1.76-2.04 (4 H, m, 2 × ring CH_2), 1.21-1.43 (7 H, m, 3 × CH_2, OH), 1.31 (3 H, s, CH_3), 0.97 (3 H, d, J = 6.5 Hz, $CHCH_3$), 0.87 (3 H, t, J = 7 Hz, CH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 163.77 (C), 147.71 (CH), 124.16 (C), 67.82 (C), 65.81 (CH), 46.25 (CH_2), 39.53 (CH_2), 36.56 (CH_2), 32.79 (CH), 29.68 (CH_2), 26.40 (CH_2), 25.27 (CH_3), 22.80 (CH_2), 22.22 (CH_2), 19.79 (CH_3), 13.98 (CH_3); *m/e* (EI) 265, 222. HRMS Calcd for $C_{16}H_{27}NO_2$ (M^+): 265.2039. Found: 265.2039.

Pumiliotoxin 251D (1) and 1·HCl.[3a] To a solution of (*Z*)-**12** (16 mg, 0.06 mmol) in ether (2 mL) was added a solution of aluminum hydride in ether (0.18 M, 1.8 mL, 5.4 equiv) at room temperature. After 10 min, the reaction was quenched with saturated aqueous sodium sulfate solution and filtered, and the solids were washed with CH_2Cl_2. Addition of methanolic HCl to the resulting solution effected complete conversion to the hydrochloride salt, and evaporation in vacuo afforded pumiliotoxin 251D hydrochloride as a colorless solid (11.7 mg, 67%). Recrystallization from ether/petroleum ether yielded colorless crystals. **1**·HCl:[32] mp 200-201 °C (evacuated sealed capillary); $[\alpha]^{20}_D$ +23.6° (*c* 0.11, MeOH); $[\alpha]^{20}_{546}$ +36.1° (*c* 0.11, MeOH); ^1H NMR (270 MHz, CD_3OD) δ 5.32 (1 H, d, J = 10 Hz, *H*-10), 4.36 (1 H, d, J = 13 Hz, *H-5β*), 3.05-3.59 (4 H, m, *H-3β*, N*H*, *H-5α*, *H-11*), 2.43) (1 H, d, J = 15 Hz, *H-7*), 2.36 (1 H, d, J = 15 Hz, *H*-7), 1.77-2.18 (6 H, m, 2 × *H*-1, 2 × *H-2*, *H-3α*, *H-8*a), 1.12-1.35 (6 H, m, 2 × *H*-12, 2 × *H*-13, 2 × *H*-14), 1.28 (3 H, s, *C-8Me*), 1.03 (3 H, d, J = 6.5 Hz, *C-11Me*), 0.89 (3 H, t, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR (68 MHz, CD_3OD) δ 140.93, 125.75, 74.05 68.96, 54.33, 52.64, 47.68, 38.60, 33.76, 31.10, 26.30, 24.10, 22.13, 21.76, 20.89, 14.69. Pumiliotoxin 251D (**1**) was obtained by neutralization of the hydrochloride salt with saturated aqueous sodium bicarbonate solution, followed by extraction of the free base with CH_2Cl_2. The extracts were dried (Na_2SO_4), and the solvents were removed in vacuo at 0 °C to avoid loss of the relatively volatile base. **1**: IR ($CHCl_3$) 3400, 1660 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.04 (1 H, d, J = 9.5 Hz, *H*-10), 3.79 (1 H, d, J = 12 Hz, *H-5β*), 3.08 (1 H, m, *H-3β*), 2.35 (1 H, d, J = 12 Hz, *H-5α*), 2.37 (1 H, m, *H-11*), 2.17 (1 H, m, *H-3α*), 2.14 (2 H, br s, 2 × *H-7*), 1.98 (1 H, m, *H-8a*), 1.66-1.78 (4 H, m, 2 × *H-1*, 2 × *H-2*), 1.11-1.34 (7 H, m, 2 × *H-12*, 2 × *H-13*, 2 × *H-14*, O*H*), 1.13 (3 H, s, *C-8Me*), 0.97 (3 H, d, J = 6.5 Hz, *C-11Me*), 0.88 (3 H, t, J = 7 Hz, CH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 134.70 (CH), 129.74 (C), 71.68 (CH), 68.31 (C), 54.65 (CH_2), 53.16 (CH_2), 48.81 (CH_2), 37.43 (CH_2), 32.05 (CH), 29.71 (CH_2), 24.26 (CH_3), 23.22 (CH_2), 22.80 (CH_2), 21.67 (CH_3), 21.05 (CH_2), 14.11 (CH_3); *m/e* (EI) 251, 166, 112, 70. HRMS Calcd for $C_{16}H_{29}NO$ (M^+): 251.2249. Found: 251.2253.

(32) Literature data[3a] for (+)-pumiliotoxin 251D hydrochloride (**1**·HCl): mp 206-206.5 °C (evacuated sealed capillary); $[\alpha]^{25}_D$ +28.0° (*c* 0.62, MeOH); $[\alpha]^{25}_{546}$ +32.0° (*c* 0.62, MeOH).

Acknowledgment. We thank Professor L. E. Overman for copies of ^1H and ^{13}C NMR spectra of both pumiliotoxin 251D and related synthetic model systems. Financial support for this work was received from the Science and Engineering Research Council (Quota award, GR/C/88130, GR/E/57024).

Registry No. 1, 73376-35-9; **1**·HCl, 73395-60-5; **6**, 126179-87-1; **7a**, 131636-08-3; **7a** alcohol, 131636-10-7; **7b**, 131636-09-4; **8**, 131636-11-8; **9**, 131636-12-9; **10**, 131722-93-5; 8-*epi*-**10**, 131722-95-7; **11**, 131636-13-0; (*Z*)-**12**, 131636-14-1; (*E*)-**12**, 131722-94-6; (*R*)-2-methylhexanal, 132151-88-3; (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone, 77943-39-6; hexanoyl chloride, 142-61-0; *N*-hexanoyl-4(*R*)-methyl-5(*S*)-phenyl-2-oxazolidinone, 131636-15-2; 4(*R*)-methyl-*N*-[2(*R*)-methylhexanoyl]-5-(*S*)-phenyl-2-oxazolidinone, 131636-16-3; (*R*)-2-methylhexanol, 66050-98-4.

Supplementary Material Available: Experimental details for the preparation of (*R*)-2-methylhexanol and tables giving the crystallographic data, the final coordinates and equivalent thermal parameters, bond lengths and angles, and dihedral angles for (*E*)-**12** (8 pages). Ordering information is given on any current masthead page.

Bromination of Imidazoles Coordinated to Cobalt(III). Kinetics and Mechanism of Bromination of $RImH^{3+}$ Systems (R = $(NH_3)_5Co$), Wheland Intermediates, and Preassociation or Diffusion Control

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Abstract: The bromination of $RImH^{3+}$ and several Me- (2-, 3-, 4-, 5-, and 2,4-) and Br- (4-, 5-, and 4,5-) substituted imidazole complexes of the pentaamminecobalt(III) ion (R = $(NH_3)_5Co^{3+}$) has been studied in aqueous solution at 25.0 °C, I = 1.0 or 0.1 M ($NaClO_4$). Reactions are generally fast and result in polybromination when more than one C site is available, even when less than stoichiometric amounts of Br_2 are used. Site reactivity order is C-4 > C-5 ≫ C-2 for both the neutral (**11**) and anionic (**12**) ligands. Br_2 is a much more powerful electrophile than Br_3^-. The pH dependence of monobromination is complex for the neutral ligand **11** and suggests proton abstraction from a Wheland addition intermediate (CoHBr) is rate-determining at acidic pHs; both spontaneous and OH^--catalyzed pathways are observed. At more neutral pHs, bromine addition becomes rate-determining. Reaction of the anionic ligand **12** is very fast with rate constants up to 3.4 × 10^{10} M^{-1} s^{-1} (for R-2,4-Me_2Im^{2+}). For such species, preassociation with Br_2 before proton abstraction is suggested as an alternative mechanism. For R-3-$MeIm^{3+}$ (*N*-methyl derivative), reaction via the ammine conjugate base is suggested for the OH^--catalyzed reaction. The effects of deuterium substitution and temperature on the reaction rate are discussed.

Introduction

When imidazole is treated with an equal amount of bromine in aqueous or nonaqueous solution, the major product is 2,4,5-tribromoimidazole,[1] eq 1. A similar result occurs with N- and C-substituted imidazoles,[2-4] all nonsubstituted carbons are readily brominated in the presence of even limited amounts of bromine, eq 2. This inability to prepare mono- (especially) and dibrominated imidazoles has resulted in more circuitous routes being devised for these synthetically useful precursors.[5]

(1) Balaban, I. E.; Pyman, F. L. *J. Chem. Soc.* **1922**, *121*, 947.
(2) Balaban, I. E.; Pyrman, F. L. *J. Chem. Soc.* **1924**, *125*, 1564. Light, L.; Pyman, F. L. *J. Chem. Soc.* **1922**, *121*, 2626. Pyman, F. L.; Timmis, G. M. *J. Chem. Soc.* **1923**, *123*, 494.
(3) Linda, P. *Tetrahedron* **1969**, *25*, 3297.
(4) Boulton, B. E.; Coller, B. A. W. *Aust. J. Chem.* **1974**, *27*, 2331.

(5) For example, 4(5)-bromoimidazole can be made by reducing 2,4,5-tribromoimidazole with aqueous Na_2SO_3[1] and 4,5-dibromoimidazole by treatment of the same starting material with triphenylphosphine in ethanol: *Chem. Abstr.* **1965**, *63*, 16369. 2-Bromoimidazole and 2,4(5)-dibromoimidazole can be made as a mixture by treating 2,5-dibromoimidazole-4-carboxy-*p*-bromoanilide with concentrated HBr in a sealed tube: King, H.; Murch, W. O. *J. Chem. Soc.* **1923**, *123*, 621.

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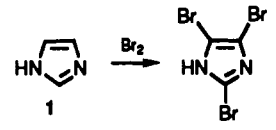
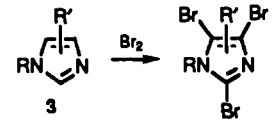
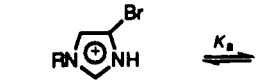


(1)

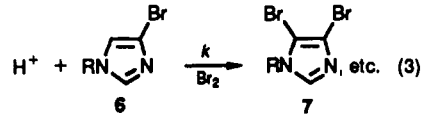


(2)

Polybromination appears to result from a combination of the fact that it is the neutral molecule that is the reactive species[6] and that many brominations are carried out in acidic solution where the imidazolium cation predominates. The increased acidity of the intermediate mono- (and di-) brominated imidazolinium cations **5**, eq 3, apparently outweighs the deactivating influence of bromine substitution, resulting in faster rates for these partly brominated species,[4] $k_{obs} = kK_a[5]/[H^+]$.

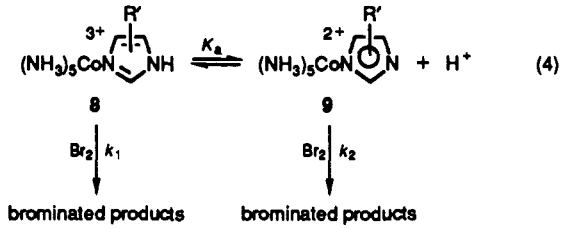


5 ($pK_a \approx 3.9$; R = Me)



(3)

We had the idea that coordination of the pyridine nitrogen to a metal might enhance the nucleophilicity of imidazole. Metal ions are known to be weaker Lewis acids than H^+ or CH_3^+, and the decreased acidity of the coordinated ligand ($RImH^{3+}$ (**8**) has a pK_a of 10.1 compared to ~7.0 for ImH_2^+ and $MeImH^+$) should appear as an increased reactivity of its conjugate base **9** toward bromine, k_2 in eq 4.



(4)

Futhermore, there might also be a useful pathway via the neutral-coordinated ligand **8** (k_1 in eq 4, since this species would be expected to be more nucleophilic than the apparently unreactive imidazolinium cation.[6] There might also be a reduced tendency for the intermediate mono- and dibrominated species to undergo further bromination due to steric interactions with the other ligands on the metal so that partial bromination might be achieved with the metal-coordinated imidazole. Good synthetic routes for Co(III)-bound imidazole complexes were available,[8,9] and the partly brominated ligands can be easily recovered from the metal by methods developed in this laboratory. Thus, the metal-coordinated reaction might provide a useful synthetic route to partly brominated products.

Although the possibility of obtaining good yields of monobrominated product was unsuccessful,[10] the reactivity of **9** toward

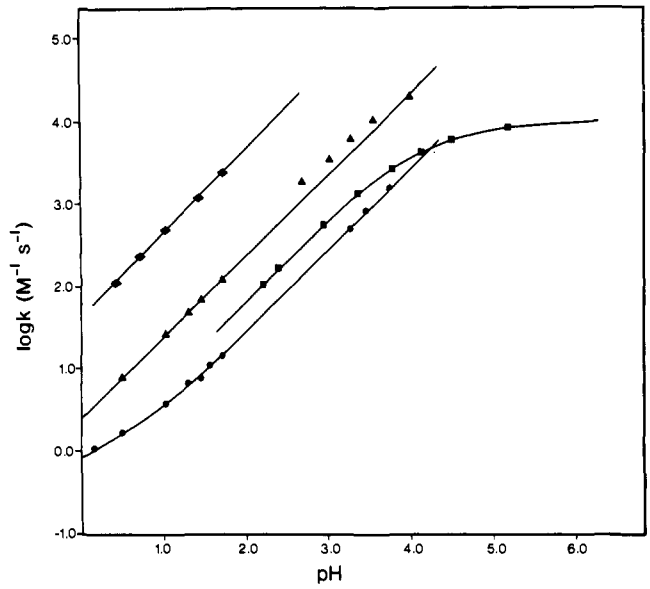


Figure 1. Plots of log k (second-order rate constant, eq 6) vs pH for the bromination of R-4-$BrImH^{3+}$ (◆), R-5-$BrImH^{3+}$ (▲), $RImH^{3+}$ (●) at I = 1.0 M ($NaClO_4$ + NaBr), and R-4,5-Br_2ImH^{3+} (■) at I = 0.10 M, all at 25.0 °C.

Br_2 is indeed very great, the rate being at (6×10^9 M^{-1} s^{-1})[10] or close to the diffusion limit for encounters in aqueous solution ($k_{en} \approx 7 \times 10^9$ M^{-1} s^{-1}).[11] However, methyl substitution was found to increase further the observed rate in acid solution even though the acidity of the coordinated ligand was known to be less.[9] This suggested either a pathway via the neutral-coordinated molecule **8** or a bimolecular rate for **9** in excess of the diffusion-controlled limit. This led to the detailed kinetic and mechanistic study described here. No such study of the bromination of imidazoles[12] or their metal-coordinated derivatives[13] has previously appeared in the literature.

Results

Detailed experimental rate and product data are given as supplementary material (Tables S1–S4).

Kinetic Data. All imidazole complexes react with aqueous bromine in the pH range 0–6 according to a second-order rate law, first-order in substrate and first-order in bromine, eq 5. Rate

$$-d[Br_2]/dt = k[RImH^{3+}][Br_2] = k_{obs}[Br_2] \quad (5)$$

data were collected under pseudo-first-order conditions in bromine ($[RImH^{3+}] \approx 0.02$ M, $[Br_2] \approx 10^{-4}$ M), and pseudo-first-order rate constants were converted into second-order rate constants (k) assuming no reaction with Br_3^-, eq 6. This assumption will

$$k = k_{obs}(1 + K[Br^-])/[Co]_T \quad (6)$$

be examined in the following text. The association constant K between Br_2 and Br^- (including its temperature dependence) has been remeasured under conditions appropriate to the present study.[14a] By keeping $[Br_2]$ low and working at pH ≤ 6, hydrolysis

(6) The imidazolium cation is considerably deactivated toward electrophiles and is apparently not reactive; cf.: Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds. Pergamon: Oxford, 1984; Vol. 5, Part 4A.

(7) These ideas have already been realized in the mononitration of $(NH_3)_5CoImH^{3+}$ under less forcing conditions than those necessary for imidazole itself; cf.: Storm, C. B.; Freeman, C. M.; Butcher, R. J.; Turner, A. H.; Rowon, N. S.; Johnson, F. O.; Sinn, E. *Inorg. Chem.* **1983**, *22*, 678.

(8) Harrowfield, J. M.; Norris, V.; Sargeson, A. M. *J. Am. Chem. Soc.* **1976**, *98*, 7282.

(9) Hoq, M. F.; Shepherd, R. E. *Inorg. Chem.* **1984**, *23*, 1851.

(10) Blackman, A. G.; Buckingham, D. A.; Clark, C. R.; Kulkarni, S. *Aust. J. Chem.* **1986**, *39*, 1465.

(11) Ridd, J. H. *Adv. Phys. Org. Chem.* **1978**, *16*, 1.

(12) The study of Boulton and Coller showed that imidazole and *N*-methylimidazole react with molecular Br_2(aq) in their neutral forms over the pH range 1–4.5. Rate constants for *N*-MeIm and its various mono- and dibrominated intermediates were compared under one condition of acidity and Br^- concentration, allowing the network of reactions leading to the tribrominated product to be expressed. However, no detailed pH study was undertaken, and the mechanisms of bromine addition and proton loss were not dealt with.

(13) One early study, the iodination of imidazole coordinated to Ni(II) (Lambert, D. G.; Jones, M. M. *J. Am. Chem. Soc.* **1966**, *88*, 5537) was hampered by an inability to identify clearly the reactants.

(14) (a) Blackman, A. G.; Buckingham, D. A.; Clark, C. R. *Aust. J. Chem.*, in press. (b) Blackman, A. G.; Buckingham, D. A.; Clark, C. R.; Simpson, J. *Inorg. Chem.*, in press.

Table I. Rate Constants for the Bromination of $RImH^{3+}$ (k_1) and RIm^{2+} (k_2) Complexes in Aqueous Solution, 25.0 °C, I = 1.0 M ($NaClO_4$)

substrate	pK_a^m	k_1 (M^{-1} s^{-1})	k_3/k_3' (M)	k_{-1}/k_3'	k_2 (M^{-1} s^{-1})
R-4,5-Br_2ImH^{3+}	4.18[a,c]				9.2×10^3 [c]
R-4-$BrImH^{3+}$	6.38[a]				1.1×10^8
R-5-$BrImH^{3+}$	8.06[a]				2.7×10^8
R-ImH^{3+}	10.10[a]	0.68			3.6×10^9
R-2-$MeImH^{3+}$	10.67[b]	32		7.3×10^{-14}	3.8×10^9
R-4-$MeImH^{3+}$	10.70[b]	350		2.8×10^{-13}	1.1×10^{10}
R-5-$MeImH^{3+}$	10.46[b]	680		1.4×10^{-15}	2.0×10^{10}
R-2,4-Me_2ImH^{3+}	11.04[b]	1.1×10^4	1.1×10^{-13}	1.05×10^{-11}	3.4×10^{10}
R-3-$MeIm^{3+}$			1.1×10^{-9}		

[a] pK_a^m data from ref 17. These represent mixed concentration–activity values and for use in eqs 12a–c have been corrected to true concentration constants by use of the expression $K_a^c = K_a^m/\gamma_\pm$ where $\gamma_\pm = 0.769$ in 1.0 M $NaClO_4$. Similarly, $K_w^c = 1.70 \times 10^{-14}$ M^2. [b] pK_a data from ref 9. [c] In 0.1 M $NaClO_4$. This pK_a^m value relates to a pK_a^c value of 4.07 obtained from fitting the kinetic data. The measured value for this complex in 1.0 M $NaClO_4$ is 4.69.[17]

to HOBr, and association to Br_5^-, is minimized.[15] It is known from other studies in these laboratories that the reaction of $RImH^{3+}$ with HOBr in aqueous solution leads to ring oxidation and ring cleavage products,[14b] but this does not occur under the conditions described here. Data were collected at constant ionic strength (I = 1.0 or 0.1 M, $NaClO_4$) under conditions of constant [Br^-] (0.26, 0.20, 0.035 M) at 25.0 °C.

Imidazole and Its Bromo Derivatives. Figure 1 shows plots of log k vs pH for the reactions of R-ImH^{3+}, R-4-$BrImH^{3+}$, R-5-$BrImH^{3+}$, and R-4,5-Br_2ImH^{3+} constructed from data given in Table S1. Apart from $RImH^{3+}$, which shows some curvature toward acid independence below pH ≈ 1.0, and R-4,5-Br_2ImH^{3+}, which approaches pH independence as the pH approaches its pK_a (4.69),[14a] these data show clear first order in [OH^-] kinetics. This suggests reaction via the conjugate base complex **9**, eq 4. It is expected that the other less acidic complexes (pK_a data, Table I) would show a similar pH-independent path above their pK_a, but it was not possible to test this in these other cases since another reaction, the specific buffer-catalyzed oxidation of the coordinated imidazole ring, becomes important under pH > 6 conditions.[14b] In this context, it is important to note that the kinetic data for R-4,5-Br_2ImH^{3+} were collected by use of self-buffering by the complex; the presence of acetate or phosphate buffers leads to ring oxidation.

The data, Figure 1 (Table S1), fit the expression

$$k = k_1 + k_2K_a[OH^-]/(K_w + K_a[OH^-]) \qquad (7)$$

with k_1 being the second-order rate constant for the neutral-coordinated ligand **8** and k_2 that for the conjugate base **9**, eq 4. The solid curves represent eq 7 and use constants listed in Table I. As expected for electron-withdrawing substituents, k_2 decreases with increasing bromine substitution,[16] but 4,5-disubstitution seems to have a larger effect than twice that for monsubstitution (k_2 ≈ 10^4 M^{-1} s^{-1} for R-4,5-Br_2Im^{2+} vs 10^8 M^{-1} s^{-1} for R-4-$BrIm^{2+}$ and R-5-$BrIm^{2+}$, and 10^9 M^{-1} s^{-1} for RIm^{2+}). However, the final act of substitution occurs at C-2, and obviously this site is less reactive than C-4 or C-5. In practical terms, the relative rates shown by Figure 1 mean that increased acidity of the imidazole (K_a) generally has a more pronounced effect than decreased reactivity of its conjugate base, **9** (k_2).

Methyl-Substituted Imidazoles. Figure 2 gives plots of log k vs pH for $RImH^{3+}$, R-5-$MeImH^{3+}$, R-2,4-Me_2ImH^{3+}, R-4-$MeImH^{3+}$, R-2-$MeImH^{3+}$, and R-3-$MeIm^{3+}$, the last complex being the *N*-methyl derivative, which lacks an acidic proton. Raw rate data are given in Table S2 and cover a number of buffer systems (Hepes, succinate, acetate, Mes). In all cases, buffer effects were found to be slight (both small positive and negative effects were noted), and the data of Figure 2 have been extrapolated to zero buffer concentration where necessary. Data collection was again restricted to pH < 7 due to competing ring oxidation and in some cases base catalyzed decomposition of the complex. This latter reaction involves complete loss of the imidazole ligand.[17]

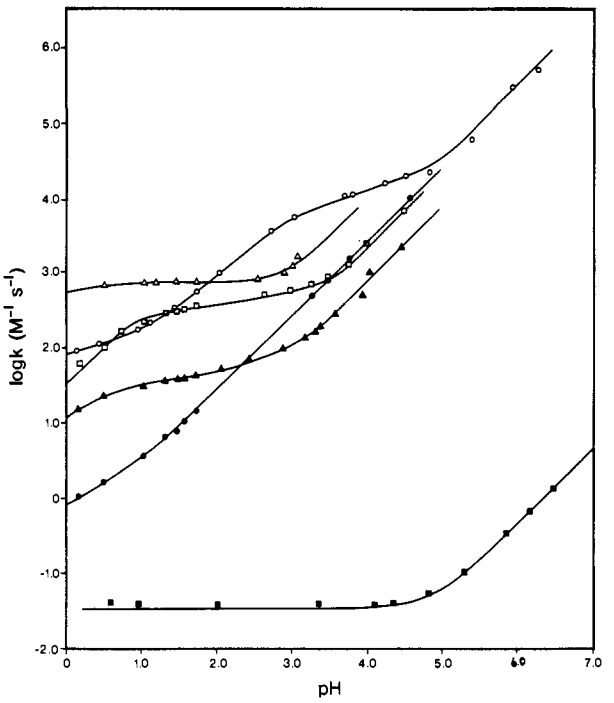


Figure 2. Plots of log k (eq 6) vs pH for the bromination of R-5-$MeImH^{3+}$ (△), R-2,4-Me_2ImH^{3+} (○), R-4-$MeImH^{3+}$ (□), R-2-$MeImH^{3+}$ (▲), $RImH^{3+}$ (●), and R-3-$MeIm^{3+}$ (*N*-methyl derivative, ■), all at I = 1.0 M ($NaClO_4$ + NaBr) and 25.0 °C.

Apart from R-3-$MeIm^{3+}$ (the *N*-methyl derivative), which is very slow to react, these methyl-substituted systems are considerably more reactive than their bromo counterparts, especially under acidic conditions. This is to be expected from the relative inductive effects of Me and Br substitution. However, the curves of Figure 2 now show large pH-independent regions, often bordered by regions first-order in [OH^-]. R-2,4-Me_2ImH^{3+} is the most informative substrate in this sense with the rate approaching pH independence at pH 0–1, first-order in [OH^-] dependence for pH 2–3, another pH-independent region from 3–5, and finally first-order in [OH^-] kinetics for pH > 5. The 5-Me, 4-Me, and 2-Me derivatives show parts of this behavior. $RImH^{3+}$ has the beginnings of pH independence below pH ≈ 1. R-3-$MeIm^{3+}$ is very slow to react but shows clear pH independence below pH 5 and first-order [OH^-] behavior above pH 5. For all substrates, only one reaction was observed spectrophotometrically (650–300 nm), and this was shown by HPIP chromatography to involve formation of the same bromo product independent of pH.

Such complexity in the pH–rate profiles requires at least two changes in the rate-determining step, but we will reserve discussion of this until later. However, it can be noted here that the final

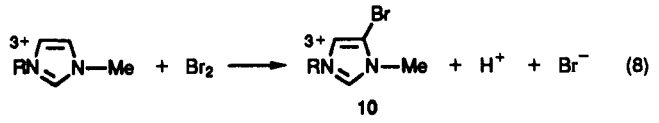
(15) Tee, O. S.; Paventi, M. *Can. J. Chem.* **1983**, *61*, 2556. Tee, O. S.; Berks, C. G. *J. Org. Chem.* **1980**, *45*, 830.

(16) de la Mare, P. B. D. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, 1976. Taylor, R. *Comprehensive Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H., Eds; Elsevier: Amsterdam, 1972; Vol. 13. Norman, R. O. C.; Taylor, R. *Electrophilic Substitution of Benzenoid Compounds*; Elsevier: London, 1965.

break to give first order in $[OH^-]$ kinetics moves to a lower pH with increasing acidity (K_a) of the complex (2,4-Me_2 < 4-Me ≤ 2-Me < 5-Me < H), and by analogy with the bromo derivatives, this suggests **9** becomes increasingly important in this same order. Thus, for R-2,4-Me_2ImH^{3+}, and decreasingly for the others, changes in rate-determining step under acidic conditions can be related to bromination of the neutral ligand **8**.

Reaction Products and Stereochemistry. Product data for $RImH^{3+}$ are given in Table S3. Each act of bromination requires one Br_2 molecule. This was demonstrated for $RImH^{3+}$ by using 0.25–1.50 mol equiv of bromine and HPIP chromatographic separation and quantitation of unreacted $RImH^{3+}$ from the products R-4,5-Br_2ImH^{3+} and R-2,4,5-Br_3ImH^{3+}. No other species was detected, and quantitation of the products used separately prepared standards.[17] Attempts to observe the small amounts of monobromo product formed under conditions of low Br_2 (see the following text) were unsuccessful, but their small amounts did not seriously affect the stoichiometric analysis.[17]

The first substitution act occurs at C-4. This was obvious for R-3-$MeIm^{3+}$, eq 8, where the only product R-4-Br,3-$MeIm^{3+}$ (**10**) was isolated following addition of 1 mol equiv of bromine. A



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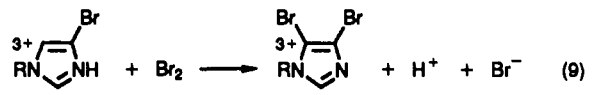
crystal structure of [R-4-Br,3-MeIm]$Br_3 \cdot 2H_2O$ is available.[17] For unsubstituted $RImH^{3+}$, however, which reacts predominantly via its conjugate base **9**, the small amounts of either R-4-$BrImH^{3+}$ or R-5-$BrImH^{3+}$ expected on addition of 0.25 mol equiv of bromine could not be distinguished by HPLC.[18] But the nonappearance of ^1H signals for R-5-$BrIm^{3+}$ in the NMR spectrum implies that further bromination occurs via the more reactive R-4-$BrImH^{3+}$ isomer. Figure 3 shows this experiment in which a standard mixture of 85% $RImH^{3+}$, 6% R-5-$BrImH^{3+}$, and 9% R-4,5-Br_2ImH^{3+} (the expected product distribution on the basis of kinetic considerations with use of 0.25 mol equiv of Br_2)[18] clearly shows two singlets at 8.00 and 7.47 ppm for H-2 and H-4 of R-5-$BrImH^{3+}$. These are absent in the spectrum of the reaction mixture. Additional support for initial bromination at C-4 is found in the fact that the rate data (Figure 2) show that bromination at C-4 in R-5-$MeImH^{3+}$ is somewhat faster than bromination at C-5 in R-4-$MeImH^{3+}$ throughout the pH range.

The second bromination act occurs at C-5, eq 9. This was clearly shown by the quantitative HPLC experiments mentioned previously, and substantial quantities of [R-4,5-Br_2ImH]Br_3 were recovered by use of 2 mol equiv of Br_2 and chromatography to separate this from the small amount of the less soluble [R-2,4,5-Br_3Im]Br_2 product. The final act of substitution, for all imidazole complexes, occurs at C-2.



Reaction Intermediates. Attempts to obtain evidence for a biphasic addition–elimination process were unsuccessful. Spectrophotometric measurements in the visible (600–300 nm) showed no evidence for an intermediate, although below ~400 nm these experiments were to some extent thwarted by the high absorbance of Br_3^-. No rapid-scan spectral evidence for an intermediate was found in the visible region when larger quantities of bromine were used (1:1 ratio), and the initial absorption of a solution containing a 1:1 mixture of $RImH^{3+}$ and Br_2(aq) was the same as the sum of the individual absorptions. Thus, no evidence for a preformed π-intermediate between $RImH^{3+}$ and Br_2 was obtained. Likewise, ^1H NMR spectra run immediately following addition of 1 mol equiv of Br_2 to R-3-$MeIm^{3+}$ (slow reacting) and to R-5-$MeImH^{3+}$ (fast reacting) gave absorptions for only the monobrominated product and unsubstituted reactant. This reaction therefore differs from the occurring with phenols where transient 4-bromo-2,5-cyclohexadienone intermediates are formed[19] and for which the kinetics of Br_2 addition has been studied separately from that of proton abstraction.[20]

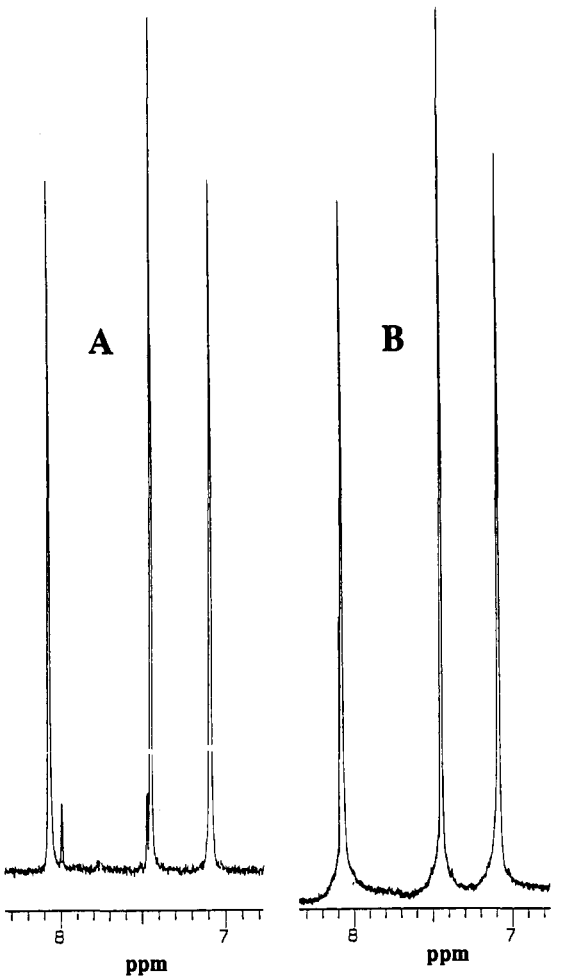


Figure 3. ^1H NMR spectra (300 MHz) in the imidazole region for (A) a standard mixture consisting of 85% $RImH^{3+}$, 6% R-5-$BrImH^{3+}$, and 9% R-4,5-Br_2ImH^{3+} and (B) the products resulting from adding 0.25 mol equiv of Br_2 to $RImH^{3+}$: Solvent, D_2O, $[D^+]$ = 0.10 M, I = 1.0 M ($NaClO_4$). In A, H-2 (8.00 ppm) and H-4 (7.47 ppm) of R-5-$BrImH^{3+}$ can be clearly seen adjacent to the larger $RImH^{3+}$ absorptions. H-2 (8.07 ppm) of R-4,5-Br_2ImH^{3+} coincides with H-2 of $RImH^{3+}$; in B, H-2 of R-4,5-Br_2ImH^{3+} can just be seen on the low-field side of H-2 of $RImH^{3+}$. Mixtures similar to A containing R-4-$BrImH^{3+}$ instead of R-5-$BrImH^{3+}$ showed H-2 and H-4 of R-4-$BrImH^{3+}$ to coincide with the same signals of $RImH^{3+}$.

Deuterium Isotope Effect. To examine the importance of proton abstraction on the bromination rate, data were collected for the protonated and fully deuterated R-*2,4,5-d_3*-ImH^{3+} and R-*2,4,5-d_3*-3-$MeIm^{3+}$ substrates under the same or similar conditions. These are collected in Table II. k_H/k_D values for $RImH^{3+}$ under conditions where the neutral ligand is partly reactive (k_1, eq 7) increase with increasing $[H^+]$, reaching a value of 2.4 in 5.42 M

(17) Blackman, A. G. Ph.D. Thesis, University of Otago, 1989.

(18) It can be shown by use of the appropriate rate constants (cf. Experimental Section) that 0.4–0.1% of R-4-$BrImH^{3+}$ and 5.9–2.7% of R-5-$BrImH^{3+}$ would be expected for the two monobromo alternatives with use of 0.25–1.50 mol equiv of Br_2(aq) at pH 1.0 (cf. Table S3). When the authentic compounds were used, these were shown to coelute with R-2,4,5-Br_3ImH^{3+} and $RImH^{3+}$, respectively, under the best conditions for separation of $RImH^{3+}$, R-2,4-Br_2ImH^{3+}, and R-2,4,5-Br_3ImH^{3+}. Their small amounts could not be determined since all species have very similar extinctions in the visible and UV regions.[14]

(19) de la Mare, P. B. D. *Acc. Chem. Res.* **1974**, *7*, 361. Brittain, J. M.; de la Mare, P. B. D. In *The Chemistry of Functional Groups*; Patai, S., Rappoport, Z., Eds., Wiley: New York, 1983; Supplement D, Chapter 12 and references therein.

(20) Tee, O. S.; Iyengar, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 455.

Table II. Effect of Deuterium Substitution on the Bromination Rates for $RImH^{3+}$ and R-3-$MeIm^{3+}$ at 25.0 °C

A. $RImH^{3+}$

$[H^+]$ (M)	$k_{obs(H)}$[a] (s^{-1})	$k_{obs(D)}$[b] (s^{-1})	k_H/k_D
0.050[c]	6.42×10^{-2}	5.06×10^{-2}	1.27
0.495[c]	1.43×10^{-2}	9.90×10^{-3}	1.44
0.940[c]	1.02×10^{-2}	6.79×10^{-3}	1.50
2.00[d]	8.08×10^{-4}	5.07×10^{-4}	1.59
5.42[d]	1.93×10^{-5}	8.02×10^{-6}	2.41

B. R-3-$MeIm^{3+}$[e]

pH	$[Co]_T$ (M)	$k_{obs(H)}$[a] (s^{-1})	$k_{obs(D)}$[b] (s^{-1})	k'[f] (M^{-1} s^{-1})	k_2[g] (M^{-1} s^{-1})	k_H/k_D
2.03	1.39×10^{-2}		5.85×10^{-5}	2.35×10^{-2}		
2.05	1.80×10^{-2}	1.18×10^{-4}		3.66×10^{-2}		1.6
6.01	1.28×10^{-2}		1.11×10^{-3}	4.84×10^{-1}	4.82×10^{7}	
6.33	1.35×10^{-2}	2.51×10^{-3}		1.04×10^{-1}	4.86×10^{7}	1.0

[a] k_{obs} values for the bromination of $RImH^{3+}$ or R-3-$MeIm^{3+}$. [b] k_{obs} values for the bromination of R-2,4,5-d_3-ImH^{3+} or R-2,4,5-d_3-3-$MeIm.^{3+}$ [c] Key: $[Co]_T$ = 0.02 M, $[Br^-]$ = 0.06 M, I = 1.0 M ($NaClO_4$). [d] Key: $[Co]_T$ = 0.01 M, $[Br^-]$ = 0.23 M, I variable. [e] Key: $[Br^-]$ = 0.26 M, I = 1.0 M ($NaClO_4$). [f] Cf. eq 6. [g] $k_2 = ka_{H+}/K_w$ ($K_w = 1.0 \times 10^{-14}$ M^2).

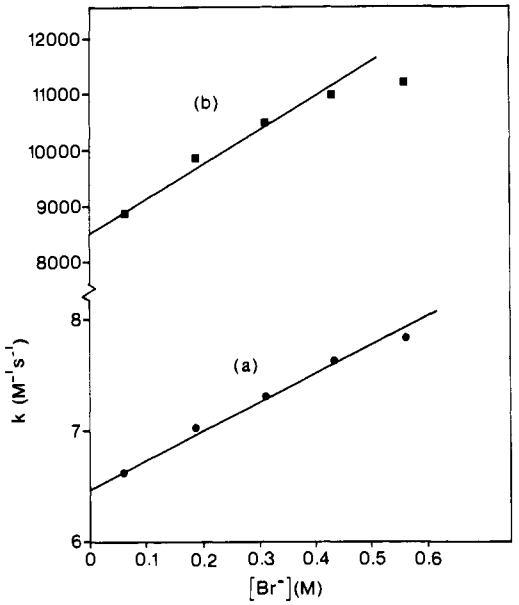


Figure 4. Plots of k (second-order rate constant, (eq 6) vs $[Br^-]$ for the reaction of $RImH^{3+}$ with Br_2 ($[Co]$ = 20 mM, I = 1.0 M ($NaClO_4$), 25.0 °C): (a) ●, pH 1.42; (b) ■, pH 4.48.

$HClO_4$. For R-3-$MeIm^{3+}$, k_H/k_D = 1.6 in acidic solution but has a value of 1.0 at pH ≈ 6 where k_2 controls the rate.

Reaction with Tribromide. Data are given in Table S4. In the above kinetic analysis, eq 6, it was assumed that there is no reaction with Br_3^-. Yet, under the experimental conditions (0.20, 0.26 M Br^-), bromine will be present mostly as Br_3^- ($[Br_3^-]/[Br_2] = K[Br^-] = 17.6^{21} \times 0.26 = 4.6$). If reaction with Br_3^- does not occur, the corrected k values would be expected to be invariant to changing $[Br^-]$ if bromine addition were rate-determining. This is not quite so, as can be seen from Figure 4 for the bromination of $RImH^{3+}$; k values increase approximately linearly with increasing $[Br^-]$ at both pH 1.42 and 4.48. Under such conditions reaction occurs entirely via **9**, and it will be shown in the following text that here addition of Br_2 is probably rate-determining. The uncorrected second-order rate will thus contain contributions from both Br_2 (k_B) and Br_3^- (k_T); viz. $k' = k_B f_B + k_T f_T$, where f_B and f_T represent the fractions of Br_2 and Br_3^- present. Then

$$k = k'/f_B = k_B + k_T f_T/f_B = k_B + k_T K[Br^-] \qquad (10)$$

where K represents the formation constant for Br_3^-.[21] Intercepts at $[Br^-]$ = 0 in Figure 4 give k_B directly,[22] and both pieces of data

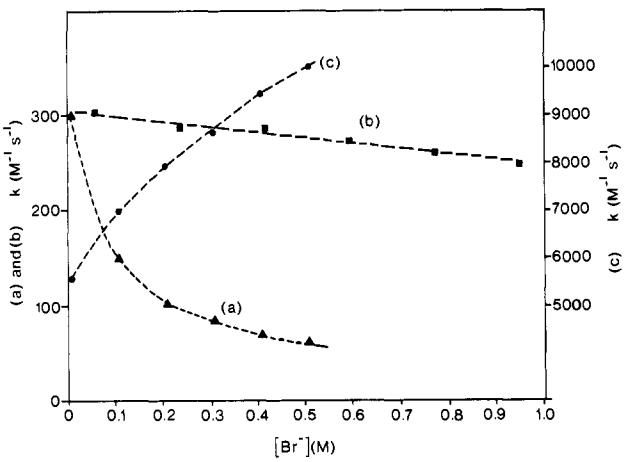


Figure 5. Plots of k (eq 6) vs $[Br^-]$ for the reaction of R-4-$MeImH^{3+}$ with Br_2 (I = 1.0 M ($NaClO_4$), 25.0 °C): (a) ▲, pH 0.51 ($[Co]$ = 2.5 mM); (b) ■, pH 1.42 ($[Co]$ = 20 mM; (c) ●, pH 4.48 ($[Co]$ = 2.5 mM).

lead to a k_2 value of 3.0×10^9 M^{-1} s^{-1} when adjusted for pH. Slopes of Figure 4[22] and similar correction for pH lead to a k_T value for reaction with Br_3^- of 6.3×10^7 M^{-1} s^{-1}. Thus, Br_3^- has only ~2% the reactivity of Br_2. For substrates **9** that are less reactive toward bromination, such as R-5-$BrImH^{3+}$, the results show that reaction with Br_3^- is undetectable compared to that with Br_2.

The situation is however somewhat more complicated for the Me-substituted substrates that react predominantly via their protonated forms, **8**. When proton loss from the Wheland intermediate is rate-determining, an inverse in $[Br^-]$ dependence is to be expected (see the following text), and this will oppose any Br_3^- dependence. This apparently does occur, as can be seen from Figure 5 for the R-4-$MeImH^{3+}$ substrate. At pH 4.48, where Br_2 addition to **9** is rate-determining, a situation similar to the previous situation occurs with a small positive role for Br_3^- (a 50% increase in k occurs for a 5-fold increase in $[Br^-]$ from ~0.1 M). But at pH 1.42 and 0.51, where Br_2 addition to **8** and proton loss from the Wheland intermediate, respectively, are rate-determining (see the following text), little, or an inverse in $[Br^-]$, dependence is seen. With the other Me-substituted substrates a similar situation was found, although for R-3-$MeIm^{3+}$ (*N*-methyl derivative) an approximate doubling of k occurs over the $[Br^-]$ range 0.06–1.0 M. It was evident from these experiments that the Br^- dependence of the rate is complicated, but it does follow expected trends, and for all substrates Br_3^- is much less reactive than Br_2. This situation apparently differs from that found for phenol bromination.[23]

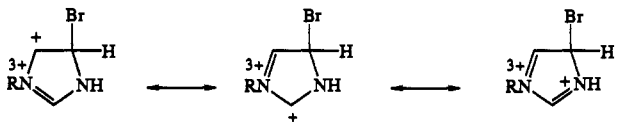
(21) Although earlier values are available, we have redetermined K for the $Br_2 + Br^- \rightleftharpoons Br_3^-$ equilibrium under our conditions (1.06 M $NaClO_4$, 0.1 M $[H^+]$). Values found were 17.6 ± 0.4 M (25.0 °C), 17.4 ± 0.5 M (30.0 °C), and 16.8 ± 0.8 M (40.0 °C); cf. ref 14a.

(22) k_B and k_T values at pH 1.42 and 4.48 are, respectively, 6.5 and 0.14 M^{-1} s^{-1} and 8500 and 175 M^{-1} s^{-1}.

(23) Tee, O. S.; Paventi, M.; Bennett, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 2233.

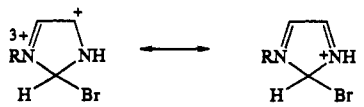
Scheme I. Wheland Intermediates

C-4 Addition Product



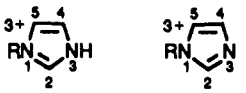
C-5 Addition Product

C-2 Addition Product



Discussion

Substitution Pattern. Initial bromination of these $(NH_3)_5Co^{3+}$-substituted imidazoles occurs at the less hindered C-4 site, if available. This holds both for the neutral-coordinated ligand **11** and for its anion **12**. The kinetic and product data for

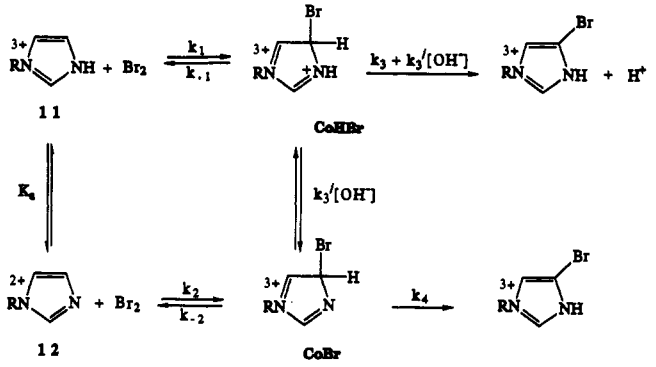


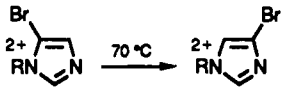
11 **12**

the parent $RImH^{3+}$ system, which reacts almost entirely via its anion **12**, support the site reactivity order C-4 > C-5 ≫ C-2. This order is also apparent in the reactions of the isolated mono- and dibrominated intermediates; R-5-$BrIm^{2+}$ is ~2 times as reactive as R-4-$BrIm^{2+}$ (k_2 values, Table I). A similar difference is found between R-5-$MeImH^{3+}$ and R-4-$MeImH^{3+}$, both as **11** and **12** (k_1 and k_2 values, Table I). Likewise, nitration of $RImH^{3+}$ in HNO_3/H_2SO_4 is known to give R-4-NO_2Im^{2+}.[7] In this case, the nitro group deactivates the imidazole ring to further substitution, allowing isolation of the monosubstituted product. Such observations differ from those of Boulton and Coller, who studied the substitution pattern for bromination of uncoordinated *N*-methylimidazole.[4] They suggested preferential bromination at C-5. We believe that this earlier study warrants reinvestigation.

Initial electrophile substitution at C-4 is favored on simple electronic grounds. Valence-bond resonance structures for the neutral-uncoordinated molecule favor attack at N-3, C-4, and C-2,[24] and the C-4 substituted Wheland intermediate (Scheme I) is stabilized relative to the C-5 and C-2 addition products from a resonance viewpoint but not from a charge delocalization viewpoint. MO calculations are also equivocal in this respect. Of the three carbon sites, C-2 is predicted to be the least reactive,[24] but such calculations produce conflicting results as to π-electron densities at C-4 and C-5.[25,26] Possibly a better guide to electron densities, and hence reactivity toward electrophiles, comes from ^{13}C chemical shift data. C-2 always appears at lowest field in these complexes (Table II of ref 14), and in every case we have looked at the most reactive unsubstituted carbon atom appearing at highest field. Substitution at C-4 in these complexes is also undoubtedly favored on steric grounds, as evidenced by the known spontaneous (but slow) intramolecular isomerization of R-5-$BrImH^{3+}$ to R-4-$BrImH^{3+}$ via the conjugate base **12**, eq 11.[17] Nonbonded interactions with the *cis*-ammine ligands on the metal are probably responsible for this isomerization, and this suggests that attack at the less hindered C-4 is more likely.

Scheme II. Stepwise Bromination Mechanism





(11)

Reaction Mechanism. In the absence of detectable intermediates, the complex rate profiles shown by Figures 1 and 2 allow a fairly detailed mechanism to be considered. We suggest that given by Scheme II. Addition of Br_2 to either the neutral **11** or deprotonated **12** reactant leads to addition intermediates CoHBr and CoBr, which subsequently lose a proton via either spontaneous or OH^--catalyzed pathways. Treating CoHBr and CoBr as steady state leads to the expression

$$k = \frac{k_1k_3 + k_1k_3'[OH^-]}{k_3 + k_3'[OH^-] + k_{-1}[Br^-]} + \frac{k_2k_4K_a[OH^-]}{K_w(k_4 + k_{-2}[Br^-])}\frac{K_w}{K_w + K_a[OH^-]} \quad (12a)$$

in which K_a represents the acidity constant for the particular imidazole complex, k_1 and k_2 represent the second-order rate constants for addition of Br_2 to **11** and **12**, respectively, and k_3, k_4, and k_3' represent the rate constants for decomposition of the Wheland intermediates via the H_2O- and OH^--catalyzed pathways. The solid curves of Figure 1 and 2 utilize eq 12a and the various constants listed in Table I. No conclusion can be drawn as to whether the OH^--catalyzed decomposition of CoHBr involves direct OH^- abstraction of the CH proton or indirect decomposition via CoBr with OH^- removing the undoubtedly reasonably acidic NH proton followed by the spontaneous, and presumably rate-determining, loss of the CH proton. Both possibilities are therefore given in Scheme II. However, if the R-3-$MeIm^{3+}$ substrate (i.e., the *N*-methyl derivative) reacts in this manner, then the former, more direct, OH^--catalyzed abstraction of the CH proton is required since this complex does not have an acidic NH proton. The k_3' pathway does not appear to be catalyzed by bases other than OH^-. Except for R-4,5-Br_2ImH^{3+}, for which $K_a[OH^-]$ approaches K_w at pH > 4, expression 12a reduces further to

$$k = \frac{k_1k_3 + k_1k_3'[OH^-]}{k_3 + k_3'[OH^-] + k_{-1}[Br^-]} + \frac{k_2k_4K_a[OH^-]}{K_w(k_4 + k_{-2}[Br^-])} \quad (12b)$$

The first part of (12b) represents reaction via the neutral complex **11**, and this assumes major importance for the more reactive Me-substituted complexes. The second part describes reaction of the conjugate base complex **12**, and this pathway is important for $RImH^{3+}$ and the bromine-subsituted complexes. Since the effects of changing $[Br^-]$ on the reactions of **12** are slight and are best accommodated by some reaction with Br_3^-, it appears that $k_4 > k_{-2}[Br^-]$ under our experimental conditions, with addition

(24) See ref 6, p 346, 347, including Table 1 containing π-electron densities.
(25) Olivella, S.; Vilarrasa, J. *J. Heterocyclic Chem.* **1981**, *18*, 1189.
(26) Kamiya, M. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3344.

of Br_2 to **12** being rate-determining. Expression 12b then reduces further to

$$k = \frac{k_1k_3 + k_1k_3'[OH^-]}{k_3 + k_3'[OH^-] + k_{-1}[Br^-]} + \frac{k_2K_a}{K_w}[OH^-] \quad (12c)$$

The different complexes all display parts of expression 12c. R-2,4-Me_2ImH^{3+}, which is the most reactive, is the most revealing. At pH < 1, spontaneous removal (pH independent) of the proton from the Wheland intermediate CoHBr is competitive with the OH^--catalyzed route (pH 1–3), while by pH ≈ 3 addition of bromine to **11** has become rate-determining. By pH 4–5, the OH^--catalyzed reaction via **12** controls the rate. For the somewhat more acidic R-4-$MeImH^{3+}$, R-5-$MeImH^{3+}$, and R-2-$MeImH^{3+}$ complexes, only OH^--catalyzed deprotonation of CoHBr is seen with k_1, and then k_2, becoming rate-determining as the pH is increased. For R-3-$MeIm^{3+}$ (which lacks an acidic NH proton), decomposition of CoHBr via the spontaneous (k_3) and OH^--catalyzed (k_3') pathways is rate-determining at all pHs. Apparently, removal of bromine from CoHBr by Br^- ($k_{-1}[Br^-]$) is more effective for this complex than for the others, and bromine addition never becomes rate-determining. Alternatively, the OH^--catalyzed pathway for this complex might involve coordinated ammine deprotonation (see the following text), and this would provide a completely different pathway. For the more acidic Br-substituted reactants, reaction occurs exclusively via **12** throughout the pH range, with addition of bromine (k_2) apparently being rate-determining. For R-4,5-Br_2ImH^{3+}, rate data were collected through the pK_a of the imidazole proton (pK_a(measured) = 4.69 in 1 M $NaClO_4$,[17] pK_a(kinetic) = 4.18 in 0.1 M $NaClO_4$) so that the limiting rate (k_2) is approached in Figure 1.

The k_1 and k_2 values listed in Table I make sense.[27] The neutral reactant **11** becomes increasingly reactive with increasing Me substitution as would be expected for electrophilic based bromination (k_1 values, Table I), and the same is true of **12** (k_2 values). The R-4-$MeImH^{3+}$ and R-5-$MeImH^{3+}$ complexes appear to reverse this trend with the more acidic R-5-$MeImH^{3+}$ complex being more reactive (via both pathways), but this can be attributed to preferential bromination at C-4 compared to C-5. The poorly nucleophilic bromo-substituted complexes require substrate deprotonation before they react, and the trend in k_1 values for the methyl derivatives suggests that reaction via **11** for these bromo derivatives will not be possible, even in very strong acid. The k_3/k_3' ratio reflects the relative ease of proton abstraction from CoHBr by H_2O (k_3) and OH^- (k_3'), and the small values (10^{-9}, 10^{-13}) show OH^- to be much more efficient. Likewise, the k_{-1}/k_3 ratio reflects the relative ease of bromine and proton abstraction from CoHBr, and again the very small values (10^{-11}–10^{-15}) show proton abstraction by OH^- to be much preferred to bromine abstraction by Br^-.

A significant kinetic isotope effect (k_H/k_D) is possible in regions where C–H bond breaking in CoHBr (or CoBr) is rate-determining. For $RImH^{3+}$, this is never so since addition of Br_2 to **12** is rate-determining over much of the pH range, but the data (Table II) show k_H/k_D to increase in acid solution, reaching a value of 2.41 in 5.42 M $HClO_4$. Under these conditions, the rate constants (Table I) would predict some contribution from k_3 and $k_3'[OH^-]$, even though k_1 would still be the major contributor. Likewise, the small k_H/k_D value of 1.6 for R-3-$MeIm^{3+}$ under acidic conditions suggests only a minor contribution from proton abstraction.

Other possibilities for the OH^--catalyzed bromination process at pH ≥ 5 are bromination by HOBr, eq 13, or an accelerated rate for the ammine conjugate base, eq 14, R′ = $(NH_3)_4(NH_2)Co^{2+}$. The first possibility can be excluded, since another

$$Br_2 + H_2O \rightleftarrows HOBr + H^+ + Br^-$$

$$HOBr + RImH^{3+} \rightarrow RBrImH^{3+} + H_2O \quad (13)$$

$$RImH^{3+} + OH^- \rightleftarrows R'ImH^{2+} + H_2O$$

$$R'ImH^{2+} + Br_2 \rightarrow RBrImH^{3+} + Br^- \quad (14)$$

study specifically aimed at investigating this reaction[14b] has shown that treatment of $RImH^{3+}$ with aqueous HOBr results in ring oxidation and ring cleavage with the formation of a number of new ligand species. Very little bromine substitution occurs, and then only as a step prior to ring oxidation. The second possibility is well-known in Co(III) chemistry where coordinated ammine deprotonation leads to accelerated loss of other cis- or trans-located ligands.[28] The same possibility exists here, with loss of an ammine proton in a preequilibrium process giving rise to a $RImH^{2+}$ species that would be expected to be somewhat more reactive toward electrophiles than $RImH^{3+}$, eq 14. This could account for at least part of the observed $[OH^-]$ dependencies, but several observations make it unlikely. Firstly, it cannot account for the OH^- catalysis observed for R-4,5-Br_2ImH^{3+}, where imidazole deprotonation is clearly implicated by the rate and pK_a data for the coordinated ligand (Figure 1, equation 12a). Secondly, the pK_a of Co(III)-coordinated ammine protons in such complexes is at least 14,[28] and hence, the concentration of $R'ImH^{2+}$ under conditions used for data collection (pH 0–6) must be very small. Such concentrations would lead to impossibly large second-order rate constants in most cases (>10^{11} M^{-1} s^{-1}). For the *N*-methylimidazole complex R-3-$MeIm^{3+}$, however, ammine deprotonation is a distinct possibility, and the OH^--catalyzed process (Figure 2) leads to a second-order rate constant for reaction of the ammine conjugate base R′-3-$MeIm^{2+}$ with Br_2 of ~3×10^7 M^{-1} s^{-1}. k_H:k_D = 1.0 under these conditions (pH ~6, Table II) supports addition of Br_2 to the conjugate base being rate-determining. However, for the other substrates imidazole deprotonation is both preferred (K_a(imidazole) > K_a(ammine)) and expected to have a more pronounced effect on imidazole reactivity.

Diffusion or Preassociation. The recent publication by Tee and co-workers[23] summarizing kinetic and product data for the bromination of a large number of phenols represents the current status on such reactions. These authors support a stepwise bromination process for the phenoxide ion with deprotonation occurring prior to diffusional encounter with bromine, eq 15. Their data, a

$$AH \rightleftarrows A^- + H^+$$

$$A^- + Br_2 \xrightarrow{K_{en}} A^-\cdot Br_2 \rightarrow ABr + Br^- \quad (15)$$

selection of which is given in Table III, would require $A^-\cdot Br_2$ to brominate at almost every encounter (i.e., $k_2 = k_{en}$). The diffusion limit of ~7×10^9 M^{-1} s^{-1} at 25 °C in water is based on the

Table III. Bimolecular Rate Constants for the Bromination (Chlorination) Reactions of Several Substrates in Aqueous Solution (25 °C, *I* Variable)

substrate	electrophile	(M^{-1} s^{-1})	ref/note
phenoxide	Br_2	1.2×10^9	23
2-bromophenoxide	Br_2	6.2×10^9	23
4-(ethoxycarbonyl)phenoxide	Br_2	6.4×10^9	23
4-carboxyphenoxide	Br_2	8.2×10^9	23
2-pyridone	Br_2	5.0×10^9	23
3,*N*,*N*-trimethylaniline	Br_2	9.8×10^8	11
aniline	NOCl	2.6×10^9	11
azulene	NOCl	5.5×10^9	11
aniline	NOBr	3.2×10^9	11
RIm^{2+}	Br_2	3.0×10^9	this work
R-2,4-Me_2Im^{2+}	Br_2	3.4×10^{10}	this work
R-5-$MeIm^{2+}$	Br_2	2.0×10^{10}	this work

(27) The possibility that polybromination can affect the rate constants (cf. ref 23) can be dismissed for R-2,4-Me_2ImH^{3+} and R-4,5-Br_2ImH^{3+} since only one substitution act is possible. For R-4-$MeImH^{3+}$, R-5-$MeImH^{3+}$ and the corresponding 4- and 5-substituted bromo complexes, the final act of substitution occurs at C-2, and this is very much slower than substitution at C-5 and C-4 (respectively) under the same conditions and therefore can be ignored. Only monobrominated products were observed with use of 1:1 ratios of these reactants. A potential problem exists with the parent molecule $RImH^{3+}$ and with R-2-$MeImH^{3+}$, but under the conditions of vast excess of substrate over Br_2 (~100 times) little dibromination is likely. In every case, good first-order spectrophotometric traces were observed.

(28) Basolo, F.; Pearson, R. G. *Mechanisms of Inorganic Reactions*; Wiley: New York, 1968; p 183. Tobe, M. L. *Adv. Inorg. Bioinorg. Mech.* **1983**, *2*, 1.

Table IV. Rate Constants (k_2) for the Reactions of Me- and $(NH_3)_5Co$-Substituted Imidazoles (25 °C)

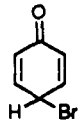
	N-Me system[a]		*N*-Co$(NH_3)_5^{3+}$ system[b]	
imidazole	pK_a	k_2 (M^{-1} s^{-1})	pK_a	k_2 (M^{-1} s^{-1})
4,5-Br_2Im	2.0	1.6×10^3	4.18	9.2×10^3
4-BrIm	3.9	4.6×10^6	6.38	8.6×10^7
5-BrIm	5.2	3.6×10^5	8.06	2.0×10^8
Im	7.0	2.3×10^6	10.1	2.1×10^9

[a] Data from ref 4. [b] This work

Smoluchowski equation for diffusion, and recent experiments support these calculated k_{en} values in nonaqueous solution[11] when experimental, rather than Stokes–Einstein-based, diffusion coefficients are used.[29] However we still have some reservations about the stepwise nature of deprotonation, diffusion, and then reaction. Some of our k_2 values (Table III) are on the high side of k_{en}, especially for 1 M electrolyte ($NaClO_4$ + NaBr), but these values are based on separately measured acidity constants (K_a) obtained in the absence of Br_2. E_a for reaction 15 (A^- = RIm^{2+}) has a value of 6 ± 5 kJ mol^{-1},[14a] but this is also based on a measured ΔH value for deprotonation of $RImH^{3+}$ (55 ± 3 kJ mol^{-1}) obtained in the absence of bromine.[14a] However, we feel that the E_a value of 6 ± 5 kJ mol^{-1} is somewhat outside the limits of ~19 kJ mol^{-1} expected[11] for a diffusional encounter in aqueous solution. We find it difficult to believe that basic species such as RIm^{2+} (and phenoxide) will survive long enough in acidic aqueous solution to diffuse together with an electrophile such as bromine before being reprotonated by the surrounding solvent cage that includes the deprotonating base (OH^- or H_2O).

Such ideas follow those of Jencks and Sayers[30] and Ridd,[11] who point out that very reactive intermediates will prefer the electrophile to be present in the immediate solvent cage at the time of deprotonation; i.e., a preassociation mechanism is favored. Such a possibility is shown by Scheme III. Now, the measured rate is controlled in part by the stability constant of the associated species, $k_{2(obs)} = K_\pi K_{a,\pi} k_2^\pi[OH^-]$,[31] and although we have not been able to identify such a species in our experiments,[32] Kochi and co-workers have obtained good evidence for π-associated complexes on the pathway for bromination of aromatics in nonaqueous solvents.[33] Their presence in aqueous solution must now be sought. Obviously, in the absence of a knowledge of K_π and $K_{a,\pi}$ further analysis of the observed spontaneous and OH^--catalyzed rates (Figures 1 and 2) cannot be undertaken.

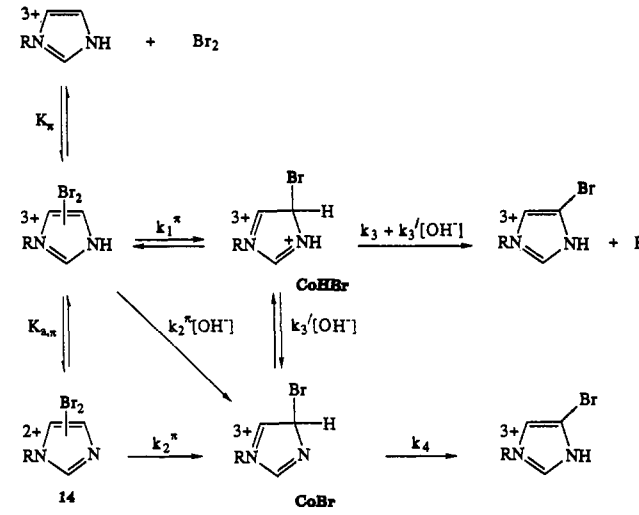
Comparisons with Other Systems. Compared to the bromination of phenols where Wheland intermediates such as **13** are sufficiently stable to be observed and their decomposition studied separately,[20,34] our Wheland intermediate CoHBr is of high energy and has not been observed. The decomposition of 4-bromo-2,5-



13

cyclohexadienone intermediates such as **13** to products has been shown to be catalyzed by general acids and bases,[20,34] whereas the decomposition of CoHBr appears to involve only H_2O- and OH^--catalyzed deprotonation. For both systems, the presence of electron-withdrawing substituents promotes reaction via the anion.

Scheme III. Preassociation Mechanism



Wheland intermediates related to **13** have been shown to be increasingly unstable under such conditions[35] so that our $(NH_3)_5Co^{3+}$-substituted species are expected to be of high energy.

Replacement of a *N*-methyl group by Co$(NH_3)_5^{3+}$ increases the rate of bromination, and this increase becomes greater as the imidazole becomes more reactive. This is shown by the data collected in Table IV. A factor of <10 is involved for 4,5-Br_2Im but increases to ~10^3 for the unsubstituted imidazole. A practical demonstration of this is found in the reactivities of 1,3-Me_2Im^+, R-3-$MeIm^{3+}$, and the bridged dimer[14] $RImR^{5+}$ (R = Co$(NH_3)_5$). The uncoordinated molecule shows no reaction with bromine overnight, R-3-$MeIm^{3+}$ gives a good yield of R-4-Br-3-$MeIm^{3+}$ over the same time, and $RImR^{5+}$ gives a quantitative yield of R-4(5)-$BrImR^{5+}$ within 45 min. Thus, Co$(NH_3)_5^{3+}$ facilitates electrophilic substitution for both the neutral ligand **11** and its conjugate base **12**.

Experimental Section

All pentaaminecobalt(III)–imidazole complexes were prepared and characterized by methods described elsewhere.[8,17] Buffer and inorganic reagents were of the highest available purity. Stock bromine solutions were made up by weight and diluted to the desired concentration as required. These were standardized by addition of excess sodium iodide and titration of the liberated iodine against standard sodium thiosulfate.

Other Preparations. **[Co$(NH_3)_5$-*2,4,5-d*$_3$-Im]Br_2.** To a solution of [Co$(NH_3)_5$-*2,4,5-d*$_3$-ImH]Br_3[17] (0.93 g) in water (5 cm^3) were added Et_3N (0.6 g) and, after ~2 min, LiBr (1.0 g). The mixture was chilled in ice for 5 min, and EtOH (4 cm^3) was added. The dark orange product was filtered off, washed with EtOH and then Et_2O, and air dried.

[Co$(NH_3)_5$-*2,4,5-d*$_3$-3-MeIm]$Br_3 \cdot H_2O$. To a suspension of [Co$(NH_3)_5$-*2,4,5-d*$_3$-Im]Br_2 (0.55 g) in dry $(CH_3O)_3PO$ (3.0 cm^3) was added $CH_3OSO_2CF_3$ (2.0 g) and the mixture stirred at room temperature for 24 h. The resultant orange solution was then diluted with water and sorbed onto a column of Sephadex SP-C25 ion-exchange resin (20 cm × 2 cm). Elution with NaCl solution (0.3 M) adjusted to pH 11.4 (Et_3N) removed unreacted [Co$(NH_3)_5$-*2,4,5-d*$_3$-Im]$^{2+}$. The eluant was then changed to aqueous NaBr (0.1–0.5 M) and the orange 3+ band recovered and rotary evaporated to dryness. The resultant solid was crystallized from the minimum volume of warm water by addition of excess LiBr. ^1H NMR (D_2O): δ 3.97. No signals were apparent in the range δ 7.0–8.2, and the product was chromatographically homogeneous by HPLC analysis at 230 nm.

Rate Data. Spectrophotometric rate data were collected with use of either Cary 219 or Durrum D110 stopped-flow spectrophotometers, thermostated at 25.0 °C. Reactions of intermediate

(29) Olea, A. F.; Thomas, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 4484.
(30) Jencks, W. P.; Sayers, J. M. *Faraday Symp.* **1975**, *10*, 41. Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345.
(31) The concerted pathway, $k_2^\pi[OH^-]$ in Scheme III, provides an alternative to the stepwise process and avoids the intermediate **14**.
(32) Attempts using rapid-scan spectrophotometry to detect such π-associated species were unsuccessful, with absorptions at $t \approx 10$ ms for the more slowly reacting systems being equal to the sum of those for the two separate reactants.
(33) Kochi, J. K. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1227 and references therein.
(34) Tee, O. S.; Iyengar, N. R. *J. Org. Chem.* **1983**, *48*, 759. Tee, O. S.; Iyengar, N. R. *Can. J. Chem.* **1987**, *65*, 1714.
(35) Kulic, J.; Vecera, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 71. Comments in ref 20.

speed used a hand-operated stopped-flow attachment to the Cary and a 1-cm flow-through cell. All data were obtained at constant ionic strength (I = 1.0 M $NaClO_4$ usually) and in the presence of excess NaBr (0.20, 0.26 M) to eliminate the effects of released bromide ion. Pseudo-first-order conditions in bromine ($[Br_2] \approx 10^{-4}$ M) and total complex concentrations, $[Co]_T$, of 20–25 mM were used in kinetic runs. Reactions were monitored at 390 nm (usually) by following the decay of Br_3^-. Attempts to detect reaction intermediates used a Harrick rapid-scan facility (300–650 nm) interfaced to the Durrum. Kinetic data from the Cary 219 were treated manually, with k_{obs} values being extracted from plots of log $(A_t - A_\infty)$ vs time or, where necessary, from Guggenheim plots of log $(A_t - A_{t+\Delta t})$ vs time ($\Delta t > t_{1/2}$). All the data were linear over at least 75% reaction. Stopped-flow data were collected and treated using an OLIS data collection system, OLIS datafit software package, and interfaced Northstar Horizon computer. k_{obs} values were converted to second-order constants (k) by use of eq 6. Runs were carried out as follows. For pH < 2, a solution of the substrate in either acid or water was mixed with a solution of bromine in acid; for pH > 2, a solution of the substrate in the appropriated neutralized buffer was mixed with a solution of bromine in water. Solution pH was measured at the completion of a run.

Reaction Products. Products were identified and quantified by RP-HPIPC separations with a μBondapak C_{18} reversed-phase column (10 μm, 100 mm × 8 mm (i.d.)) equipped with a Waters Guard-Pak precolumn insert and enclosed in a Waters radial compression Z-module. This was coupled to a Varian 5000 microprocessor-controlled pump assembly and a Varian Varichrome UV–vis detector. The sample cell was thermostated to 30 °C. Samples were injected into a Waters U6-K injector assembly with use of a Hamilton 25-μL syringe. Chromatograms were recorded on a Varian 9176 chart recorder and peak areas integrated using a Hewlett-Packard 3390A integrator. Base-line separations of $RImH^{3+}$ (~5.5 min), R-2,4,5-Br_3Im^{2+} (~7.5 min), and R-4,5-Br_2ImH^{3+} (~10 min) were obtained with use of an isocratic eluant consisting of 58 parts of 96% methanol–water containing 25 mM dibutyl phosphate and 75 mM triethylamine adjusted to pH 3.5 with hydrochloric acid and 42 parts of a similar aqueous phase. The flow rate was 2.0 cm^3 min^{-1}. Detection was at 250 nm. Peak positions and areas were standarized against appropriate mixtures of the authentic compounds[17] at the conclusion of each set of analyses. Product runs were carried out as follows: To 500 μL of stock $RImH^{3+}$ (50 mM, 1.0 M in $NaClO_4$) were added 1 M $HClO_4$ (150 μL) and enough 1 M $NaClO_4$ to ensure the final volume after addition of bromine was 1.50 cm^3. The appropriate amount of a standarized aqueous bromine solution (~0.1 M, 1.0 M $NaClO_4$) was then added and the solution stored in the dark for 10 min (15 min for 1.5 mol equiv of bromine). Aliquots (10 μL) were then analyzed. Data are given in Table S3.

Comparative rate data for determining the reaction sequence (with use of the previous product data) were obtained with use of authentic $RImH^{3+}$, R-4-$BrImH^{3+}$, R-5-$BrImH^{3+}$, and R-4,5-Br_2ImH^{3+} complexes as follows. A cobalt solution ($[Co]_T$ = 0.01 M, $[Br^-]$ = 0.05 M, $[H^+]$ = 0.1 M, I = 1.0 M ($NaClO_4$)) was mixed with an equal volume of bromine solution ($[Br_2] \approx 2 \times 10^{-4}$ M, $[Br^-]$ = 0.05 M, $[H^+]$ = 0.1 M, I = 1.0 M ($NaClO_4$)) and the consumption of bromine (Br_3^-) monitored at 390 nm. Rate constants k_{obs} (s^{-1}) and k (M^{-1} s^{-1}) obtained were as follows: $RImH^{3+}$, 9.63 × 10^{-3} (3.62); R-5-$BrImH^{3+}$, 0.130 (0.489); R-4-$BrImH^{3+}$, 2.21 (831); and R-4,5-Br_2ImH^{3+}, 6.03 × 10^{-3} (2.27).

^1H NMR spectra were recorded by use of a Varian VXR 300 spectrometer. Attempts to detect the R-5-$BrImH^{3+}$ and R-4-$BrImH^{3+}$ intermediates were carried out as follows. To $[RImH]Br_3$ in D_2O (500 μL, 0.15 M, I = 1.0 M ($NaClO_4$)) were added $HClO_4$ in D_2O (71 μL, 1 M) and bromine in D_2O (140 μL, 0.135 M, I = 1.0 M ($NaClO_4$)) and the solutions stored in the dark for 10 min before recording the ^1H spectrum (256 transients). Calculated mixtures of $RImH^{3+}$, R-5-$BrImH^{3+}$, R-4-$BrImH^{3+}$, and R-4,5-Br_2ImH^{3+} were prepared by weighing out the appropriate solid bromide salts of these complex cations[17] and their ^1H spectra recorded in D_2O under the previous conditions ($[H^+]$ = 0.1 M, I = 1.0 M ($NaClO_4$)).

Supplementary Material Available: Tables S1–S4 containing raw experimental rate constant and product data (9 pages). Ordering information is given on any current masthead page.