representative plots of k_{obsd} *vs.* $[Hg^{2+}]$ or $[Tl^{3+}]$. ○, $C_6H_5Co(DH)_2(H_2O)$ + Tl^{3+} (1.0 M H^+); □, $CH_3Co(DH)_2(H_2O)$ + Tl^{3+} (1.4 M H^+); ◇, p-$CH_3OC_6H_4Co(DH)_2(H_2O)$ + Hg^{2+} (1.0 M H^+).

Table I. Kinetic Data for the Reactions of $RCo(DH)_2(H_2O)$ with Hg^{2+} at 25° (μ = 1.0)

R	k_1, M^{-1} sec^{-1}	K_B, M^{-1}
CH_3	54 (65)[a]	3.5 (3.5)[a]
C_2H_5	1.2×10^{-1} (1.2×10^{-1})[a]	3.9 (4.2)[a]
n-C_3H_7	9.4×10^{-2} (9.2×10^{-2})[a]	4.7 (4.3)[a]
$C_6H_5CH_2$	7.5×10^{-2}	2.4
p-$NO_2C_6H_4CH_2$	6.5×10^{-3}	1.1
p-$FC_6H_4CH_2$	2.8×10^{-2}	1.7
p-$CH_3C_6H_4CH_2$	9.0×10^{-2}	1.9
p-$CH_3OC_6H_4CH_2$	11.3×10^{-2}	2.6
C_6H_5	4.0×10^{2}	1.0
p-FC_6H_4	2.5×10^{2}	1.4
p-$CH_3C_6H_4$	4.5×10^{3}	0.8
p-$CH_3OC_6H_4$	3.0×10^{4}	2.4

[a] Values in parentheses are from ref 7.

Our data for the several *alkyl* complexes listed in Table I are in excellent agreement with those already reported by Adin and Espenson[7] and with the trends found by other workers on related systems including those involving alkylcobalamins.[6] This trend, *i.e.*, $k_{CH_3Co} > k_{C_2H_5Co} > k_{i\text{-}C_3H_7Co}$, is consistent with that expected for the electrophilic displacement (S_E2) mechanism[12] in terms of which these reactions have been interpreted.[5] The lowering of reactivity by electron-withdrawing substituents, as reflected in the immeasurably slow reaction of $CF_3CH_2Co(DH)_2(H_2O)$ with Hg^{2+}, is also consistent with this interpretation.

The principal new contributions of the present study relate to the reactions of the aryl and benzyl compounds. The reactivities of the arylcobalt compounds were found to be considerably higher than those of the alkyl compounds and to exhibit substituent effects (*i.e.*, rate enhancement by electron-donating substituents and rate reduction by electron-withdrawing substituents), in accord with the expectation for an electrophilic displacement mechanism. The influence of substituents is depicted by the Hammett plot in Figure 4, the slope

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(12) F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials," McGraw-Hill, New York, N. Y., 1968.

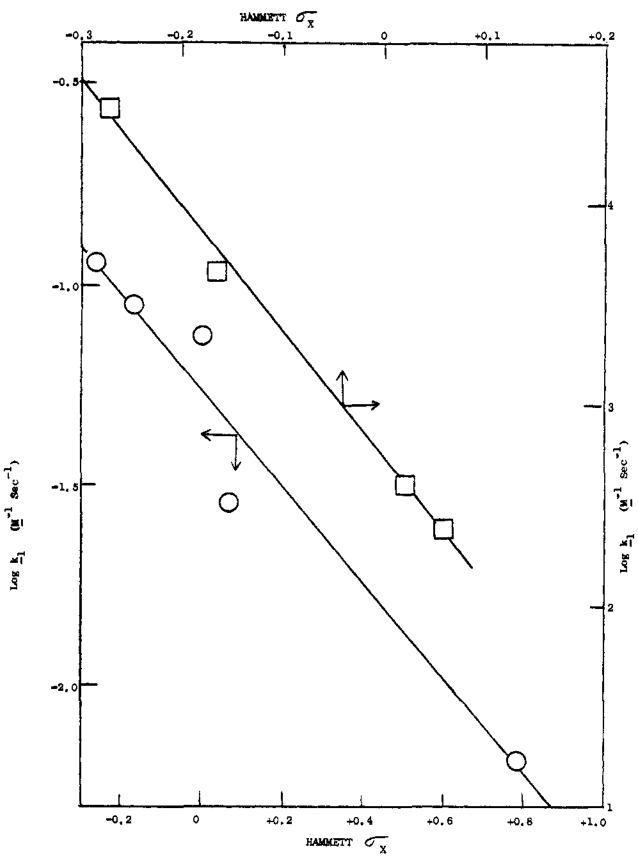

Figure 4. Hammett plots of k_1 for para-substituted benzyl (○) and phenyl (□) compounds.

of which corresponds to the very high ρ value of -6.3. This is close to the value of $\rho = -5.9$ reported by Dessy and Lee[13] for the series of reactions, $(p\text{-}ZC_6H_4)_2Hg + HgI_2 \rightarrow 2p\text{-}ZC_6H_4HgI$, and interpreted by them in terms of the weak electrophilicity of the Hg atom of the attacking HgI_2 species.

The reactivities of the benzylcobalt compounds are of the same order as those of the primary alkyl compounds (*e.g.*, $k_1 = 7.5 \times 10^{-2}$ for $R = C_6H_5CH_2$ *vs.* 9.4×10^{-2} for $R = CH_3CH_2$) and the pattern of influence of para substituents is qualitatively similar to that for the phenyl compounds, *i.e.*, rate enhancement by electron-donating substituents and suppression by electron-withdrawing substituents. The Hammett plot for these compounds (Figure 4) exhibits some scatter. Not unexpectedly, the value of ρ, *i.e.*, *ca.* -1.2, is much lower than for the phenyl compounds but of the same order as that reported for the exchange of benzylmercury(II) halides with mercury(II) salts, *i.e.*, $p\text{-}ZC_6H_4CH_2HgBr + HgBr_2 \rightarrow p\text{-}ZC_6H_4CH_2HgBr + HgBr_2$ ($\rho \sim -1$).[14] In this connection it should be noted, however, that the reactivity sequence for the reactions of the alkylcobalt compounds with mercury(II) (*i.e.*, $CH_3 > C_2H_5 \sim n\text{-}C_3H_7 \gg i\text{-}C_3H_7$) differs from that found by Dessy and Lee[13] for the reactions $R_2Hg + HgI_2 \rightarrow 2RHgI$ (*i.e.*, $CH_3 < C_2H_5 \sim n\text{-}C_3H_7 \sim i\text{-}C_3H_7$). The significance of this difference is unclear.

In contrast to the behavior of k_1, the spread of K_B values is very small and no systematic dependence on substituents is apparent.

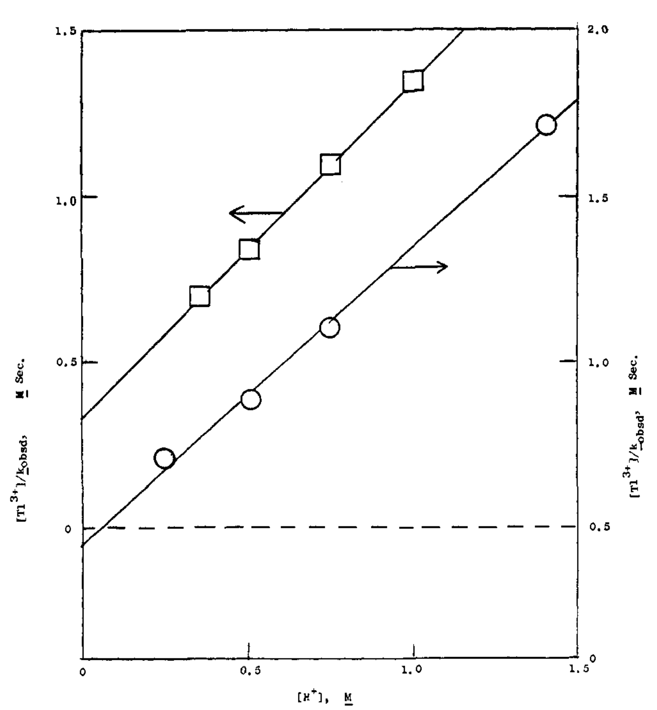

Figure 5. Plots of $[Tl^{3+}]/[k_{obsd}]$ *vs.* $[H^+]$ for the reactions of $RCo(DH)_2(H_2O)$ with Tl^{3+}. ○, $R = CH_3$; □, $R = C_6H_5$ (curves displaced for clarity).

Reactions with Thallium(III). Kinetic measurements on the reactions of the $RCo(DH)_2(H_2O)$ compounds with thallium(III) were confined to two representative systems, *i.e.*, those for which $R = CH_3$ and C_6H_5. The general form of the kinetics was similar to that for the reactions with Hg^{2+} as reflected in the linear plots of $[Tl^{3+}]/[k_{obsd}]$ *vs.* H^+ in Figure 5 and of k_{obsd} *vs.* Tl^{3+} in Figure 3. However, the interpretation of the H^+ dependence in this case is complicated by the fact that, in contrast to Hg^{2+}, the hydrolysis of the Tl^{3+} ion (for which $K_{hydrolysis} = 0.073\ M$)[15] is appreciable in the pH range of the kinetic experiments and thus cannot be neglected. The significance of the apparent values of k_2 and K_B obtained by fitting the plots of Figure 5 to an equation analogous to eq 7 is therefore ambiguous. Not surprisingly, the values of K_B determined in this way, while of the same order as those derived from the experiments on Hg^{2+}, are not in good quantitative accord with the latter. The values of k_2 (and corresponding values of K_B in parentheses) yielded by this treatment are CH_3, 2.2 M^{-1} sec^{-1} (1.9 M^{-1}) and C_6H_5, 3.0 (3.1). While the exact values of k_2 are subject to some uncertainty, as noted above, it is evident that the spread of these values is much smaller than the corresponding spread of rate constants for Hg^{2+} (*i.e.*, of k_1).

Formation of Higher Organomercury and Organothallium Compounds. Only the first stage of alkylation or arylation could be detected under the conditions of our experiments, with no indication whatsoever of the formation of R_2Hg or R_2Tl^+ by further reactions of RHg^+ or RTl^{2+} with $RCo(DH)_2(H_2O)$. This is consistent with the markedly reduced electrophilic characters of RHg^+ and RTl^{2+}, compared with Hg^{2+} and Tl^{3+}, respectively, and is also reflected, for example, in the relative reactivities of Hg^{2+} and RHg^+ toward

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[13] R. E. Dessy and Y. K. Lee, *J. Amer. Chem. Soc.*, 82, 689 (1960).

[14] O. A. Reutov, T. A. Smolma, and V. A. Kalyavin, *Proc. Acad. Sci. USSR, Chem. Sect.*, 139, 697 (1961).

[15] G. Biederman, *Ark. Kemi*, 5, 441 (1953).

oxymercuration of olefinic compounds.[16,17] This particular feature of the behavior of these systems is significant in the light of the demonstrated formation of $Hg(CH_3)_2$ through the methylation of mercury(II) by methylcobalamin.[2,8] The circumstances which favor the dialkylation of mercury(II) in this and certain other cases are still unclear and warrant further attention.

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(17) P. Abley, J. E. Byrd, and J. Halpern, *J. Amer. Chem. Soc.*, **94**, 1985 (1972).

Copper(II)-Catalyzed Hydrolysis of the Methyl Esters of Glycylglycine and Glycylsarcosine

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Abstract: The ester hydrolysis of glycylglycine methyl ester (GGOMe) is catalyzed by Cu(II) in the 6.5–8.0 pH range. Under these conditions the ester is bound in $Cu(H_{-1}GGOMe)^+$ *via* the terminal amino group, the deprotonated amide nitrogen, and possibly the ester group. Coordination by the deprotonated amide nitrogen moves the ester group in position to bind to the metal ion, which promotes the hydrolysis of the ester. The first-order dependence on $[OH^-]$ suggests a mechanism in which rate-determining OH^- attack occurs at the coordinated ester carbon atom. This rate is approximately 10^8 times faster than the hydrolysis in the absence of the Cu(II). To illustrate the importance of amide deprotonation to the catalysis, the effect of Cu(II) on the hydrolysis of glycylsarcosine methyl ester (GSOMe) in which the amide proton is replaced by a CH_3 group was studied. In this case, there is no evidence for Cu(II) catalysis. Also, the hydrolysis of GGOMe in the presence of Zn(II) was examined. While Zn(II) is known to be an effective catalyst for amino acid ester hydrolysis, it does not facilitate amide proton dissociation in dipeptides and therefore shows no significant catalysis of GGOMe hydrolysis. Kinetic studies of the ester hydrolysis of $Cu(H_{-1}GGOMe)_2$ and the glycylglycine (GG) complex $Cu(H_{-1}GG)(GGOMe)$ are also discussed and contrasted with the above results.

Transition metals have long been known to promote the hydrolysis of α-amino acid esters and their derivatives.[2] We have now extended these investigations to dipeptide esters. The present paper reports kinetic studies on the Cu(II)-promoted hydrolysis of glycylglycine methyl ester (GGOMe) and glycylsarcosine methyl ester (GSOMe) to give the corresponding dipeptides, GG and GS, and methanol. The results indicate that ionization of the amide hydrogen in GGOMe is of major importance to the Cu(II)-catalyzed hydrolysis of this ester. In contrast, there is no evidence for Cu(II) catalysis of the hydrolysis of GSOMe which has no amide hydrogen. In addition to catalyzing GGOMe hydrolysis, Cu(II) constrains the reaction to give GG as the only product, in contrast to the uncatalyzed reaction which yields the cyclized product 2,5-piperazinedione as well.[3] Thus, the presence of Cu(II) brings about some major changes in the hydrolysis of dipeptide esters.

Experimental Section

Reagents. Baker Analyzed Reagent Grade $Cu(NO_3)_2 \cdot 3H_2O$ and $Zn(NO_3)_2 \cdot 6H_2O$ were used for all metal solutions, which were standardized *via* standard ion exchange techniques. Aliquots of the metal ion solutions were passed through Dowex 50W-X8 strongly acidic cation exchange resin, and the effluent solutions were titrated with standard NaOH solution using phenolphthalein as an indicator.

Glycylglycine (GG) and the hydrochloride salt of glycylglycine methyl ester were purchased from Mann Research Laboratories and were of the highest purity available. They were used without further purification. Glycylglycine solutions were standardized by pH titration. Solutions of the hydrochloride salt of glycylglycine methyl ester and glycylsarcosine methyl ester were standardized *via* ion exchange methods using Dowex 50W-X8 strongly acidic cation exchange resin. The calculated amount of hydrochloride salt based on weight and the amount obtained *via* the ion exchange technique were the same within 2%, indicating no hydrolysis of the ester occurred on the column.

Preparation of Glycylsarcosine Methyl Ester (GSOMe). Glycylsarcosine was purchased from Sigma Chemical Co. and was recrystallized three times from water–ethanol prior to use. Two grams of the dipeptide was then mixed with 25 ml of methanol, and HCl gas was bubbled into the mixture. After the glycylsarcosine dissolved, HCl addition was continued for 0.5 hr. Attempts to crystallize the hydrochloride salt of the dipeptide ester result in the formation of an oil.[4] The oil was dried under vacuum, and the solidified product was dissolved in ethanol. Crystals were obtained by adding ethyl acetate until the solution became cloudy and then cooling to −40°. The product was then recrystallized from ethanol by the addition of dioxane or ethyl acetate. The melting point of the purified dipeptide ester hydrochloride was 144.5–146°.

The infrared spectrum of the product in D_2O at pD 2.45 contained two strong carbonyl absorption maxima at 1740 and 1686 cm^{-1} corresponding to ester and amide carbonyl absorptions, respectively.[5] The proton nmr spectrum was obtained with a Varian Associates Model A-60 spectrometer on GSOMe at pD 2.45 in

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