Physical Organic Chemistry of Transition Metal Carbene Complexes. 26.[†] Kinetics and Mechanism of the Reactions of [Phenyl(thiomethyl)carbene]pentacarbonylchromium(0) with Amines in Aqueous Acetonitrile

Claude F. Bernasconi* and Santanu Bhattacharya

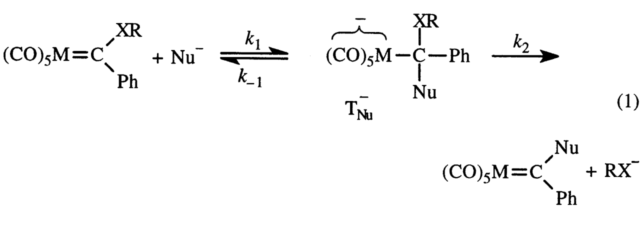
Department of Chemistry and Biochemistry of the University of California, Santa Cruz, California 95064

Received September 10, 2002

The kinetics of the reactions of $(CO)_5Cr{=}C(SMe)Ph$ (**4-Cr**) with five primary aliphatic and four secondary alicyclic amines have been investigated in 50% MeCN−50% water (v/v) at 25 °C. With *n*-butylamine, 2-methoxyethylamine, 2-chloroethylamine, glycinamide, piperidine, piperazine, and 1-(2-hydroxyethyl)piperazine, the reaction is strictly second order, i.e., first order in **4-Cr** and first order in the amine. With morpholine, base catalysis by the amine and by OH^- was observed while with aminoacetonitrile, OH^- catalysis but no amine catalysis was detected. These results are interpreted in terms of a three-step reaction mechanism (Scheme 1): the first step is nucleophilic attachment of the amine to the carbene complex, to form a zwitterionic intermediate, $T_A^{\pm}$; the second step is a fast equilibrium deprotonation of $T_A^{\pm}$ to generate the anionic intermediate T_A^-; the third step is MeS^- expulsion by two concurrent pathways, one being spontaneous (solvent catalyzed) expulsion of MeS^-, the other being $RR'NH_2^+$ catalyzed loss of MeS^- from T_A^-. For the reactions that follow the second-order rate law, the first step is rate limiting, while for the reactions that show amine and/or OH^- catalysis, the third step is rate limiting. The factors that determine which steps are rate limiting are discussed in detail.

Introduction

A major characteristic of transition metal carbene complexes of the Fischer type is the electrophilic nature of the carbene carbon.[1] Hence such carbene complexes can easily undergo nucleophilic addition or substitution at the carbene carbon, as exemplified by the prototypical reaction shown in eq 1 where X is typically oxygen. Such reactions have been documented with OH^-,[2] water,[2] methoxide ion,[3] amines,[4] thiolate ions,[5] carbanions,[6] and other nucleophiles.[7]



$$(CO)_5M{=}C(XR)Ph + Nu^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underbrace{(CO)_5M^{-}{-}C(XR)(Nu){-}Ph}_{T_{Nu}^-} \xrightarrow{k_2} (CO)_5M{=}C(Nu)Ph + RX^- \qquad (1)$$

The mechanism described by eq 1 is quite general for anionic nucleophiles and is strictly analogous to that for reactions of carboxylic esters with anionic nucleophiles. With amine nucleophiles the reaction involves an additional step that converts the initially formed zwitterionic intermediate into its anionic form before it breaks down to products, as indicated in Scheme 1.[4f,g]

This three-step mechanism has generated particular interest because of possible changes in the rate-limiting steps with changing reaction conditions. Indeed, in the

---

[†] Part 25: Bernasconi, C. F.; Ruddat, V. *J. Am. Chem. Soc.* **2002**, *124*, 14968.

(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) Aumann, R.; Hinterding, P.; Krüger, C.; Goddard, R. *J. Organomet. Chem.* **1993**, *459*, 145. (b) Bernasconi, C. F.; Flores, F. X.; Kittredge, K. W. *J. Am. Chem. Soc.* **1997**, *119*, 2103.

(3) (a) Bernasconi, C. F.; Flores, F. X.; Gandler, J. R.; Leyes, A. E. *Organometallics* **1994**, *13*, 2186. (b) Bernasconi, C. F.; García-Río, L. *J. Am. Chem. Soc.* **2000**, *122*, 3821.

(4) (a) Klabunde, U.; Fischer, E. O. *J. Am. Chem. Soc.* **1967**, *89*, 7141. (b) Connor, J. A.; Fischer, E. O. *J. Chem. Soc. A* **1969**, 578. (c) Fischer, E. O.; Kollmeier, H.-J. *Chem. Ber.* **1971**, *104*, 1339. (d) Fischer, E. O.; Leupold, M. *Chem. Ber.* **1972**, *105*, 599. (e) Fischer, E. O.; Heckl, B.; Werner, H. *J. Organomet. Chem.* **1971**, *28*, 359. (f) Bernasconi, C. F.; Stronach, M. W. *J. Am. Chem. Soc.* **1993**, *115*, 1341. (g) Bernasconi, C. F.; Whitesell, C.; Johnson, R. A. *Tetrahedron* **2000**, *56*, 4917.

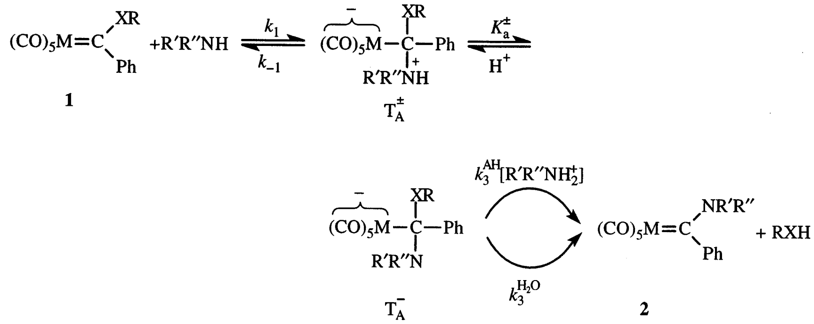
(5) (a) Fischer, E. O.; Leupold, M.; Kreiter, C. G.; Müller, J. *Chem. Ber.* **1972**, *105*, 150. (b) Lam, C. T.; Senoff, C. V.; Ward, J. E. H. *J. Organomet. Chem.* **1974**, *70*, 273. (c) Aumann, R.; Schröder, J. *Chem. Ber.* **1990**, *123*, 2053. (d) Bernasconi, C. F.; Kittredge, K. W.; Flores, F. X. *J. Am. Chem. Soc.* **1999**, *121*, 6630.

(6) (a) Fischer, E. O.; Riedmüller, S. *Chem. Ber.* **1976**, *109*, 3358. (b) Fischer, E. O.; Held, W.; Kreissl, F. R. *Chem. Ber.* **1977**, *110*, 3842. (c) Burkhardt, T. J.; Casey, C. P. *J. Am. Chem. Soc.* **1973**, *95*, 5833. (d) Fischer, E. O.; Held, F. R.; Kreissl, F. R.; Frank, A.; Hattner, G. *Chem. Ber.* **1977**, *110*, 656. (e) Casey, C. P.; Burkhardt, T. J.; Bunnell, C. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 2127.

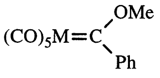
(7) (a) Fischer, E. O.; Kreis, G.; Kreissl, F. R.; Kreiter, C. G.; Müller, J. *J. Chem. Ber.* **1973**, *106*, 3910. (b) Casey, C. P.; Brunsvold, W. P. *Inorg. Chem.* **1977**, *16*, 391. (c) Bell, R. A.; Chisholm, M. H.; Couch, D. A.; Rankel, L. A. *Inorg. Chem.* **1977**, *16*, 677.

10.1021/om020748l CCC: $25.00
Publication on Web 12/31/2002

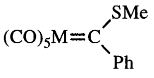
Scheme 1



reactions of **3-Cr** and **3-W** with primary aliphatic amines it was shown that general acid catalyzed MeO$^-$ departure (k_3^{AH}, $k_3^{H_2O}$) is rate limiting at low amine concentrations and relatively low pH, while at high amine concentrations or high pH nucleophilic addition (k_1) is rate limiting.[4f] Deprotonation of $T_A^{\pm}$ always appears to be faster than any other step, which contrasts with the aminolysis of esters where deprotonation of the corresponding intermediate has been shown to be rate limiting in some cases.[8] This contrast does not arise because proton transfer in ester aminolysis is inherently slower than in the aminolysis of carbene complexes,[9] but because the k_{-1}, k_3^{AH}, $k_3^{H_2O}$ steps are slower for the carbene complex than for the ester reactions. As discussed in detail elsewhere,[4f] there are two main reasons why the k_{-1}, k_3^{AH}, $k_3^{H_2O}$ steps are slower for the carbene complexes. The first is the greater stability of $T_A^{\pm}$ and T_A^{-} relative to reactants and products compared to that of the corresponding intermediates in the ester reactions. The second is the higher intrinsic barrier[11] for the k_{-1}, k_3^{AH}, $k_3^{H_2O}$ steps in the carbene complex reactions.



3-Cr (M = Cr)
3-W (M = W)



4-Cr (M = Cr)
4-W (M = W)

In the present paper we wish to examine how the change from a MeO to a MeS leaving group (e.g. **3-Cr** to **4-Cr**) may affect what step(s) is (are) rate limiting in the aminolysis reactions and how the overall reactivity may change. To this end we have studied the reactions of **4-Cr** with a series of primary aliphatic and a series of secondary alicyclic amines in 50% MeCN−50% water (v/v) at 25 °C. If the reactions of **4-Cr** with thiolate ion nucleophiles[12] may serve as a guide, significant changes in the rate constants of all elementary steps of Scheme 1 can be anticipated upon substituting the MeO with a MeS leaving group.

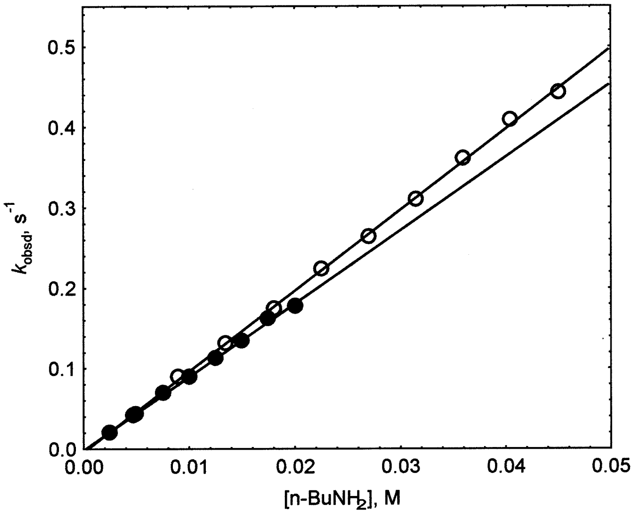


Figure 1. Plots of k_{obsd} vs [n-BuNH$_2$] for the reaction of **4-Cr** with n-BuNH$_2$: (●) pH 10.40 and (○) 11.35.

Results

General Features. The kinetics of the reaction of **4-Cr** with five primary aliphatic amines (*n*-butylamine, 2-methoxyethylamine, glycinamide, 2-chloroethylamine, and aminoacetonitrile) and with four secondary alicyclic amines (piperidine, piperazine, 1-(2-hydroxyethyl)piperazine, and morpholine) were measured in 50% MeCN−50% water (v/v) at 25 °C. The reactions were easily followed by monitoring the decrease in absorbance of **4-Cr** at 466 nm. All kinetic runs were performed under pseudo-first-order conditions with the carbene complex as the minor component. In most cases the kinetic experiments were run at constant pH, with k_{obsd} being determined as a function of free amine concentration. Typically two series of experiments were conducted: one with [RR′NH]:[RR′NH$_2^+$] = 1:1 and another with [RR′NH]:[RR′NH$_2^+$] = 9:1. In some cases other ratios were used and/or k_{obsd} was determined as a function of [OH$^-$] at constant free amine concentration.

A. Primary Aliphatic Amines. The reactions with the primary aliphatic amines all showed strictly second-order kinetics, i.e., k_{obsd} is given by eq 2, with k_A being the second-order rate constant for aminolysis. Figure 1 shows plots of k_{obsd} vs [RR′NH] for the reaction of **4-Cr** with n-BuNH$_2$ at [RR′NH]:[RR′NH$_2^+$] = 1 (pH 10.40) and [RR′NH]:[RR′NH$_2^+$] = 9:1 (pH 11.35). The slopes

$$k_{obsd} = k_A[\mathrm{RR'NH}] \tag{2}$$

---

(8) (a) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018. (b) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963. (c) Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 580. (d) Yang, C. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 2972.

(9) In both types of reactions the proton transfers are essentially diffusion controlled.[10]

(10) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

(11) The intrinsic barrier is the barrier in the absence of a thermodynamic force, i.e., when $\Delta G° = 0$.

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

Table 1. Summary of k_A Values for the Reactions of 4-Cr with Primary Aliphatic Amines and with Piperidine, Piperazine, and 1-(2-Hydroxyethyl)piperazine in 50% MeCN–50% Water (v/v) at 25°C[a]

amine	pK_a^{AH}	$k_A(1:1)$,[b] $M^{-1} s^{-1}$	$k_A(9:1)$,[b] $M^{-1} s^{-1}$	k_A(av), $M^{-1} s^{-1}$
n-$BuNH_2$	10.40	9.11 ± 0.16	10.0 ± 0.1	9.56
$MeOCH_2CH_2NH_2$	9.39	4.25 ± 0.24	3.12 ± 0.03	3.69
$H_2NCOCH_2NH_2$	8.14	1.52 ± 0.02	1.43 ± 0.02	1.48
$ClCH_2CH_2NH_2$	8.05	1.20 ± 0.02	1.19 ± 0.02	1.20
$NCCH_2NH_2$[c]	5.29	0.078 ± 0.002	0.194 ± 0.005	N/A
piperidine	11.01	2.84 ± 0.09	2.91 ± 0.09	2.88
piperazine	9.97	0.86 ± 0.03	0.94 ± 0.03	0.90
HEPA[d]	9.33	0.263 ± 0.009	0.319 ± 0.007	0.291

[a] μ = 0.1 M (KCl). [b] 1:1 and 9:1 refer to the [RR′NH]:[RR′NH_2^+] ratio. [c] See Table 2 for k_A values at other [RR′NH]:[RR′NH_2^+] ratios. [d] HEPA = 1-(2-hydroxyethyl)piperazine.

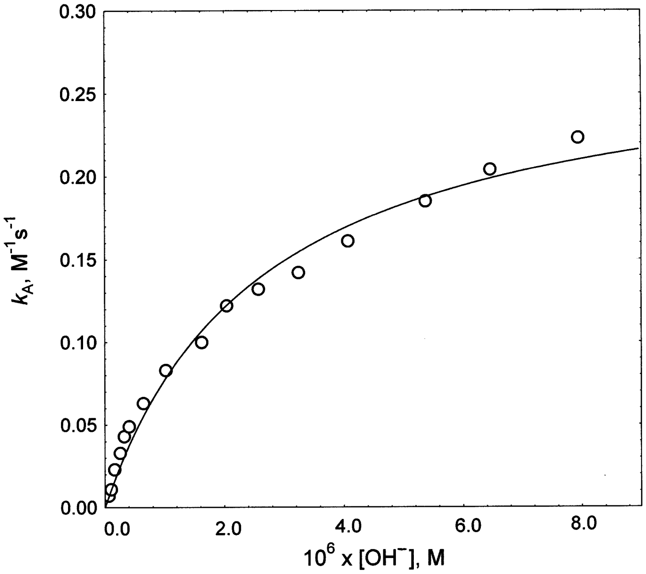


Figure 2. Plot of k_A vs [OH^-] for the reaction of **4-Cr** with $NCCH_2NH_2$ at constant 0.01 M [$NCCH_2NH_2$].

(k_A) are virtually the same at both pH values. Similar plots (not shown) were obtained for the reactions with $MeOCH_2CH_2NH_2$, $ClCH_2CH_2NH_2$, and $H_2NCOCH_2NH_2$. The k_A values are summarized in Table 1.

With $NCCH_2NH_2$, k_A was found to be 2.5-fold higher for [RR′NH]:[RR′NH_2^+] = 9:1 than for [RR′NH]:[RR′NH_2^+] = 1:1. Hence the pH dependence of k_A was more fully investigated. Figure 2 shows a plot of k_A vs [OH^-].

B. Secondary Alicyclic Amines. The reactions of **4-Cr** with piperidine, piperazine, and 1-(2-hydroxyethyl)piperazine follow the rate law of eq 2. The k_A values obtained with [RR′NH]:[RR′NH_2^+] = 1:1 and 9:1 are included in Table 1.

For the reactions of **4-Cr** with morpholine, the plot of k_{obsd} vs [RR′NH] is characterized by upward curvature (Figure 3) which is reminiscent of the reactions of **3-Cr** with primary aliphatic amines and indicates base catalysis by the amine.[4f] The plot has a small intercept (4×10^{-4} s^{-1}), which arises from competing hydrolysis of **4-Cr** by water.[13]

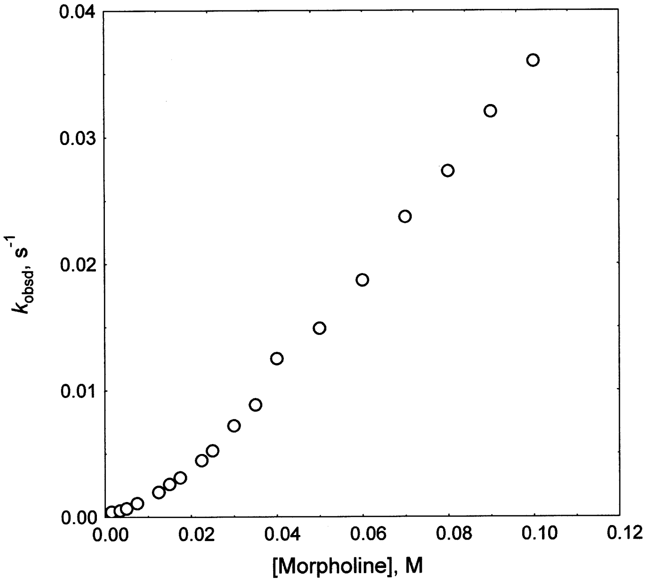


Figure 3. Plot of k_{obsd} vs [morpholine] for the reaction of **4-Cr** with morpholine.

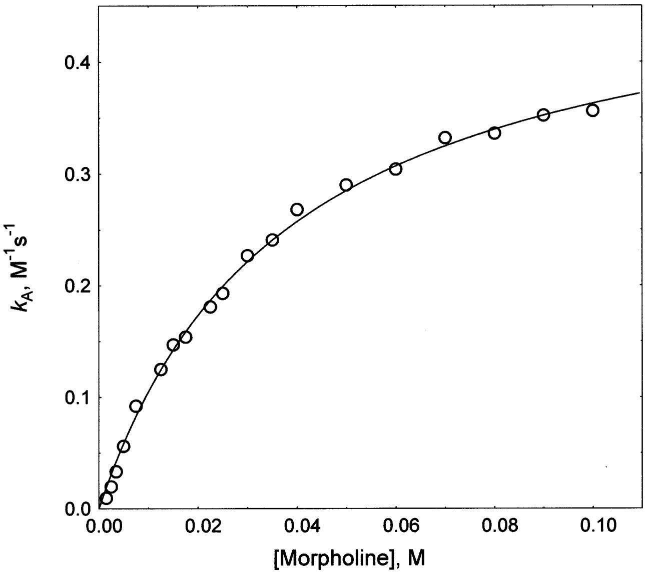


Figure 4. Plot of k_A vs [morpholine] for the reaction of **4-Cr** with morpholine.

The data were analyzed via eq 3, with int referring to the intercept of the plot of k_{obsd} vs [RR′NH]. A plot of

$$k_A = \frac{k_{obsd} - \text{int}}{[RR'NH]} \qquad (3)$$

k_A vs [RR′NH] is shown in Figure 4. The raw data are reported in Table S1 (Supporting Information).[14]

The reactions of **4-Cr** with morpholine were also tested for OH^- catalysis. These experiments were conducted at constant free amine concentration (0.01 M) and increasing [OH^-]. The relative contribution of the hydrolysis to k_{obsd} in these experiments was more significant than that in the experiments which probed the dependence on amine concentrations for two reasons. (1) The experiments had to be conducted at relatively low amine concentrations, i.e., well below the

---

[13] Bernasconi, C. F.; Perez, G. S. *J. Am. Chem. Soc.* **2000**, *122*, 12441.

[14] See paragraph concerning Supporting Information at the end of this paper.

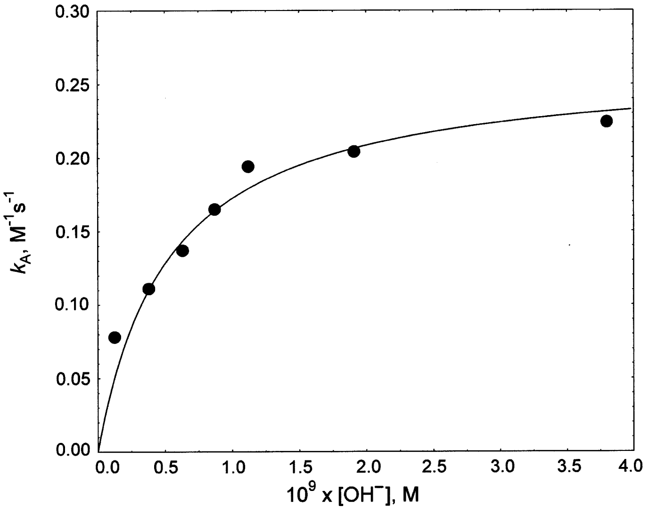


Figure 5. Plot of k_A vs [OH$^-$] for the reaction of **4-Cr** with morpholine at constant 0.01 M [morpholine].

saturation point in Figure 4, to be able to see the OH$^-$ catalysis (more on this below). (2) Amine catalysis of the hydrolysis adds a significant though unknown increment to the hydrolysis rate.[15] The data, which are summarized in Table S2,[14] were analyzed according to eq 4 where k_h refers to the rate constant for hydrolysis;

$$k_A = \frac{k_\mathrm{obsd} - k_\mathrm{h}}{[\mathrm{RR'NH}]} \tag{4}$$

in the pH range of our study, $k_\mathrm{h} \approx 10^{-3}$ s^{-1}.[13] A plot of k_A vs OH$^-$ is shown in Figure 5 for the morpholine reaction.

Discussion

Analysis of Data in Terms of Scheme 1. There is no reason to believe that the change from the MeO leaving group (**3-Cr**) to a MeS leaving group (**4-Cr**) should change the mechanism and hence our discussion will be based on Scheme 1. Since no intermediate was detectable, $\mathrm{T_A^{\pm}}$ and $\mathrm{T_A^{-}}$ may be treated by the steady-state approximation, which leads to eq 5 for k_A, where K_a^AH is the acid dissociation constant of RR′NH$_2{}^+$ and K_w is the ionic product of the solvent.

$$k_\mathrm{A} = \frac{k_1\left(\dfrac{k_3^{\mathrm{AH}}K_\mathrm{a}^{\pm}}{k_{-1}K_\mathrm{a}^{\mathrm{AH}}}[\mathrm{RR'NH}] + \dfrac{k_3^{\mathrm{H_2O}}K_\mathrm{a}^{\pm}}{k_{-1}K_\mathrm{w}}[\mathrm{OH^-}]\right)}{1 + \dfrac{k_3^{\mathrm{AH}}K_\mathrm{a}^{\pm}}{k_{-1}K_\mathrm{a}^{\mathrm{AH}}}[\mathrm{RR'NH}] + \dfrac{k_3^{\mathrm{H_2O}}K_\mathrm{a}^{\pm}}{k_{-1}K_\mathrm{w}}[\mathrm{OH^-}]} \tag{5}$$

There are several limiting situations that are of special interest. (1) Formation of $\mathrm{T_A^{\pm}}$ is rate limiting, i.e., conversion of $\mathrm{T_A^{\pm}}$ via $\mathrm{T_A^{-}}$ to products ($\{k_3^{\mathrm{AH}}K_\mathrm{a}^{\pm}[\mathrm{RR'NH}]/K_\mathrm{a}^{\mathrm{AH}}\} + \{k_3^{\mathrm{H_2O}}K_\mathrm{a}^{\pm}[\mathrm{OH^-}]/K_\mathrm{w}\}$) is much faster than the collapse of $\mathrm{T_A^{\pm}}$ back to reactants (k_{-1}). This is expressed by eq 6 and hence eq 5 reduces to eq 7. This situation applies to the reactions of **4-Cr** with *n*-butylamine, 2-methoxyethylamine, glycinamide, 2-chloroethylamine, piperidine, piperazine, and 1-(2-hydroxyethyl)piperazine over the entire range of [RR′NH] and [OH$^-$] used in this study.

Table 2. Summary of k_A Values for the Reaction of 4-Cr with Aminoacetonitrile in 50% MeCN−50% Water (v/v) at 25 °C[a]

[RR′NH]:[RR′NH$_2{}^+$]	pH	[OH$^-$], M	k_A, M^{-1} s^{-1}
1	5.29	1.26×10^{-10}	0.078 ± 0.002
3	5.77	3.80×10^{-10}	0.111 ± 0.004
5	5.99	6.31×10^{-10}	0.137 ± 0.005
7	6.13	8.71×10^{-10}	0.165 ± 0.003
9	6.24	1.12×10^{-9}	0.194 ± 0.005
15	6.47	1.91×10^{-9}	0.204 ± 0.011
30	6.77	3.80×10^{-9}	0.224 ± 0.008

$$\frac{k_3^{\mathrm{AH}}K_\mathrm{a}^{\pm}}{k_{-1}K_\mathrm{a}^{\mathrm{AH}}}[\mathrm{RR'NH}] + \frac{k_3^{\mathrm{H_2O}}K_\mathrm{a}^{\pm}}{k_{-1}K_\mathrm{w}}[\mathrm{OH^-}] \gg 1 \tag{6}$$

$$k_\mathrm{A} = k_1 \tag{7}$$

(2) Concurrent ammonium ion catalyzed (k_3^{AH}) and solvent promoted ($k_3^{\mathrm{H_2O}}$) loss of MeS$^-$ from $\mathrm{T_A^{-}}$ is rate limiting, with the first two steps acting as preequilibria, i.e., eq 8 holds and eq 5 becomes eq 9.

$$\frac{k_3^{\mathrm{AH}}K_\mathrm{a}^{\pm}}{k_{-1}K_\mathrm{a}^{\mathrm{AH}}}[\mathrm{RR'NH}] + \frac{k_3^{\mathrm{H_2O}}K_\mathrm{a}^{\pm}}{k_{-1}K_\mathrm{w}}[\mathrm{OH^-}] \ll 1 \tag{8}$$

$$k_A = k_1\frac{k_3^{\mathrm{AH}}K_\mathrm{a}^{\pm}}{k_{-1}K_\mathrm{a}^{\mathrm{AH}}}[\mathrm{RR'NH}] + k_1\frac{k_3^{\mathrm{H_2O}}K_\mathrm{a}^{\pm}}{k_{-1}K_\mathrm{w}}[\mathrm{OH^-}] \tag{9}$$

Equation 9 calls for a linear increase of k_A with increasing [RR′NH] and [OH$^-$]. This situation applies to the reaction of **4-Cr** with morpholine at low [RR′NH] and low [OH$^-$] (see Figures 4 and 5). As the amine and/or OH$^-$ concentration is increased, $k_3^{\mathrm{AH}}K_\mathrm{a}^{\pm}[\mathrm{RR'NH}]/k_{-1}K_\mathrm{a}^{\mathrm{AH}}$ and/or $k_3^{\mathrm{H_2O}}K_\mathrm{a}^{\pm}[\mathrm{OH^-}]/k_{-1}K_\mathrm{w}$ become comparable to 1, leading to downward curvature in the plots of k_A vs [RR′NH] or [OH$^-$] until a plateau is reached (eqs 6 and 7), which should correspond to $k_\mathrm{A} = k_1$. Figures 4 and 5 show the expected behavior. Least-squares analysis of the dependence of k_A on [RR′NH] and [OH$^-$] yields the parameters summarized in Table 3.

(3) The third special case applies to the reaction of **4-Cr** with aminoacetonitrile, which is subject to OH$^-$ catalysis but not to amine catalysis. This situation can be understood if the relationships of eqs 10 and 11 hold throughout the concentration ranges used and if, at the same time, $k_3^{\mathrm{H_2O}}K_\mathrm{a}^{\pm}[\mathrm{OH^-}]/k_{-1}K_\mathrm{w}$ changes from <1 to >1 as [OH$^-$] is increased. Under these conditions eq 5

$$\frac{k_3^{\mathrm{AH}}K_\mathrm{a}^{\pm}}{k_{-1}K_\mathrm{a}^{\mathrm{AH}}}[\mathrm{RR'NH}] \ll 1 \tag{10}$$

$$\frac{k_3^{\mathrm{AH}}K_\mathrm{a}^{\pm}}{k_{-1}K_\mathrm{a}^{\mathrm{AH}}}[\mathrm{RR'NH}] \ll \frac{k_3^{\mathrm{H_2O}}K_\mathrm{a}^{\pm}}{k_{-1}K_\mathrm{w}}[\mathrm{OH^-}] \tag{11}$$

---

(15) Catalysis by triethylamine, *N*-methylmorpholine, and acetate ion was observed in the hydrolysis of **4-Cr** and **4-W**.[13]

Table 3. Kinetic Parameters for the Reactions of 4-Cr with Morpholine and Aminoacetonitrile in 50% MeCN−50% Water at 25 °C

amine	pK_a^{AH}	k_1, M^{-1} s^{-1}	$k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$, M^{-1}	$k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$, M^{-1}	$\{k_3^{H_2O}K_a^{\pm}/k_{-1}K_w\}[OH^-]^b$
morpholine	8.70	0.39 ± 0.11^a	26.7 ± 1.3	$(3.83 \pm 0.67) \times 10^5$	1.24×10^{-1}
$NCCH_2NH_2$	5.29	0.26 ± 0.02		$(1.89 \pm 0.17) \times 10^9$	2.38×10^{-1}

[a] Average value based on $k_1 = 0.50$ M^{-1} s^{-1} from dependence on [RR′NH] and $k_1 = 0.28$ M^{-1} s^{-1} from dependence on $[OH^-]$. [b] $[OH^-]$ when pH = pK_a^{AH}; $[OH^-]$ calculated from $pK_w = 15.19$.[21]

Table 4. Kinetic Parameters for the Reactions of 3-Cr with Primary Aliphatic Amines in 20% MeCN−80% Water at 25 °C[a]

amine	pK_a^{AH}	k_1, M^{-1} s^{-1}	$k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$, M^{-1}	$k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$, M^{-1}	$\{k_3^{H_2O}K_a^{\pm}/k_{-1}K_w\}[OH^-]^b$
n-$BuNH_2$	10.67	2900	33.7	8.1×10^3	2.45×10^{-1}
$MeOCH_2CH_2NH_2$	9.52	400	21.1	8.4×10^4	1.80×10^{-1}
$ClCH_2CH_2NH_2$	8.61	91	19.5	2.8×10^5	7.36×10^{-2}
$H_2NCOCH_2NH_2$	8.03	100	17.3	1.25×10^6	8.65×10^{-2}
$EtOCOCH_2NH_2$	7.70	36	9.7	1.49×10^6	4.82×10^{-2}

[a] Reference 4f. [b] $[OH^-]$ corresponds to pH = pK_a^{AH}; $[OH^-]$ calculated from $pK_w = 15.19$.[21]

becomes eq 12 which is consistent with the absence of

$$k_A = \frac{k_1\left(\frac{k_3^{H_2O}K_a^{\pm}}{k_{-1}K_w}[OH^-]\right)}{1 + \frac{k_3^{H_2O}K_a^{\pm}}{k_{-1}K_w}[OH^-]} \qquad (12)$$

amine catalysis and the curvilinear dependence of k_A on $[OH^-]$ (Figure 2). A curve fit of the plot of k_A vs $[OH^-]$ yields $k_1 = 0.26 \pm 0.02$ M^{-1} s^{-1} and $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w = (1.89 \pm 0.17) \times 10^9$ M^{-1}.

Factors That Determine the Presence or Absence of Catalysis. To understand the factors that determine the presence or absence of amine and/or OH^- catalysis, it is useful to briefly review the results for the reactions of **3-Cr** with primary amines.[4f] In these reactions both amine and OH^- catalysis was observed at low amine and OH^- concentrations for all amines studied, which included four of the same amines investigated in the present work (n-$BuNH_2$, $MeOCH_2CH_2NH_2$, $H_2NCOCH_2NH_2$, and $ClCH_2CH_2NH_2$) as well as $EtOCOCH_2NH_2$ but not $NCCH_2NH_2$. Furthermore, in all cases the limiting situation of eqs 6 and 7 was reached at high amine and/or OH^- concentration. Hence, this allowed a determination of k_1 and the various ratios summarized in Table 4.

The absence of base catalysis in most of the reactions of **4-Cr** implies that, for any given amine, the $k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$ and/or $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ ratios are larger than those for the reactions of **3-Cr**, so that eq 6 is valid even at low [RR′NH] and $[OH^-]$ in most cases. This conclusion is directly verifiable for the reaction of **4-Cr** with aminoacetonitrile, where $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w = 1.85 \times 10^9$ M^{-1}. This ratio is not known for the reaction of **3-Cr** with aminoacetonitrile but it can be estimated by extrapolation of the data in Table 4;[16] it yields a value of ≈1.30×10^8 M^{-1}, which is 15-fold lower than that for the reaction of **4-Cr**.

There are several factors that contribute to the change in the $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ and $k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$ ratios.

(1) The k_{-1} values are likely to be substantially smaller for the reactions of **4-Cr** than those of **3-Cr**. This assertion is based on a comparison of the reactions of **3-Cr**[5d] and **4-Cr**[12] with thiolate ions. In these reactions, the respective intermediates (T_{Nu}^- in eq 1) were directly observable, which allowed a determination of k_1, k_{-1}, and $K_1 = k_1/k_{-1}$. For example, for the reaction of **3-Cr** with n-PrS^-, $k_1 = 1.34 \times 10^4$ M^{-1} s^{-1}, $k_{-1} = 1.26$ s^{-1}, and $K_1 = 1.06 \times 10^4$ M^{-1},[5d] while for the reaction of **4-Cr** with the same nucleophile $k_1 = 5.33 \times 10^2$ M^{-1} s^{-1}, $k_{-1} = 4.85 \times 10^{-4}$ s^{-1}, and $K_1 = 1.10 \times 10^6$ M^{-1}.[12] The reduction in k_{-1} from **3-Cr** to **4-Cr** is the combined result of the larger equilibrium constant (K_1) and an enhanced intrinsic barrier[11] for the reaction of **4-Cr**. Note that the solvent change from 20% MeCN−80% water for the reactions of **3-Cr** to 50% MeCN−50% water for the reactions of **4-Cr** is unlikely to affect these changes in k_{-1} in a significant way.

(2) The $k_3^{H_2O}$ value for **4-Cr** is likely to be higher than that for **3-Cr** because when MeX^- leaves as anion, MeS^- is a better leaving group than MeO^-.[17] This should enhance the $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ ratio. On the other hand, acid-catalyzed MeS^- departure (leaving as MeSH) is typically slower than acid-catalyzed MeO^- (leaving as MeOH)[18] and hence k_3^{AH} for **4-Cr** is likely to be lower than that for **3-Cr**. Note that this factor increases the contribution of the OH^--catalyzed pathway relative to the amine-catalyzed pathway. Again, the solvent change is not expected to alter these conclusions.

(3) For the $K_a^{\pm}/K_w$ ratio, it is the change in the solvent that is more important than the change in the leaving group; in 50% MeCN−50% water, this ratio is expected to be about 10-fold larger than in 20% MeCN−80% water because of a significant decrease in K_w and a small increase in $K_a^{\pm}$.[19] The change in the leaving group from MeO^- to MeS^- should reduce $K_a^{\pm}$ somewhat

---

(16) The dependence of $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ on pK_a^{AH} follows the relationship $\log(k_3^{H_2O}K_a^{\pm}/k_{-1}K_w) = 12.2 - 0.773pK_a^{AH}$.

(17) Bernasconi, C. F.; Ketner, R. J.; Chen, X.; Rappoport, Z. *Can. J. Chem.* **1999**, *77*, 584.

(18) Bernasconi, C. F.; Ketner, R. J.; Brown, S. D.; Chen, X.; Rappoport, Z. *J. Org. Chem.* **1999**, *64*, 8829.

(19) In 20% MeCN−80% water $pK_w = 14.46$,[20] while in 50% MeCN−50% water, $pK_w = 15.19$,[21] hence $K_w(50\%)/K_w(20\%) = 5.37$. In a first approximation $K_a^{\pm}(50\%)/K_a^{\pm}(20\%) = K_a^{AH}(50\%)/K_a^{AH}(20\%)$ which, for the example of n-$BuNH_2$, yields $K_a^{\pm}(50\%)/K_a^{\pm}(20\%) \approx 1.86$. Thus $K_a^{\pm}(50\%)/K_w(50\%) \approx 9.98K_a^{\pm}(20\%)/K_w(20\%)$.

Table 5. Summary of Effects of Changing from 3-Cr in 20% MeCN−80% Water to 4-Cr in 50% MeCN−50% Water on Various Kinetic Parameters

k_3^{AH}	↓	$K_a^{\pm}/K_a^{AH}$	↓	$k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$	↓↑
$k_3^{H_2O}$	↑	$K_a^{\pm}/K_w$	↑	$k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$	↑
k_{-1}	↓				

due to the weaker electron-withdrawing inductive effect of the MeS group compared to the MeO group.[22] Thus the combined solvent and leaving group effect on the $K_a^{\pm}/K_w$ ratio and hence on the $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ ratio is probably an enhancement which, however, is less than a factor of 10. For the $K_a^{\pm}/K_a^{AH}$ ratio no significant solvent effect is expected and hence there is a net small reduction in this ratio due to the leaving group effect and, with it, on the $k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$ ratio. Note that, as for (2), the combined effects on $K_a^{\pm}/K_w$ and $K_a^{\pm}/K_a^{AH}$ increase the importance of the OH^--catalyzed pathway relative to the amine-catalyzed pathway.

A schematic summary of the expected effects on k_{-1}, k_3^{AH}, $k_3^{H_2O}$, $K_a^{\pm}/K_a^{AH}$, and $K_a^{\pm}/K_w$ as well as the resulting changes in the $k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$ and $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ ratios is provided in Table 5. The following conclusions emerge.

(1) The absence of amine and OH^- catalysis in the reactions of **4-Cr** with the four most basic primary amines is primarily due to the high $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ ratios. This leads to eq 6 under all experimental conditions used in this study, even if $k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$ is too small for the $k_3^{AH}K_a^{\pm}[RR'NH]/k_{-1}K_a^{AH}$ term to make a significant contribution.

(2) In the reaction of **4-Cr** with aminoacetonitrile the observation of OH^- catalysis but absence of amine catalysis clearly shows that the contribution of the $k_3^{AH}K_a^{\pm}[RR'NH]/k_{-1}K_a^{AH}$ term is indeed negligible compared to that of the $k_3^{H_2O}K_a^{\pm}[OH^-]/k_{-1}K_w$ term. This is not necessarily true for the more basic amines, however. As the data summarized in Table 4 show, the $k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$ ratios increase slightly while the $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ ratios strongly decrease with increasing amine basicity so that for more basic amines the two become more equal to each other.

Reaction of 4-Cr with Morpholine. For this reaction, amine and OH^- catalysis is clearly evident. The fact that both OH^- and amine catalysis is observed confirms the point made in the preceding section that for amines more basic than aminoacetonitrile the relative contribution of the $k_3^{AH}K_a^{\pm}[RR'NH]/k_{-1}K_a^{AH}$ term becomes more important.

It is also noteworthy that, with the secondary alicyclic amines, catalysis is observed for an amine that is substantially more basic than aminoacetonitrile. This implies that the $k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$ and $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ ratios for secondary amines are smaller than for primary amines of comparable basicity. Indeed, for the morpholine reaction these ratios (Table 3) are remarkably similar to the corresponding ratios for the reaction of **3-Cr** with $ClCH_2CH_2NH_2$, an amine of comparable basicity (Table 4).

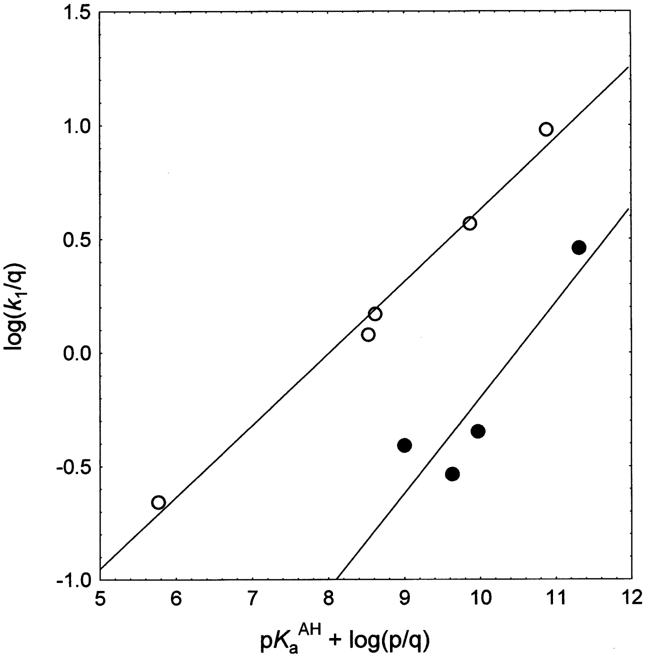


Figure 6. Brønsted plots for the reactions of **4-Cr** with primary aliphatic amines (○) and secondary alicyclic amines (●).

The reduction of the $k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$ and $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ ratios for the secondary amines relative to those for the primary amines must be the result of steric factors that enhance the steps that lead to the collapse of $T_A^{\pm}$ (k_{-1}) and T_A^- ($k_3^{H_2O}$, k_3^{AH}). Since it is likely that greater steric release is achieved when the more bulky cyclic amines leave $T_A^{\pm}$ (k_{-1}) than when MeO^- or MeS^- leave T_A^- generated by a cyclic amine, the net effect should be a decrease in the k_3^{AH}/k_{-1} and $k_3^{H_2O}/k_{-1}$ ratios.

Nucleophilic Attack Step (k_1). Brønsted plots for k_1 are shown in Figure 6. For the reactions of **4-Cr** with n-$BuNH_2$, $MeOCH_2CH_2NH_2$, $H_2NCOCH_2NH_2$, $ClCH_2CH_2NH_2$, piperidine, piperazine, and 1-(2-hydroxyethyl)piperazine (HEPA), k_1 was equated with k_A(av) from Table 1, while for the reactions with aminoacetonitrile and morpholine the k_1 values from Table 3 were used. There is a good correlation between logk_1 and pK_a^{AH} for the primary amines ($\beta_{nuc} = 0.30 \pm 0.02$). For the secondary alicyclic amines, the correlation is not as good; it yields $\beta_{nuc} = 0.42 \pm 0.14$. The reason for the greater scatter is unclear. One factor may be some uncertainty in the k_1 value for the morpholine reaction because this value was obtained form a curve-fitting procedure while those for the other secondary amines were obtained from slopes of straight lines. If the point for morpholine is omitted from the plot, one obtains $\beta_{nuc} = 0.59 \pm 0.01$.

For purposes of comparison, the β_{nuc} value for the reaction of **3-Cr** with primary aliphatic amines in 20% MeCN−80% water is 0.60[4f]

---

(20) Barbosa, J.; Sanz-Nebot, V. *Anal. Chim. Acta* **1991**, *244*, 183.

(21) Bernasconi, C. F.; Sun, W. *J. Am. Chem. Soc.* **1993**, *115*, 12526.

(22) $\sigma_F = 0.30$ and 0.20 for MeO and MeS, respectively.[23]

The following points call for comment.

(1) The k_1 values for the reactions with the secondary amines are smaller than those for the reactions with the primary amines of comparable basicity. For example, for HEPA, $k_1 = 0.263\ M^{-1}\ s^{-1}$ while for 2-methoxyethylamine, which has about the same pK_a^{AH}, $k_1 = 4.25\ M^{-1}\ s^{-1}$. These results indicate the presence of a strong steric effect that mainly reduces the reactivity of the bulkier secondary amines; in the absence of steric effects, secondary amines generally react faster than primary amines of comparable basicity.[24,25]

(2) The higher β_{nuc} value for the reactions with the secondary amines implies that, at the transition state, C−N bond formation is more advanced with the secondary amines. This may mainly represent a Hammond effect[26,27] resulting from a thermodynamically less favorable $T_A^{\pm}$ formation in the reaction of the secondary amines due to increased steric crowding in $T_A^{\pm}$.

(3) The lower β_{nuc} for the reaction of **4-Cr** with primary amines (0.32) compared to the reaction of **3-Cr** with the same amines (0.60) suggests a smaller degree of C−N bond formation at the transition state when MeX = MeS than when MeX = MeO. These findings may again reflect a Hammond effect[26,27] if one assumes that formation of $T_A^{\pm}$ is thermodynamically more favorable in the reactions of **4-Cr** than in the reaction of **3-Cr**. This assumption is based on the observation that for the reactions of **3-Cr** and **4-Cr** with thiolate ions the equilibrium constants for nucleophilic attack are significantly larger for **4-Cr** compared to **3-Cr**; for example, with n-PrS$^-$, K_1(**4-Cr**)/K_1(**3-Cr**) = 104. It should be noted, though, that the *rate* constants were found to be *lower* for nucleophilic attack by thiolate ion on **4-Cr** than for attack on **3-Cr**;[12] for example, with n-PrS$^-$, k_1(**4-Cr**)/k_1(**3-Cr**) = 3.98×10^{-2}. This indicates that the *intrinsic* barrier[11] is higher for the reactions of **4-Cr** than for the reactions with **3-Cr**. The reasons for the higher intrinsic barriers, which are caused by imbalances with respect to the development of steric and inductive effects at the transitions state, have been discussed in detail elsewhere.[12] It appears that the reactions of **3-Cr** and **4-Cr** with amines follow the same pattern, i.e., kinetically **4-Cr** is less reactive than **3-Cr**; for example, with n-BuNH$_2$, k_1(**4-Cr**)/k_1(**3-Cr**) = 3.14×10^{-3}, and with $H_2NCOCH_2NH_2$, k_1(**4-Cr**)/k_1(**3-Cr**) = 1.52×10^{-2}.

Conclusions

(1) For the reactions of **4-Cr** with n-BuNH$_2$, $MeOCH_2CH_2NH_2$, $ClCH_2CH_2NH_2$, $H_2NCOCH_2NH_2$, piperidine, piperazine, and 1-(2-hydroxyethyl)piperazine, no base catalysis is observed, implying that the k_1 step (Scheme 1) is rate limiting.

(2) For the reaction of **4-Cr** with morpholine, catalysis by both the amine and OH$^-$ is observed at low concentrations, indicating that leaving group departure from T_A^- is rate limiting. At high amine and/or OH$^-$ concentrations, the catalysis levels off as the k_1 step becomes rate limiting.

(3) For the reaction of **4-Cr** with aminoacetonitrile, the situation is similar to that with morpholine except that the amine catalysis is too weak to be measurable.

(4) From the dependence of the second-order rate constant, k_A, on [RR′NH] and [OH$^-$], the $k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$ and $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ ratios could be calculated for the reaction of **4-Cr** with morpholine, and $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ for the reaction with aminoacetonitrile.

(5) The $k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$, and especially the $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$, ratios for the reaction of **4-Cr** with a given amine are generally higher than those for the reaction of **3-Cr** with the same amine. Several factors contribute to this increase. One is a decrease in k_{-1} that affects both ratios the same. In the case of the $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ there is also an increase in $k_3^{H_2O}$ and in $K_a^{\pm}/K_w$ while in the case of the $k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$ there is a slight decrease in k_3^{AH} and $K_a^{\pm}/K_a^{AH}$.

(6) The $k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$ and $k_3^{H_2O}K_a^{\pm}/k_{-1}K_w$ ratios are smaller for the reactions of **4-Cr** with secondary alicyclic amines than for the reactions with primary aliphatic amines because of a decrease in k_3^{AH}/k_{-1} and $k_3^{H_2O}/k_{-1}$ due to more severe steric crowding in $T_A^{\pm}$ and T_A^-.

(7) The k_1 values are lower for the reactions of **4-Cr** with secondary amines than for the reactions with primary amines due to a steric effect. The higher β_{nuc} values for the secondary amines are consistent with a Hammond effect caused by the steric effect.

(8) The lower β_{nuc} value for the reaction of **4-Cr** with primary amines compared to the reaction of **3-Cr** with the same amines can also be understood in terms of a Hammond effect.

Experimental Section

Materials. Standard Schlenk techniques were used in synthesizing and handling the carbene complex, with argon as the protecting gas. The [phenyl(thiomethyl)carbene]pentacarbonylchromium(0) (**4-Cr**) was prepared by reaction of the corresponding methoxy complex[28] (**3-Cr**) with NaSMe, using the procedure of Lam and Senoff.[5b] The product was identified by NMR (500 MHz, $CDCl_3$) as follows: ^1H NMR δ 2.29 (s, 3H, CH_3S), 6.64 (d, Ph), 7.25 (d, pH), 7.46 (t, Ph). ^{13}C NMR ($CDCl_3$) δ 27.9 (CH_3S), 116.5, 126.6, 128.1 and 156.6 (Ph), 215.0 (CO, cis), 228.1 (CO, trans), 362.2 (=C). UV/vis (50% MeCN−50% water) λ_{max} at 446 nm.

All reagents were Analar Grade (Aldrich). Liquid amines (*n*-butylamine, 2-methoxyethylamine, piperidine, morpholine, and 1-(2-hydroxyethyl)piperazine) were refluxed over Na/CaH_2 and freshly distilled prior to use. Piperazine, glycinamidehydrochloride, 2-chloroethylaminehydrochloride, and aminoacetonitrilehydrochloride were recrystallized from 2-propanol or water−2-propanol. KOH and HCl solutions were prepared using "Dilute it" from Baker Analytical. Dry acetonitrile was prepared by stirring with P_2O_5 for 24 h, followed by distillation into a receiving flask containing 4 Å molecular sieves. For buffer preparation, acetonitrile was used as received (Fischer Scientific) and water was taken from a Milli-Q purification system. The pK_a^{AH} value of 2-chloroethylamine in 50% acetonitrile−50% water was determined by standard potentiometric pH method as the pH of 1:1 buffer. The pK_a^{AH} values for other

---

[23] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

[24] Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; p 95.

[25] Bernasconi, C. F.; Murray, C. J.; Fox, J. P.; Carré, D. J. *J. Am. Chem. Soc.* **1983**, *105*, 4349.

[26] Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

[27] Leffler, J. E.; Grunwald, E. *Rates and Equilibrium of Organic Reactions*; Wiley: New York, 163; p 156.

[28] Fischer, E. O.; Heckl, B.; Dötz, K. H.; Müller, J.; Werner, H. *J. Organomet. Chem.* **1969**, *16*, P29.

buffers in 50% acetonitrile−50% water were obtained from a previous study.[29]

Instrumentation. NMR spectra were recorded on a Bruker 500-MHz instrument. UV−vis spectra were obtained on a Perkin-Elmer Lambda 2 or Hewlett-Packard 8453 Agilent diode array spectrophotometer. Kinetic measurements were carried out in an Applied Photophysics DX.17MV stopped-flow apparatus or, for some of the slower reactions, in the Hewlett-Packard 8453 Agilent spectrophotometer. pH measurements were performed on an Orion 611 pH meter equipped with a glass electrode and a Sureflow reference electrode from Corning.

Solutions and pH Measurements. All solutions were prepared in 50% MeCN−50% water (v/v) and an ionic strength of 0.1 M was maintained with KCl. Stock solutions of the carbene complex were relatively stable in pure acetonitrile and were used to make appropriate solutions in 50% MeCN−50% water prior to use. The pH meter was calibrated with standard aqueous buffers at pH 4.00, 7.00, and 10.00. pH readings of different amine buffer solutions in 50% MeCN−50% water taken at 25°C were adjusted to the actual value by adding 0.18 to the measured pH, according to Allen and Tidwell.[30]

Kinetic Experiments. All kinetic runs were conducted under pseudo-first-order conditions ensured by a large excess of buffer over the substrate. The reactions were monitored at 466 nm corresponding to the λ_{max} of the carbene complex. Typical substrate concentrations were on the order of 10^{-4} M. Excellent first-order kinetic traces were observed for at least 5 half-lives in all experiments.

Acknowledgment. This work was supported by Grant CHE-0098553 from the National Science Foundation.

Supporting Information Available: Tables S1 and S2 (kinetic data). This material is available free of charge via the Internet at http://pubs.acs.org.

OM020748L

---

(29) Bernasconi, C. F.; Ali, M. *J. Am. Chem. Soc.* **1999**, *121*, 3309.

(30) Allen, D. A.; Tidwell, T. T. *J. Am. Chem. Soc.* **1987**, *109*, 2774.