Physical Organic Chemistry of Transition Metal Carbene Complexes. 29.[†] Kinetics of Reactions of [Ethoxy(phenyl)carbene]pentacarbonylchromium(0) and [Ethoxy(phenyl)(Cr(CO)₃)carbene]pentacarbonylchromium(0) with Water, OH⁻, and Amines. Mechanistic Changes Induced by the Cr(CO)₃ Group

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A kinetic study of the aminolysis of $(CO)_5Cr=C(OEt)C_6H_5$ (**7-Cr**) and $(CO)_5Cr=C(OEt)$-$C_6H_5(Cr(CO)_3)$ (**8-Cr**) by five primary aliphatic amines and of the hydrolysis of **8-Cr** in 50% MeCN−50% water (v/v) at 25 °C is reported. The introduction of the $Cr(CO)_3$ group has only a minor effect on the electrophilic reactivity of the carbene carbon; that is, the nucleophilic attack by OH^- and the amines on **7-Cr** and **8-Cr** occurs at similar rates. However, the $Cr(CO)_3$ group exerts a strong influence on the mechanisms of both types of reactions, which results in changes of what steps are rate limiting. In the hydrolysis reaction these changes lead to a more complex rate versus pH profile for **8-Cr** compared to the previously reported one for **7-Cr**. In the aminolysis the effect is to change the mechanism of general base catalysis from rate-limiting leaving group departure for the reactions of **7-Cr** to rate-limiting proton transfer for the reactions of **8-Cr**. We provide a detailed analysis of the reasons for these changes.

Introduction

Fisher carbene complexes are electrophilic and undergo facile nucleophilic substitution by a mechanism that involves tetrahedral intermediates.[1,2] As illustrated with the prototypical carbene complex **1-Cr**, for reactions with anionic nucleophiles such as alkoxide and thiolate ions, the mechanism consists of two steps (eq 1), while with amine nucleophiles there are three
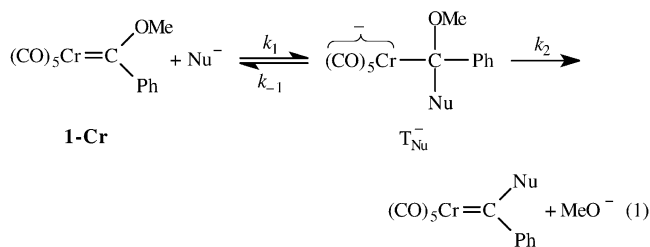
steps (eq 2). For the reactions with OH^-/H_2O the situation is more complex, as discussed below (Scheme 1).
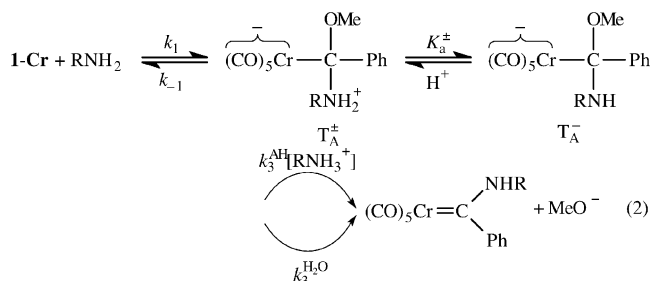
Electron-withdrawing substituents in the phenyl group are known to enhance the reactivity toward nucleophiles appreciably. Quantitative studies of this reactivity enhancement have been reported for a number of systems, e.g., the reactions of **2-Cr** and **2-W** with MeO^- in $MeOH$[3] and in 90% MeCN−10% MeOH,[3] of **2-Cr** and **2-W** with $HC\equiv CCH_2O^-$,[3] OH^-,[3] and amines in 50% MeCN−50% water,[4] of **3-Cr** with amines in 50% MeCN−50% water,[5] and of **4-Cr** with $HOCH_2CH_2S^-$ in 50% MeCN−50% water,[6] the cyclization of **4-Cr⁻** by intramolecular nucleophile attachment in the same

† Part 28: Bernasconi, C. F.; Ragains, M. L.; Bhattacharya, S. *J. Am. Chem. Soc.* **2003**, *125*, 12328.

(1) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissl, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Deerfield Beach, FL, 1983.

(2) (a) Bernasconi, C. F. *Chem. Soc. Rev.* **1997**, *26*, 299. (b) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **2002**, *37*, 137.
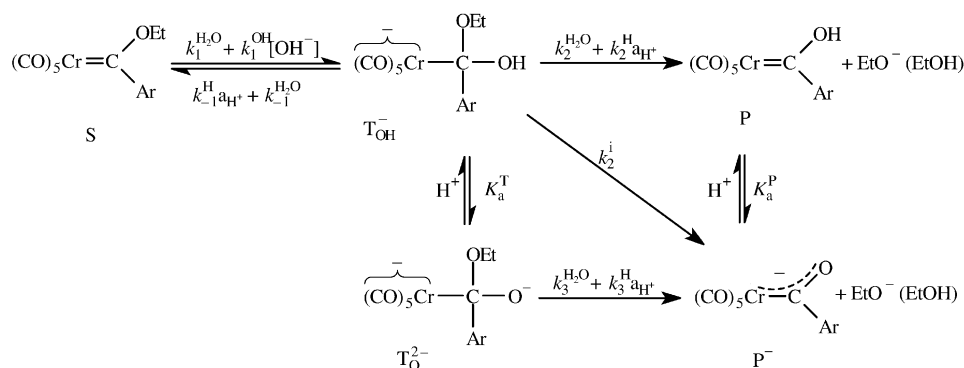
(3) Bernasconi, C. F.; García-Río, L. *J. Am. Chem. Soc.* **2000**, *122*, 3821.

(4) Bernasconi, C. F.; Whitesell, C.; Johnson, R. A. *Tetrahedron* **2000**, *56*, 4917.
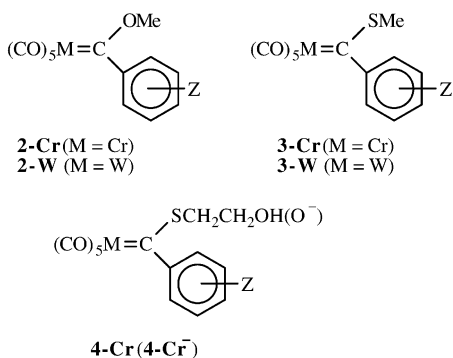
(5) Bernasconi, C. F.; Bhattacharya, S. *Organometallics* **2003**, *23*, 1310.

(6) Bernasconi, C. F.; Ali, M. *J. Am. Chem. Soc.* **1999**, *121*, 11384.

Scheme 1

solvent,[7] and the equilibrium addition of (n-Bu)₃Ph to **2-W** in toluene.[8]

The Hammett ρ-values for the nucleophilic attack step (k_1) are typically in the range 1.7–2.5 for carbene complexes with a methoxy leaving group (**2-Cr** and **2-W**), but substantially smaller (0.5–0.8) when there is a thioalkyl leaving group (**3-Cr**, **4-Cr**) or for the cyclization of **4-Cr⁻** (1.06). There are two main factors that contribute to the increased reactivity with electron-withdrawing substituents. One is the stabilization of the incipient negative charge at the transition state (**5** and **6**). Because in the reactions with amine nucleophiles
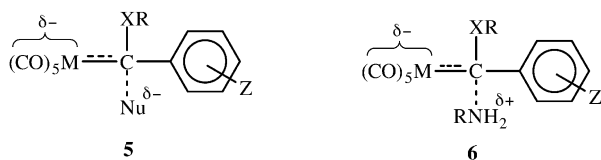

there is not only an incipient negative charge but also a partial positive charge, the substituent effects on the two charges should largely offset each other, which implies that the ρ-values for the amine reactions should be significantly smaller than for the reactions with anionic nucleophiles. This, however, is not the case and suggests that another, potentially more important, factor comes into play. This factor is the π-donor effect of the X atom (resonance structure B).
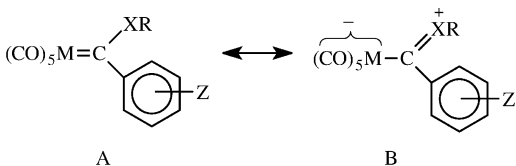
When the π-donor effect is strong (X = O), the resonance form B contributes importantly to the carbene complex structure. As a result, electron-withdrawing substituents in the phenyl group destabilize the carbene complex, which enhances its reactivity. This is because the negative charge is largely delocalized into the CO ligands, while the positive charge is concentrated on the X atom. Hence the destabilizing substituent effect on the positive charge is stronger than its stabilizing effect on the negative charge.[9] When the π-donor effect is weak (X = S), the importance of B is reduced, and hence the substituent effect on the reactant is diminished.

In this paper we report a kinetic study of the reactions of **7-Cr** and **8-Cr** with water, OH⁻, and several primary aliphatic amines in 50% MeCN–50% water (v/v) with the objective of evaluating the effect of the Cr(CO)₃ group on the reactivity of **8-Cr** and on the respective reaction mechanisms. Even though the Cr(CO)₃ group
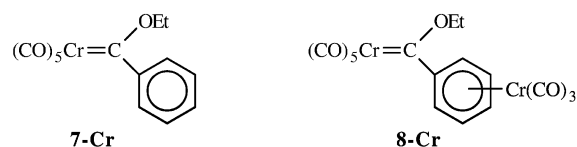
is electron withdrawing, its effect on the electrophilic reactivity of **8-Cr** toward most nucleophiles except for water is surprisingly small, and with most amines, **8-Cr** is actually somewhat *less* reactive than **7-Cr**. Even more interestingly, the introduction of the Cr(CO)₃ group leads to significant differences in the respective reaction mechanisms. Potential reasons for these unexpected results will be discussed.

Results

General Features. All kinetic measurements were performed in 50% MeCN–50% water (v/v) at 25 °C and an ionic strength of 0.1 M maintained with KCl. Pseudo-first-order conditions with the carbene complex as the minor component were used throughout. Rates were monitored spectrophotometrically at or near λ_{max} of the carbene complex, i.e., 397 nm for **7-Cr** and 493 nm for **8-Cr**; at these wavelengths there is little interference by the absorption of products.

Hydrolysis. The hydrolysis of carbene complexes such as **1-Cr**, **2-Cr**, **2-W**, **3-Cr**, **3-W**, **7-Cr**, and **8-Cr**

(7) Bernasconi, C. F.; Ali, M. *Organometallics* **2001**, *20*, 3383.
(8) Fischer, H. *J. Organomet. Chem.* **1979**, *170*, 309.
(9) The relatively high ρ-value for the equilibrium constants for (n-Bu)₃P addition to **2-W**[8] was interpreted in a similar way.[2b]
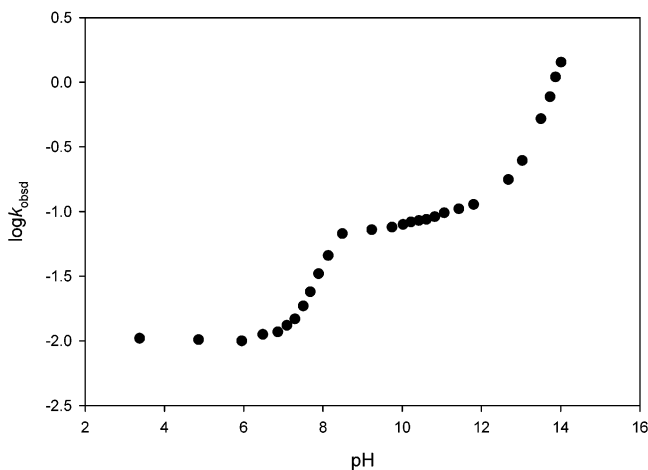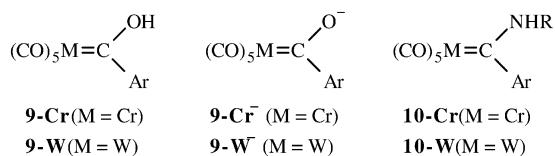
Figure 1. Rate versus pH profile for the hydrolysis of **8-Cr**.

proceeds in two stages. Depending on the pH, the first stage leads to **9-Cr** (**9-Cr⁻**) or **9-W** (**9-W⁻**), while in the second stage **9-Cr** (**9-Cr⁻**) or **9-W** (**9-W⁻**) is converted to ArCH=O and $Cr(CO)_5OH^-$ ($W(CO)_5OH^-$) + ROH.[10,11] Our kinetic measurements refer to the first stage only.

$(CO)_5M=C$ with OH and Ar groups

$(CO)_5M=C$ with O⁻ and Ar groups

$(CO)_5M=C$ with NHR and Ar groups

9-Cr (M = Cr)   **9-Cr⁻** (M = Cr)   **10-Cr** (M = Cr)

9-W (M = W)   **9-W⁻** (M = W)   **10-W** (M = W)

Hydrolysis rates of **8-Cr** were determined between pH 3.37 and 14.01. At pH ≥ 11.8 the measurements were made in KOH solution, at pH 9.23–11.43 in triethylamine buffers, at pH 7.09–8.49 in *N*-methylmorpholine buffers, at pH 5.95–7.02 in acetate buffers, and at pH 3.37–4.86 in chloroacetate buffers. No buffer catalysis was detected in the chloroacetate, acetate, and *N*-methylmorpholine buffers, but modest catalysis was observed with triethylamine, amounting to an approximately 30–40% rate increase at 0.05 M free amine concentration. However, at the low triethylamine concentrations used in most experiments this catalysis was negligible, and hence there was no need for extrapolation to zero buffer concentrations in order to obtain the rate versus pH profile shown in Figure 1. This contrasts with the hydrolysis of **7-Cr** reported previously,[11] where triethylamine catalysis was somewhat stronger and catalysis by all buffers was observed, necessitating such extrapolations. Another contrast between the hydrolysis of **7-Cr** and **8-Cr** is that for **7-Cr** the rate versus pH profile has only one break,[12] while that for **8-Cr** has three breaks, indicating that there must be mechanistic differences between the two carbene complexes.

Reactions of 7-Cr and 8-Cr with Primary Aliphatic Amines. The aminolysis of Fischer carbenes leads to the substitution of the leaving group by the amine, generating products such as **10-Cr**.[1,2,13] Reactions with the following primary aliphatic amines were

(10) Aumann, R.; Hinterding, P.; Krüger, C.; Goddard, R. *J. Organomet. Chem.* **1993**, *459*, 145.
(11) Bernasconi, C. F.; Flores, F. X.; Kittredge, K. W. *J. Am. Chem. Soc.* **1997**, *119*, 2103.
(12) Figure 3 in ref 11.
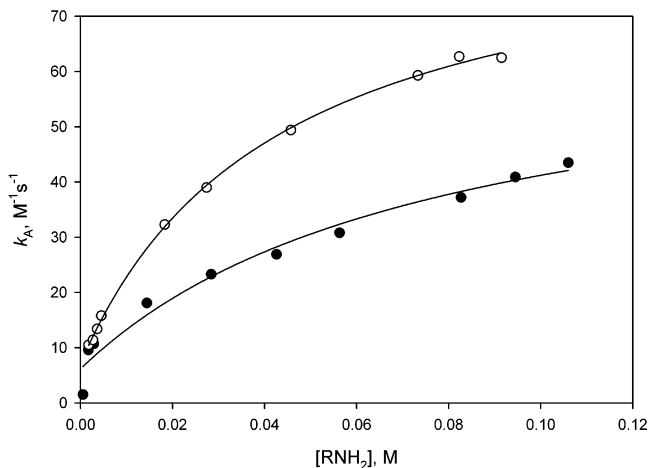(13) Bernasconi, C. F.; Stronach, M. W. *J. Am. Chem. Soc.* **1993**, *115*, 1341.

Figure 2. Plots of k_A versus [RNH$_2$] for the reactions of **7-Cr** (○) and **8-Cr** (●) with 2-methoxyethylamine; pH held constant at 10.39 for **7-Cr** and 9.49 for **8-Cr**.
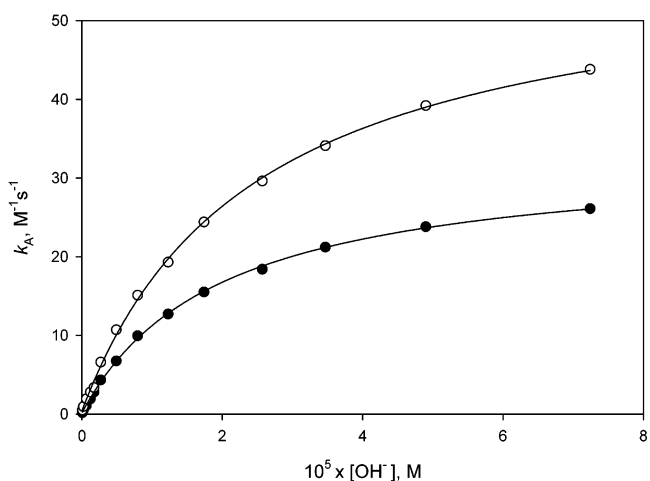

Figure 3. Plots of k_A versus [OH⁻] for the reactions of **7-Cr** (○) and **8-Cr** (●) with glycinamide; [RNH$_2$] held constant at 0.025 M.

examined: *n*-butylamine, 2-methoxyethylamine, glycinamide, 2-chloroethylamine, and aminoacetontrile. Pseudo-first-order rate constants, k_{obsd}, for aminolysis were obtained as a function of amine concentration at constant pH and as a function of hydroxide ion concentration at constant amine concentration. The raw data are reported in Tables S1–S21 of the Supporting Information.[14] Second-order rate constants for aminolysis, k_A, were calculated according to eq 3

$$k_A = \frac{k_{obsd} - k_h}{[RR'NH]} \quad (3)$$

where k_h is the pseudo-first-order rate constant for hydrolysis taken from the respective rate versus pH profiles.

In most cases k_A increases nonlinearly with increasing amine and/or OH⁻ concentration, indicating general base catalysis. Some representative plots are shown in Figures 2 and 3. In one case, the reaction of **8-Cr** with glycinamide, OH⁻ catalysis (Figure 3) but no amine catalysis was observed.

(14) See paragraph concerning Supporting Information at the end of this paper.

Discussion

Hydrolysis. A. Mechanism. In previous studies[11,15] it was shown that the mechanism of hydrolysis of **7-Cr** and similar carbene complexes such as **2-Cr**, **2-W**, **3-Cr** (Z = H), and **3-W** (Z = H) can be described by Scheme 1. The k_{-1}^H, k_2^H, and k_3^H pathways represent H⁺-catalyzed steps, the $k_{-1}^{H_2O}$, $k_2^{H_2O}$, and $k_3^{H_2O}$ represent spontaneous or water-catalyzed steps, while k_2^i refers to intramolecular acid catalysis of leaving group departure by the OH group. The inclusion of a pathway through the deprotonated intermediate T_O^{2-} and the k_2^i pathway was necessary to explain why the intermediate T_{OH}^- does not accumulate to detectable levels; these additional pathways are faster than the conversion of T_{OH}^- into products, at least at high pH, and turn T_{OH}^- into a steady state intermediate.[16]

For **2-Cr**, **2-W**, and **7-Cr** the rate versus pH profile had only one break, with a pH-independent region ranging from pH 2 to about 10 followed by an ascending region consistent with a linear dependence on [OH⁻].[11] These findings were interpreted by assuming that nucleophilic attack is rate limiting over the entire pH range, with k_{obsd} given by eq 4. The implication is

$$k_{obsd} = k_1^{H_2O} + k_{-1}^{OH}[OH^-] \qquad (4)$$

that the inequality of eq 5 holds over the entire pH range.

$$k_2^{H_2O} + k_2^H a_{H^+} + k_2^i + K_a^T k_3^{H_2O}/a_{H^+} + K_a^T k_3^H \gg k_{-1}^H a_{H^+} + k_{-1}^{H_2O} \qquad (5)$$

Regarding the hydrolysis of **8-Cr**, there is no good reason to assume a mechanism different from that of Scheme 1, yet the rate versus pH profile looks quite different. This implies that with **8-Cr** there are several changes in the rate-limiting step with changing pH. We offer the following interpretation.

Region I (pH > 12.7). Nucleophilic attack by OH⁻ is rate limiting, i.e., eqs 6−8 hold.

$$k_1^{OH}[OH^-] \gg k_1^{H_2O} \text{ and } k_{-1}^{H_2O} \gg k_{-1}^H a_{H^+} \qquad (6)$$

$$k_2^{H_2O} + k_2^i + K_a^T k_3^{H_2O}/a_{H^+} + K_a^T k_3^H \gg k_{-1}^{H_2O} \qquad (7)$$

$$k_{obsd} = k_1^{OH}[OH^-] \qquad (8)$$

Region II (pH 8.5−12.7). Nucleophilic attack by water is rate limiting, i.e., eqs 9−11 hold.

$$k_1^{H_2O} \gg k_1^{OH}[OH^-] \text{ and } k_{-1}^H a_{H^+} \gg k_{-1}^{H_2O} \qquad (9)$$

$$k_2^{H_2O} + k_2^H a_{H^+} + k_2^i + K_a^T k_3^{H_2O}/a_{H^+} + K_a^T k_3^H \gg k_{-1}^H a_{H^+} \qquad (10)$$

$$k_{obsd} = k_1^{H_2O} \qquad (11)$$

(15) Bernasconi, C. F.; Perez, G. S. *J. Am. Chem. Soc.* **2000**, *122*, 12441.

(16) Without these additional pathways T_{OH}^- would accumulate to detectable levels at high pH because $k_1^{OH}[OH^-] > (\gg) 1$.[11]

The observation of buffer catalysis by triethylamine is consistent with a class *n* concentrated mechanism[17] (**11**) for rate-limiting water attachment in this region.
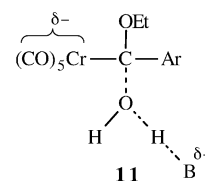
Region III (pH 7.0−8.5). In this region eq 9 remains valid, but eq 10 changes to eq 12.

$$k_{-1}^H a_{H^+} \gg k_2^{H_2O} + k_2^H a_{H^+} + k_2^i + K_a^T k_3^H \qquad (12)$$

Note that in this region the $K_a^T k_3^{H_2O}/a_{H^+}$ term becomes negligible and hence has been omitted from eq 12. Equation 12 implies that the first step in Scheme 1 is no longer rate limiting but acts as a preequilibrium, and k_{obsd} is given by eq 13 with $K_1^{H_2O} = k_1^{H_2O}/k_{-1}^H$ being the

$$k_{obsd} = \frac{K_1^{H_2O}}{a_{H^+}}(k_2^{H_2O} + k_2^H a_{H^+} + k_2^i + K_a^T k_3^H) \qquad (13)$$

equilibrium constant for nucleophilic attack by water. This interpretation is consistent with the absence of buffer catalysis in this region. The fact that the slope of the plot of log k_{obsd} versus pH is somewhat less than unity indicates the growing relative importance of the $k_2^H a_{H^+}$ term in eq 13 as the pH is decreased.

Region IV (pH 3.4−7.0). Here the $k_2^H a_{H^+}$ term becomes dominant, and eq 13 turns into eq 14; that is, H⁺-catalyzed collapse of T_{OH}^- is now the sole rate-limited step. Again, this is consistent with the absence of buffer catalysis.

$$k_{obsd} = K_1^{H_2O} k_2^H \qquad (14)$$

B. Reasons for the Change in Rate-Limiting Step. The question arises, why is there a change in rate-limiting step from nucleophilic attack (regions I and II) to rate-limiting conversion of T_{OH}^- to products (regions III and IV) for the hydrolysis of **8-Cr** but not for the hydrolysis of **7-Cr**? For **7-Cr** the relationships of eqs 7 and 10 apparently hold over the entire pH range, which is not the case for **8-Cr**. Since at low pH the $k_2^H a_{H^+}$ term becomes the dominant pathway for the collapse of T_{OH}^- to products, the crucial difference between the two carbene complexes must be that for the **7-Cr** $k_2^H \gg k_{-1}^H$, while for **8-Cr** $k_{-1}^H \gg k_2^H$.

This situation is reminiscent of the hydrolysis of **3-Cr** (Z = H) and **3-W** (Z = H), where $k_{-1}^H \gg k_2^H$, which leads to rate profiles similar to that for **8-Cr** in Figure 1.[15] In these cases the relationship $k_{-1}^H \gg k_2^H$ was attributed to the much lower sensitivity of thioalkyl versus alkoxy leaving groups to H⁺ catalysis. For **8-Cr** such reasoning is not possible, necessitating a different explanation.

In principle, the electron-withdrawing effect of the Cr(CO)₃ group is not expected to substantially affect the k_{-1}^H/k_2^H ratio; that is, both k_{-1}^H and k_2^H should decrease by a comparable amount. This decrease in k_{-1}^H and k_2^H

(17) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345.

Table 1. Rate Constants for Nucleophilic Attack by OH^-, H_2O, and Amines and Rate Constant Ratios for the Amine Reactions[a]

nucleophile	pK_a^{NuH}	$k_1/M^{-1}\,s^{-1}$	k_{cat}^A/k_{-1} M^{-1}	k_{cat}^{OH}/k_{-1} M^{-1}	k_{cat}^{OH}/k_{cat}^A
		$(CO)_5Cr=C(OEt)C_6H_5$ $(Cr(CO)_3)$ (**8-Cr**)			
OH^-	16.63	20.1 ± 0.3			
H_2O	−1.44	0.08 ± 0.02^d			
n-BuNH$_2$	10.40	434	66	1.3×10^5	2.0×10^3
MeOCH$_2$CH$_2$NH$_2$	9.39	93.8	14	9.5×10^4	6.8×10^3
H$_2$NCOCH$_2$NH$_2$	8.14	33.2		5.1×10^4	
ClCH$_2$CH$_2$NH$_2$	8.05	68.0	15.5	5.2×10^4	3.4×10^3
NCCH$_2$NH$_2$	5.29	≤ 0.11			
		$(CO)_5Cr=C(OEt)C_6H_5$ (**7-Cr**)			
OH^{-b}	16.63	10.5			
H_2O^b	−1.44	$4.5 \times 10^{-4}\,^d$			
n-BuNH$_2$	10.40	851	183	3.1×10^3	1.7×10^1
MeOCH$_2$CH$_2$NH$_2$	9.39	277	25.5	1.9×10^3	7.5×10^1
H$_2$NCOCH$_2$NH$_2$	8.14	58.3	34.5	4.1×10^4	1.2×10^3
ClCH$_2$CH$_2$NH$_2$	8.05	34.2	20.5	3.9×10^4	1.9×10^3
NCCH$_2$NH$_2$	5.29	0.58	0.76	7.2×10^6	9.5×10^6
		$(CO)_5Cr=C(OMe)C_6H_5$ (**1-Cr**)			
OH^{-b}	16.63	26.6			
H_2O^b	−1.44	$2.9 \times 10^{-3}\,^d$			
n-BuNH$_2^c$	10.40	1600	100	1.2×10^4	1.2×10^2
ClCH$_2$CH$_2$NH$_2^c$	8.05	130	35	1.15×10^5	3.5×10^3

[a] Error limits for k_1, k_{cat}^A/k_{-1}, k_{cat}^{OH}/k_{-1}, and k_{cat}^{OH}/k_{cat}^A for the amine reactions are estimated to be up to $\pm 40\%$, see text. [b] Reference 11. [c] Reference 4. [d] In units of s^{-1}.

comes about because the reactant state (T_{OH^-}) is more stabilized by the $Cr(CO)_3$ group than the two transition states (**12** and **13**). The decrease in the two rate
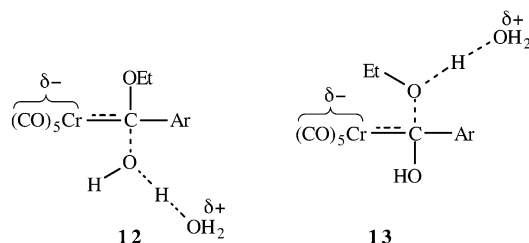
constants should be similar due to the similarity of the two transition states. However, there are some indications suggesting that **12** is more intermediate-like than **13**, rendering k_{-1}^H quite insensitive to the electronic effect of the $Cr(CO)_3$ group. This suggestion is based on the $k_1^{H_2O}$(**8-Cr**)/$k_1^{H_2O}$(**7-Cr**) ratio of 180, which is much larger than the k_1^{OH}(**8-Cr**)/k_1^{OH}(**7-Cr**) ratio of 2 (Table 1) and implies that the transition states for the $k_1^{H_2O}$ step are much closer to T_{OH^-} than the transition states for the k_1^{OH} step.[18] In other words, the high $k_1^{H_2O}$(**8-Cr**)/$k_1^{H_2O}$(**7-Cr**) ratio suggests that most of the electronic effect of the $Cr(CO)_3$ group on the equilibrium constant $K_1^{H_2O}$ is expressed in $k_1^{H_2O}$, and thus the effect on k_{-1}^H must be minimal.

For the k_2^H step the transition state is probably less T_{OH^-}-like, which makes k_2^H more sensitive to electronic effects. This is because the ethoxy leaving group is bulkier than the hydroxy leaving group, rendering a transition state where the C−O bond cleavage is further advanced more favorable; as has been shown before[2b,6,21]

and will also become more apparent when we discuss the amine reactions, steric effects play a major role in nucleophilic reactions of carbene complexes.[22]

The overall result of the effects discussed above is to increase the k_{-1}^H/k_2^H ratio for **8-Cr**. An additional steric effect that is expected to further increase the k_{-1}^H/k_2^H ratio for **8-Cr** is steric hindrance of the approach of the H_3O^+ ion to the leaving group oxygen. The large $Cr(CO)_5$ and phenyl groups are primarily responsible for this steric hindrance in both transition states **12** and **13**, but the effect should be particularly strong in **13** because the ethyl group on the leaving oxygen further increases the steric hindrance. This should result in a reduction in k_2^H, but this reduction is expected to be more pronounced in the case of **8-Cr** because the $Cr(CO)_3$ group further increases the bulk of the phenyl group.

Reactions with Amines. A. Mechanism. The mechanism of aminolysis of all carbene complexes studied thus far[4,5,13,24] conforms to the scheme of eq 2. Specifically, it was shown that the interconversion of the two steady state intermediates ($T_A^\pm$ and T_A^-) is fast on the time scale of the other steps and hence can be treated as a rapid acid−base equilibrium.[4,13] However, it is conceivable that, in some cases, the interconversion between $T_A^\pm$ and T_A^- could be kinetically significant, and hence a more general representation of the mechanism including this possibility is shown in Scheme 2.[25] The results obtained in the present study suggest this to be the case for the aminolysis of **8-Cr**.

An expression for the second-order rate constant, k_A, that applies to either mechanistic extremes is given by

(18) Since water is a much weaker nucleophile than OH^-, our findings are consistent with the Hammond−Leffler[19,20] postulate.

(19) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

(20) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963; p 156.

(21) Choi, H. S.; Sweigart, D. A. *J. Organomet. Chem.* **1982**, *228*, 249.

(22) The importance of steric effects in nucleophilic reactions of carbene complexes is reminiscent of the situation in nucleophilic vinylic substitution reactions which proceed via tetrahedral intermediates.[23]

(23) Bernasconi, C. F.; Ketner, R. J.; Ragains, M. L.; Chen, X.; Rappoport, Z. *J. Am. Chem. Soc.* **2001**, *123*, 2155.

(24) Bernasconi, C. F.; Bhattacharya, S. O*rganometallics* **2003**, *22*, 426.

(25) In principle, steps involving water or H_3O^+ should be included such as $k_2^{H_2O}$, $k_{-2}^H a_{H^+}$ and $k_3^H a_{H^+}$, but these are negligible in the pH range used.

Scheme 2
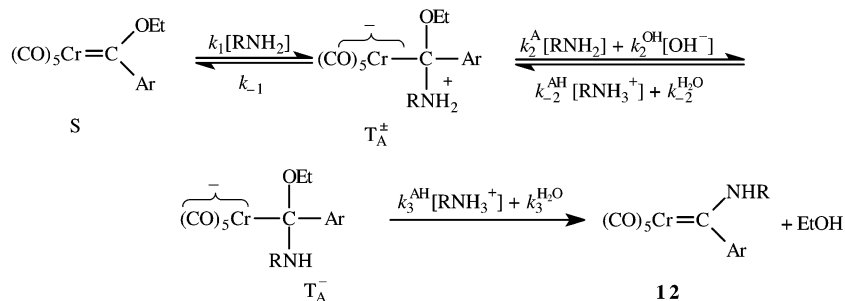
eq 15. If the inequality of eq 16 holds, the interconversion of the two intermediates can be treated as a rapid

$$k_A = \frac{k_1 \left(\frac{k_{cat}^A}{k_{-1}}[RNH_2] + \frac{k_{cat}^{OH}}{k_{-1}}[OH^-] \right)}{1 + \frac{k_{cat}^A}{k_{-1}}[RNH_2] + \frac{k_{cat}^{OH}}{k_{-1}}[OH^-]} \qquad (15)$$

$$k_{-2}^{AH}[RNH_3^+] + k_{-2}^{H_2O} \gg k_3^{AH}[RNH_3^+] + k_3^{H_2O} \quad (16)$$

equilibrium (see eq 2), and the expressions for k_{cat}^A and k_{cat}^{OH} are given by eqs 17 and 18, respectively.

$$k_{cat}^A = k_3^{AH} K_a^{\pm}/K_a^{AH} \qquad (17)$$

$$k_{cat}^{OH} = k_3^{H_2O} K_a^{\pm}/K_w \qquad (18)$$

K_a^{AH} refers to the acidity constant of RNH_3^+, while K_w is the ionic product of the solvent.[26] If, on the other hand, eq 19 holds, deprotonation of $T_A^{\pm}$ is rate limiting

$$k_{-2}^{AH}[RNH_3^+] + k_{-2}^{H_2O} \ll k_3^{AH}[RNH_3^+] + k_3^{H_2O} \quad (19)$$

for the conversion of $T_A^{\pm}$ to final products and eqs 20 and 21 hold.

$$k_{cat}^A = k_2^A \qquad (20)$$

$$k_{cat}^{OH} = k_2^{OH} \qquad (21)$$

Note, however, that irrespective of whether the interconversion of the two intermediates is rapid or kinetically significant at low amine and/or hydroxide ion concentrations, at high concentrations the plateau of the plots of k_A versus $[RNH_2]$ or versus $[OH^-]$ represent k_1; that is, nucleophilic attack becomes rate limiting.

We have analyzed our results according to eq 15. Curve fitting of plots to k_A versus $[OH^-]$ yielded k_1 and k_{cat}^{OH}/k_{-1} values, while curve fitting of plots of k_A versus $[RNH_2]$ yielded the k_{cat}^A/k_{-1} ratios; for more details see the Experimental Section. The various k_1, k_{cat}^A/k_{-1}, and k_{cat}^{OH}/k_{-1} values are summarized in Table 1. For reasons discussed in detail in a previous paper,[4] the k_{cat}^{OH}/k_{-1} and k_{cat}^A/k_{-1} ratios are subject to experimental errors that are likely to be greater than their standard deviations and could be as large as ±40% in some cases. However, these potential uncertainties do not affect the qualitative conclusions drawn from these ratios. We also

note that for the reaction of **8-Cr** with glycinamide, the k_{cat}^A/k_{-1} ratio could not be obtained because the dependence of k_A on amine concentration was too weak for an accurate determination. A possible reason is that the larger steric bulk of glycinamide diminishes its catalytic effect so that OH^- catalysis dominates. As discussed below, steric effects on the amine-catalyzed pathway are quite pronounced. For the reaction of **8-Cr** with aminoacetonitrile competing hydrolysis prevented an accurate determination of k_A altogether, and only an upper limit for k_1 but no k_{cat}^A/k_{-1} or k_{cat}^{OH}/k_{-1} ratios could be obtained.

B. Different Rate-Limiting Steps for 7-Cr and 8-Cr. For the reactions of **7-Cr** the k_{cat}^A/k_{-1} ratios decrease with increasing amine basicity, while the k_{cat}^{OH}/k_{-1} ratios increase. As a result, the k_{cat}^{OH}/k_{cat}^A ratios increase strongly, from 1.7×10^1 for *n*-butylamine to 9.5×10^6 for aminoacetonitrile. These trends are similar to those observed for the aminolysis of **1-Cr**[13] and consistent with rate-limiting ethoxide departure from T_A^- catalyzed by RNH_3^+ (k_3^{AH}) and water ($k_3^{H_2O}$), respectively; that is, eqs 16 and 17 hold. The decrease in the $k_{cat}^A/k_{-1} = k_3^{AH} K_a^{\pm}/K_a^{AH} k_{-1}$ ratios mainly reflects the expected increase in k_{-1} with decreasing amine basicity.[28] $K_a^{\pm}/K_a^{AH}$ should be essentially independent of amine basicity since changes in $pK_a^{\pm}$ parallel those in pK_a^{AH}; k_3^{AH} is not expected to show a strong dependence on amine basicity either, because the enhancement of k_3^{AH} resulting from the more acidic protonated amine catalyst is counteracted by a reduced electronic push from the nitrogen base pair on T_A^-, which leads to the resonance form **12**$^{\pm}$.[1,2]
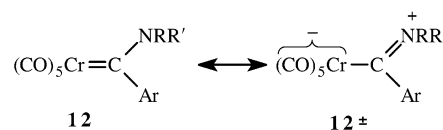
The increase in $k_{cat}^{OH}/k_{-1} = k_3^{H_2O} K_a^{\pm}/K_w k_{-1}$ is the result of a strong increase in the $K_a^{\pm}/K_w$ ratio for the less basic amines, which more than offsets the increase in k_{-1}; a slight decrease in $k_3^{H_2O}$ resulting from a diminished electronic push by the amine-nitrogen on T_A^- probably contributes to the attenuation of the effect of the $K_a^{\pm}/K_w$ ratio.

For the reactions of **8-Cr** the observed patterns are quite different. The k_{cat}^A/k_{-1} ratio decreases less than the corresponding ratios for **7-Cr** and the k_{cat}^{OH}/k_{-1}

(26) $pK_w = 15.19$ in 50% MeCN−50% water at 25 °C, $\mu = 0.1$ M.[27]

(27) Bernasconi, C. F.; Sun, W. *J. Am. Chem. Soc.* **1993**, *115*, 12526.
(28) A less basic amine is a better leaving group.

ratios show a slight decrease rather than the strong increase found for **7-Cr**. This results in k_{cat}^{OH}/k_{cat}^{A} ratios that are essentially independent of amine basicity. These trends are difficult to reconcile with rate-limiting leaving group departure, but they are consistent with rate-limiting proton transfer; that is, eqs 19–21 hold. The approximately constant k_{cat}^{OH}/k_{cat}^{A} ratios reflect the fact that the thermodynamically favorable deprotonation of an ammonium ion such as $T_A^{\pm}$ by amines or OH^- should depend little on the pK_a of $T_A^{\pm}$.[30] The decrease in the $k_{cat}^{OH}/k_{-1} = k_2^{OH}/k_{-1}$ and $k_{cat}^{A}/k_{-1} = k_2^{A}/k_{-1}$ ratios with decreasing amine basicity reflects the increase in k_{-1}; this increase appears to be weaker than for the aminolysis of **7-Cr**, consistent with the larger β_{nuc} value for k_1 discussed below.

C. Why Is There a Change in Rate-Limiting Step? The change from rate-limiting leaving group departure to rate-limiting proton transfer reflects a change from eq 16 for **7-Cr** to eq 19 for **8-Cr** and is probably the combined result of a decrease in k_{-2}^{AH} and $k_{-2}^{H_2O}$, respectively, and an increase in k_3^{AH} and $k_3^{H_2O}$, respectively.

Lower k_{-2}^{AH} and $k_{-2}^{H_2O}$ values for **8-Cr** can result from two factors. (1) The acidity of $T_A^{\pm}$ is higher because of the electron-withdrawing effect of the $Cr(CO)_3$ group. Since protonation of T_A^- by water and by RNH_3^{+} [29] is thermodynamically unfavorable and the rate constants for the thermodynamically favorable *de*protonation of $T_A^{\pm}$ (k_2^{A} and k_2^{OH}) should be essentially independent of $pK_a^{\pm}$,[30] there will be a decrease in k_{-2}^{AH} and $k_{-2}^{H_2O}$ that is inversely proportional to the increase in $K_a^{\pm}$. (2) The increased steric crowding around the nitrogen of T_A^- due to the $Cr(CO)_3$ group may reduce access of the proton donor to that nitrogen, thereby reducing k_{-2}^{AH} and $k_{-2}^{H_2O}$ even further. This latter effect is expected to be more pronounced for the ammonium ion proton donors than for water because of their larger size. Direct evidence for this steric effect comes from the $k_{cat}^{OH}/k_{cat}^{A} = k_2^{OH}/k_2^{A}$ ratios, which have values between 2×10^3 and 6×10^3. These ratios are significantly higher than is typical for thermodynamically favorable and essentially diffusion-controlled deprotonation of normal acids,[30] but they are consistent with such ratios when the acid is sterically crowded.[31,32]

As to the k_3^{AH} and $k_3^{H_2O}$ values for **8-Cr**, they are likely to be higher than for **7-Cr** because of relief of the greater steric crowding in T_A^- upon leaving group departure.

Effect of the $Cr(CO)_3$ Group on k_1. Brønsted plots of log k_1 versus pK_a^{AH} for the amine reactions are shown in Figure 4. They suggest a somewhat stronger dependence of k_1 on amine basicity for the reaction of **8-Cr** ($\beta_{nuc} \geq 0.69 \pm 0.11$) than for the reaction of **7-Cr** ($\beta_{nuc} = 0.63 \pm 0.03$). Assuming that $\beta_{eq} = $ d log K_1/d

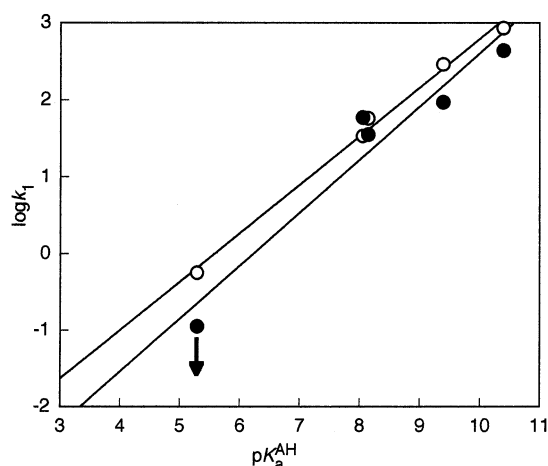(29) As discussed elsewhere,[13] $T_A^{\pm}$ derived from **1-Cr** is likely to be more acidic than the corresponding RNH_3^{+}; due to the electron-withdrawing $Cr(CO)_3$ group, the acidity of $T_A^{\pm}$ derived from **8-Cr** is expected to be even higher.
(30) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.
(31) (a) Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147. (b) Bernasconi, C. F.; Carré, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 2698. (c) Bernasconi, C. F.; Murray, C. J.; Fox, J. P.; Carré, D. J. *J. Am. Chem. Soc.* **1983**, *105*, 4349.
(32) Crampton, M. R.; Gibson, B. *J. Chem. Soc., Perkin Trans. 2* **1981**, 533.

Figure 4. Brønsted plot of log k_1 versus pK_a^{AH} for **7-Cr** (○) and **8-Cr** (●).

pK_a^{AH} is the same for the two reaction series, this result implies that $\beta_{lg} = -$d log k_{-1}/d pK_a^{AH} is somewhat smaller for **8-Cr** than for **7-Cr**, consistent with the observation that for **8-Cr** the dependence of k_{cat}^{OH}/k_{-1} and k_{cat}^{A}/k_{-1} on amine basicity is smaller than for **7-Cr**.

The reactivities of **7-Cr** and **8-Cr** toward nucleophilic addition by amines are very similar, with **8-Cr** being slightly less reactive than **7-Cr**. On the other hand, for the reactions of OH^- (k_1^{OH}), **8-Cr** is somewhat more reactive than **7-Cr**. These results show the competing influences of the reactivity-enhancing electronic effect and the reactivity-reducing steric effect of the $Cr(CO)_3$ group; for reactions with the sterically larger amines the steric effect is stronger and more than offsets the electronic effect. The negative deviation of the glycinamide point from the Brønsted plot for **8-Cr** is probably a steric effect, too, caused by the larger size of this amine; as discussed earlier, the larger size of glycinamide also reduces the deprotonation rate of the corresponding $T_A^{\pm}$ by glycinamide.

For the reaction with water ($k_1^{H_2O}$), the reactivity difference between **7-Cr** and **8-Cr** is much larger than for the reaction with OH^-. As mentioned earlier, this probably reflects a transition state for the water reaction that is very T_{OH}^--like.

Comparison between 7-Cr and 1-Cr. Previously reported kinetic parameters for the reactions of **1-Cr** with *n*-butylamine and 2-chloroethylamine under the same conditions are included in Table 1. They allow an evaluation of the effect of changing the leaving group from MeO to EtO on k_1, k_{cat}^{A}/k_{-1}, and k_{cat}^{OH}/k_{-1}. As had been observed before for the reactions with OH^- and water,[11] the electrophilic reactivity of the carbene carbon of **7-Cr** is lower than that of **1-Cr**, with k_1^{OH}(**7-Cr**)/k_1^{OH}(**1-Cr**) = 0.39 and $k_1^{H_2O}$(**7-Cr**)/$k_1^{H_2O}$(**1-Cr**) = 0.16. The main reason for the lower reactivity appears to be the stronger π-donor effect of the ethoxy group, which stabilizes the carbene complex. The same is the case for the reactions with amines, where we have $k_1^{n-BuNH_2}$(**7-Cr**)/$k_1^{n-BuNH_2}$(**1-Cr**) = 0.53 and $k_1^{ClCH_2CH_2NH_2}$(**7-Cr**)/$k_1^{ClCH_2CH_2NH_2}$(**1-Cr**) = 0.26. The trend toward higher selectivity with decreasing reactivity of the nucleophile is again consistent with the Hammond[19]–Leffler[20] postulate that calls for more product-like transition states with the weaker nucleophiles.

Regarding the $k_{cat}^A/k_{-1} = k_3^{AH}K_a^\pm/K_a^{AH}k_{-1}$ and $k_{cat}^{OH}/k_{-1} = k_3^{H_2O}K_a^\pm/K_w k_{-1}$ ratios, the former show little change within the experimental uncertainty, while the latter are approximately 3-fold lower for **7-Cr** than for **1-Cr**. In analyzing the reasons for the observed results we only need to focus on k_{-1}, k_3^{AH}, and $k_3^{H_2O}$ since $K_a^\pm$ is unlikely to depend significantly on the leaving groups and K_a^{AH} and K_w are not related to the carbene complex. For the change from the MeO to the EtO derivative, k_{-1} is expected to increase due to the stronger π-donor effect of the ethoxy group, while $k_3^{H_2O}$ is expected to decrease because the more basic EtO⁻ is a worse leaving group than MeO⁻. Both of these effects result in a decrease in the $k_3^{H_2O}K_a^\pm/K_w k_{-1}$ ratio as observed. On the other hand, the k_3^{AH} step is likely to be faster for **7-Cr** because it involves acid catalysis by RNH_3^+, and the more basic leaving group typically benefits more from acid catalysis.[15,33] Hence the effect on k_3^{AH} offsets the effect on k_{-1}, leaving the $k_3^{AH}K_a^\pm/K_a^{AH}k_{-1}$ ratio essentially unchanged.

Conclusions

The introduction of the Cr(CO)₃ group into the phenyl ring of **7-Cr** has only a minor effect on the electrophilic reactivity of the carbene carbon of **8-Cr**, as seen by the fact that the k_1^{OH} value for hydrolysis and the k_1^A values for aminolysis of **8-Cr** differ only modestly from their respective values for **7-Cr**. This is because the reactivity-enhancing effect of the Cr(CO)₃ is largely offset by the reactivity-reducing steric effect; this latter effect plays a particularly important role in the amine reactions.

In contrast, the Cr(CO)₃ group exerts a large effect on the relative rates by which the respective intermediates revert back to their precursors and proceed forward toward products. This leads to differences between **8-Cr** and **7-Cr** regarding what steps are rate limiting in the overall mechanism. Specifically, in the hydrolysis reaction, there is a change from $k_2^H \gg k_{-1}^H$ for **7-Cr** to $k_{-1}^H \gg k_2^H$ for **8-Cr**. This change is attributed to a combination of a low sensitivity of k_{-1}^H but relatively high sensitivity of k_2^H to the electronic effect of the Cr(CO)₃ group, and a steric reduction of k_2^H due to sterically more hindered access of the H_3O^+ catalyst in the k_2^H step. In the aminolysis reaction there is a change in the rate-limiting step of the conversion of $T_A^\pm$ to final products: For **7-Cr** the proton transfer equilibrium between $T_A^\pm$ and T_A^- is rapid, with the collapse of T_A^- to products being rate limiting, while for **8-Cr** deprotonation of $T_A^\pm$ is rate limiting followed by rapid leaving group departure from T_A^-. This change is the combined result of a decrease in k_{-2}^{AH} and $k_{-2}^{H_2O}$, respectively, and an increase in k_3^{AH} and $k_3^{H_2O}$, respectively. The decrease in the k_{-2}^{AH} and $k_{-2}^{H_2O}$ values is due to the lower $pK_a^\pm$ for $T_A^\pm$ derived from **8-Cr** and greater steric crowding around the nitrogen of T_A^-; the increase in the k_3^{AH} and $k_3^{H_2O}$ values for **8-Cr** reflects relief of increased crowding in T_A^- upon leaving group departure.

In comparing the reactions of **7-Cr** and **1-Cr** with amines, the k_1 values for **7-Cr** are lower because of the strong π-donor effect of the ethoxy group, the k_{cat}^{OH}/k_{-1} ratios for **7-Cr** are lower because k_{-1} is enhanced by the stronger π-donor effect and $k_3^{H_2O}$ is reduced because EtO⁻ is a poorer leaving groups than MeO⁻, and the k_{cat}^A/k_{-1} ratio is essentially unchanged because acid catalysis of alkoxide ion departure (k_3^{AH}) is stronger for the reaction of **7-Cr**, which offsets the effect on k_{-1}.

Experimental Section

Materials. **7-Cr** was available from a previous study,[11] while **8-Cr** was a gift from Prof. Amitava Sarkar.[34] All other reagents were as described in ref 24.

Methods. All experimental procedures, instrumentation, preparation of solutions, pH measurements, and kinetic methodology were as described in ref 24. For the evaluation of k_1 and the k_{cat}^A/k_{-1} and k_{cat}^{OH}/k_{-1} ratios, the second-order aminolysis rate constants k_A were fitted to eq 15. For the plots of k_A versus [RNH₂], the contribution of the k_{cat}^A/k_{-1} term to k_A was much greater than that of the k_{cat}^{OH}/k_{-1} term, and hence these plots yielded only dependable k_{cat}^A/k_{-1} ratios. In contrast, for the plots of k_A versus [OH⁻], the contribution by the k_{cat}^{OH}/k_{-1} term was dominant, and hence these plots yielded only dependable k_{cat}^{OH}/k_{-1} ratios. Furthermore, the plots of k_A versus [RNH₂] typically did not reach a plateau (k_1), whereas the plateau was easily reached for the plots of k_A versus [OH⁻]. Hence the k_1 values obtained from these latter plots were deemed more reliable, and it is these values that are reported in Table 1.

Supporting Information Available: Tables S1−S21 (kinetic data). This material is available free of charge via the Internet at http://pubs.acs.org.

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