

# Nucleophilic Attacks on Carbon–Nitrogen Double Bonds.

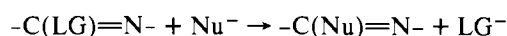
## 3.1 Diversity of Mechanisms for the Substitution of Diarylimidoyl Chlorides by Amines in Acetonitrile

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**Abstract:** The reactions of diarylimidoyl chlorides  $\text{XC}_6\text{H}_4\text{C}(\text{Cl})=\text{NC}_6\text{H}_4\text{Y}$  with amines in acetonitrile show multiplicity of kinetic behavior. (i) When  $\text{X} = \text{H}$ ,  $\text{Y} = m\text{-Cl}$  or  $p\text{-Cl}$ , the first-order rate constant ( $k_{\text{obsd}}$ ) for the reaction with piperidine increases nonlinearly with the [amine], and  $1/k_{\text{obsd}}$  is linear in  $1/[\text{R}_2\text{NH}]$ . (ii) For several systems, e.g., when  $\text{X} = \text{H}$ ,  $\text{Y} = p\text{-NO}_2$ , with several amines  $k_{\text{obsd}} = k^0 + k'[\text{amine}]$ . (iii) When  $\text{X} = \text{Y} = p\text{-NO}_2$ , the reaction with piperidine is of overall second order. (iv) When  $\text{X} = \text{H}$ ,  $\text{Y} = \text{H}$  or  $p\text{-NO}_2$  and  $\text{R}_2\text{NH} = i\text{-Pr}_2\text{NH}$ ,  $k_{\text{obsd}}$  decreases during the reaction or by addition of external chloride ion. These results are explained by a unified reaction scheme with three different substitution routes: (a) a bimolecular, probably a nucleophilic addition–elimination reaction which predominates with strong nucleophiles and when  $\text{X}$  and  $\text{Y}$  are strong electron-attracting groups; (b) reaction via the ion pair **3** which is formed in the initial heterolysis; this route occurs simultaneously with route a when either  $\text{X}$  or  $\text{Y}$  is strongly electron attracting and becomes dominant when  $\text{X} = \text{H}$ ,  $\text{Y} = p\text{-Cl}$  or  $m\text{-Cl}$ ; (c) reaction via a free nitrilium ion **4** which is formed from the dissociation of **3** is the main substitution route by the sterically hindered diisopropylamine.

The mechanism of displacement of a leaving group (LG) attached to the carbon atom of a carbon–nitrogen double bond (an azomethine system) by a nucleophile (Nu)<sup>2</sup> was much



less extensively studied than the analogous reactions at a carbonyl<sup>3</sup> or at an activated carbon–carbon double bond.<sup>4</sup> Most of our knowledge on the substitution at the  $\text{C}=\text{N}$  bond comes from the extensive work of Hegarty, Scott, and their coworkers<sup>5,6</sup> on the hydrolysis of hydrazonyl halides  $\text{R}^1\text{C}(\text{X})=\text{NNR}^2\text{R}^3$  and halodiazaabutadienes in solvolytic media. Less information is available on the hydrolysis of simple substituted imidoyl chlorides  $\text{RC}(\text{Cl})=\text{NR}'$ .<sup>7,8</sup> Most of these hydrolysis reactions proceed by the  $\text{S}_{\text{N}}1$  route via an intermediate nitrilium ion which is stabilized by a heteroatom, by an aryl group, or by an alkyl group on the nitrogen. The evidence for this route is the common ion rate depression by  $\text{X}^-$ <sup>5i,1-n,8</sup> which is very extensive in several cases,<sup>5n,8</sup> the rate increase on increasing the solvent polarity,<sup>5h,m,7</sup> or on addition of a noncommon ion salt,<sup>5j,1</sup> and the rate increase by electron-donating substituents.<sup>5h,i,o</sup> Reaction via an intermediate ion pair was invoked in the hydrolysis of compounds  $\text{RC}(\text{Cl})=\text{NR}'$  ( $\text{R} = \text{alkyl}$ , aryl) in aqueous acetone,<sup>7</sup> although the presence of common ion rate depression suggests that the reaction proceeds, at least partially, via a free nitrilium ion.<sup>9</sup>

An alternative mechanism via initial elimination of  $\text{HX}$  was found in the substitution of several hydrazonyl halides when  $\text{R}^3 = \text{H}$ .<sup>5i,o</sup>

Bimolecular routes via tetrahedral intermediates which are common in the reactions at  $\text{C}=\text{O}$ <sup>3</sup> and activated  $\text{C}=\text{C}^{\text{4a}}$  systems were observed only in few cases. The second-order reaction and the rate enhancement by electron-donating substituents suggest that the hydrolysis of diarylchloroimidates  $\text{ArOC}(\text{Cl})=\text{NAr}'$  proceeds via this route,<sup>8</sup> while the kinetics and the  $k_{\text{Br}}/k_{\text{Cl}}$  ratio of 1.9 fit this mechanism for the substitution of *O*-methylbenzohydroximoyl chlorides by methoxide ion in methanol.<sup>10</sup>

There are only two stereochemical studies of the substitution. Retention of configuration was found in the substitution of *Z*-hydrazonyl halides  $\text{RC}(\text{X})=\text{NN}(\text{Me})\text{Ar}$  by methoxide ion,<sup>6</sup> while inversion of configuration was found in the substitution of *O*-methylbenzohydroximoyl chlorides by methoxide ion.<sup>10</sup> The details of the bimolecular reaction are therefore not yet clear.<sup>11</sup>

Due to the configurational instability of imidoyl halides<sup>12</sup> stereochemical studies are not always possible, and the kinetics become the main tool for studying the mechanism of the substitution. In order to obtain kinetic data under nonsolvolytic conditions we investigated the reaction of diarylimidoyl chlorides with amines in benzene.<sup>13</sup> Diversity of kinetic behaviors, e.g., first-order reaction in the amine or both first- and second-order reactions in the amine, was observed. Analysis of the substituent effects with the aid of Hammett-type correlations, the nature of the amine-catalyzed route, the effect of the nucleophile and the leaving group, and the activation parameters suggested multiplicity of mechanistic routes.<sup>1,13</sup> For systems substituted by electron-donating substituents the bimolecular substitution proceeds via an  $\text{S}_{\text{N}}2(\text{IP})$  mechanism<sup>14</sup> where an intermediate ion pair is formed initially in a pre-equilibrium step and is then captured by the amine in a rate-determining step. For systems substituted by electron-withdrawing substituents, a nucleophilic addition–elimination route was suggested. Third-order, amine-catalyzed routes are superimposed on the bimolecular routes.<sup>1,13</sup> No reaction via a free nitrilium ion was observed in this low-dielectric media.

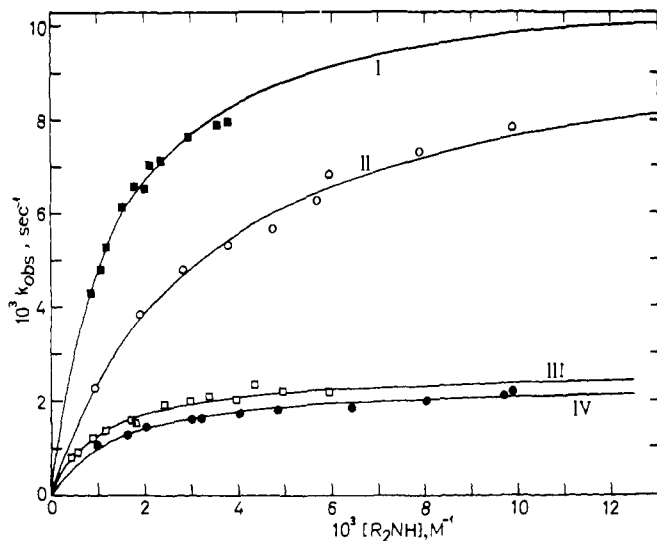
It is expected that in a solvent with higher dielectric constant less assistance by an additional amine molecule would be required, while the free nitrilium ion would be better stabilized than in benzene. Hence, while amine-catalyzed routes would be less important, it is predicted that reactions via cationoid intermediates would increase in importance. Competition of the bimolecular route with monomolecular routes would again depend on the nature of the substituents. For this reason we studied the reaction of diarylimidoyl chlorides with secondary amines in acetonitrile—a nonsolvolytic solvent with relatively high dielectric constant.

### Results

The rates of the reactions of diarylimidoyl chlorides **1c–g**, **1j**, and **1l**<sup>15</sup> with secondary amines in acetonitrile which give the corresponding amidines **2** (eq 1) were followed spectrophotometrically. The amine was always in large excess and pseudo-first-order rate constants,  $k_{\text{obsd}}$ , were calculated.

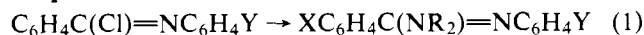
The substitution rates were one or two orders of magnitude higher than those in benzene. Four different types of kinetic behavior were distinguished for different systems;

(i) In the reactions of compounds **1d** and **1e** with piperidine and morpholine the substitution rate is first order in the imidoyl



**Figure 1.**  $k_{\text{obsd}}$  vs. [amine] for the reactions of **1d** and **1e**. The points are experimental, and the lines were calculated from the  $k_2/k_{-1}$  ratios of eq 8. (I) **1d** with piperidine; (II) **1d** with morpholine; (III) **1e** with piperidine; (IV) **1e** with morpholine (the scale of the amine concentrations should be multiplied by 2).

$\text{XR}_2\text{NH} +$



<b>1c</b>	X = H, Y = H:	<b>2c</b>
<b>1d</b>	X = H, Y = <i>p</i> -Cl:	<b>2d</b>
<b>1e</b>	X = H, Y = <i>m</i> -Cl:	<b>2e</b>
<b>1f</b>	X = H, Y = <i>p</i> -CN:	<b>2f</b>
<b>1g</b>	X = H, Y = <i>p</i> -NO <sub>2</sub> :	<b>2g</b>
<b>1j</b>	X = <i>p</i> -NO <sub>2</sub> , Y = H:	<b>2j</b>
<b>1l</b>	X = <i>p</i> -NO <sub>2</sub> , Y = <i>p</i> -NO <sub>2</sub> :	<b>2l</b>

chloride, i.e.,  $k_{\text{obsd}}$  values are constant either during a run or with different initial concentrations of **1** (Table I; microfilm edition<sup>38</sup>). The dependence of the  $k_{\text{obsd}}$  values on the [amine] is nonlinear: at low amine concentrations  $k_{\text{obsd}}$  increases strongly on increasing the amine concentration but a plateau is achieved at high [amine]. The same  $k_{\text{obsd}}$  value at the plateau is obtained for compound **1e** with either piperidine or morpholine, while for compound **1d**, where plateau was not achieved at our amine concentrations, the curves for the two amines tend to converge (Figure 1).

(ii) The reaction is first order in the imidoyl chloride, and  $k_{\text{obsd}}$  values show both a zero- and a first-order term in the amine (eq 2). This behavior was observed for **1g** with pi-

$$k_{\text{obsd}} = k^0 + k'[\text{amine}] \quad (2)$$

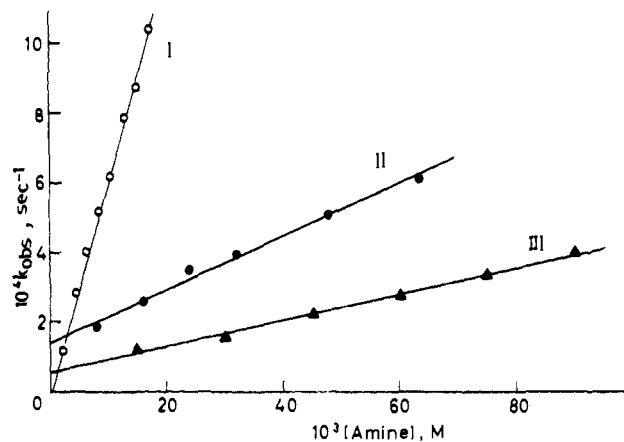
peridine, morpholine, imidazole, and diethylamine, for compound **1f** with piperidine and morpholine, and for **1j** with piperidine. This behavior is demonstrated for **1g** in Figure 2, and the data are given in Table I (microfilm edition<sup>38</sup>).

(iii) An overall second-order reaction, first order both in **1** and in the amine, was found for **1l** with piperidine (Table II; microfilm edition<sup>38</sup>).

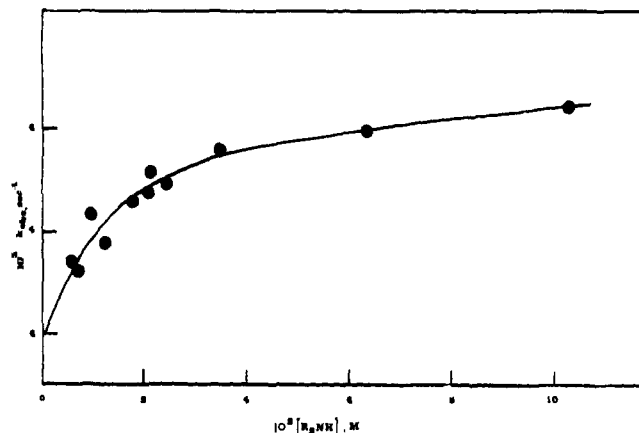
(iv) In the reaction of **1c** and **1g** with diisopropylamine the integrated pseudo-first-order constants, which were calculated from eq 3, decreased during the kinetic run (Table III; microfilm edition<sup>38</sup>). The rate decrease is larger at lower amine concentrations; e.g., at the lowest [amine] studied  $k_{\text{obsd}}$  at 90%

$$k_{\text{obsd}} = \frac{1}{t} \ln \frac{a}{a-x} \quad (3)$$

reaction was 25% of the initial extrapolated ( $k_{\text{obsd}}^0$ ) value,



**Figure 2.**  $k_{\text{obsd}}$  vs. [amine] plots for the reactions of **1g**: (I) with piperidine at 30 °C; (II) with morpholine at 45 °C; (III) with imidazole at 30 °C.



**Figure 3.**  $k_{\text{obsd}}^0$  vs. [amine] for the reaction of **1g** with diisopropylamine.

Reaction in the presence of tetraethylammonium chloride or diisopropylammonium chloride showed a rate decrease, suggesting that the rate decrease is due to common ion rate depression. Due to the complex nature of the reaction (see Discussion)  $k_{\text{obsd}}^0$  was not calculated analytically but was evaluated graphically from a large scale plot of  $k_{\text{obsd}}^0$  vs. percent reaction, by extrapolation to 0% reaction when  $[\text{Cl}^-] = 0$ . This method was previously used for other systems which showed common ion rate depression within a kinetic run.<sup>5c,f,7,16,17</sup> It is not very accurate, and duplicate experiments showed that the error in  $k_{\text{obsd}}^0$  can be  $\pm 10\%$ .

The dependence of  $k_{\text{obsd}}^0$  values on the amine concentration differs for the reactions of **1c** and **1g**. For *N-p*-nitrophenylbenzimidoyl chloride a nonlinear convex dependence was observed (Figure 3), while in the reaction of *N*-phenylbenzimidoyl chloride (**1c**) the  $k_{\text{obsd}}^0$  values increased linearly with the diisopropylamine concentration. The slope and the intercept of this line are  $0.98 \pm 0.02 \text{ M}^{-1} \text{ s}^{-1}$  and  $(8.7 \pm 0.6) 10^{-4} \text{ s}^{-1}$ , respectively.

Table IV summarizes the overall first- and second-order rate constants and their ratios for all the reactions;  $k^0$  and  $k'$  are given for systems obeying eq 2, the plateau values are given under  $k^0$  for systems showing curved  $k_{\text{obsd}}$  (or  $k_{\text{obsd}}^0$ ) vs. [amine] plot, and the average second-order constant for **1l** is given under  $k'$ .

**Salt Effects.** Addition of tetraethylammonium chloride to the reactions which show kinetic behaviors i-iii showed a negligible salt effect. On the other hand, on addition of excess of  $\text{Et}_4\text{NCl}$  to the reaction of **1c** or **1g** or addition of diisopropylammonium chloride to the reaction of **1c** with diisoprop-

**Table IV.** First-Order ( $k^0$ ) and Second-Order ( $k'$ ) Rate Constants for the Reaction of  $\text{XC}_6\text{H}_4\text{C}(\text{Cl})=\text{NC}_6\text{H}_4\text{Y}$  with Amines in Acetonitrile

Compd	X	Y	$\text{R}_2\text{NH}$	Concn, <sup>a</sup> 10 <sup>3</sup> M	$10^5 k^0, \text{s}^{-1}$ <sup>b</sup>		$10^4 k', \text{M}^{-1} \text{s}^{-1}$ <sup>b</sup>		$k'/k^0, \text{M}^{-1}$ at 30 °C	Kinetic behavior
					At 30 °C	At 45 °C	At 30 °C	At 45 °C		
<b>1c</b>	H	H	( <i>i</i> -Pr) <sub>2</sub> NH	0.7–4.5	87 ± 6 <sup>c</sup>					(iv)
<b>1d</b>	H	<i>p</i> -Cl	Piperidine	0.9–3.8	1120 ± 40					(i)
			Morpholine	1.0–12.0	1020 ± 30					(i)
<b>1e</b>	H	<i>m</i> -Cl	Piperidine	0.5–60	260 ± 10					(i)
			Morpholine	2.0–40	240 ± 10					(i)
<b>1f</b>	H	<i>p</i> -CN	Piperidine	1.4–35	17.3 ± 0.5		258 ± 3		149	(ii)
			Morpholine <sup>d</sup>	4.0–90	18.6 ± 0.7		26 ± 1		14	(ii)
<b>1g</b>	H	<i>p</i> -NO <sub>2</sub>	Piperidine	0.8–17	3.5 ± 1.4	15 ± 2	590 ± 13	1860 ± 60	1685	(ii)
			Morpholine	4.0–160	6.3 ± 1.4	15 ± 2	41 ± 2	76 ± 4	65	(ii)
			Imidazole	15–90	5.2 ± 0.8		39 ± 1		75	(ii)
			Et <sub>2</sub> NH	97–880	8.2 ± 0.2		4.7 ± 0.05		5.7	(ii)
			( <i>i</i> -Pr) <sub>2</sub> NH	5.0–530	5.9 ± 0.1				(iv)	
<b>1j</b>	<i>p</i> -NO <sub>2</sub>	H	Piperidine	2.5–19	21.6 ± 0.6	44 ± 1	181 ± 6	670 ± 2	84	(ii)
<b>1l</b>	<i>p</i> -NO <sub>2</sub>	<i>p</i> -NO <sub>2</sub>	Piperidine	0.5–3.0			3560 ± 150	6220 ± 200		(iii)

<sup>a</sup> The amine concentration used for the kinetic study. <sup>b</sup> The correlation coefficients of the linear plots of eq 2 are >0.995. <sup>c</sup>  $k^0_{\text{obsd}}$  value at [amine] = 0. (see text). <sup>d</sup> Three points at the lowest amine concentrations deviate downward from the linear  $k_{\text{obsd}}$  vs. [amine] plot.

**Table V.** Pseudo-First-Order Rate Constants for the Reactions of **1c** and **1g** with Diisopropylamine in Acetonitrile at 30 °C

RCl	10 <sup>4</sup> [RCl], M	Salt	10 <sup>4</sup> [salt], M	10 <sup>3</sup> [ <i>i</i> -Pr <sub>2</sub> NH], M	10 <sup>5</sup> $k_{\text{obsd}}, \text{s}^{-1}$
<b>1c</b>	0.61	Et <sub>4</sub> N <sup>+</sup> Cl <sup>-</sup>		1.2	210 <sup>a</sup>
				1.28	88 <sup>a</sup>
				12.3	5.2
				18.5	4.2
				6.0	210 <sup>a</sup>
				12.0	30
		18.0	20		
	0.58	<i>i</i> -Pr <sub>2</sub> NH <sub>2</sub> <sup>+</sup> Cl <sup>-</sup>		1.2	17
				1.5	244
				2.0	77
				4.0	60
				8.0	38
			12.0	37	
<b>1g</b>	1.16	Et <sub>4</sub> N <sup>+</sup> Cl		16	4.5 <sup>a</sup>
				1.04	2.22
				1.56	1.85
				2.08	1.67
				3.0	5.4 <sup>a</sup>
				6.0	1.20
		21	0.97		
		21	5.0 <sup>a</sup>		
		21	0.59		
		20.6	0.55		
		1.24	4.8 <sup>a</sup>		
		2.48	4.8 <sup>a</sup>		
0.92	<i>i</i> -Pr <sub>2</sub> NH <sub>2</sub> <sup>+</sup> Br <sup>-</sup>		18.4	5.3 <sup>a</sup>	
			10.4	3.8 <sup>a</sup>	
			1.0	5.8 <sup>a</sup>	
	2.0	10.4	7.3 <sup>a</sup>		

<sup>a</sup>  $k^0_{\text{obsd}}$  value.

ylamine,  $k_{\text{obsd}}$  remained constant during the kinetic run but its value was much lower than that of  $k_{\text{obsd}}^0$ . The “normal” salt effect<sup>18</sup> was evaluated by studying the dependence of  $k_{\text{obsd}}^0$  value on the salt concentration when the reaction of **1g** with diisopropylamine was conducted in the presence of NaClO<sub>4</sub> or of diisopropylamine hydrobromide. The data are given in Table V.

### Discussion

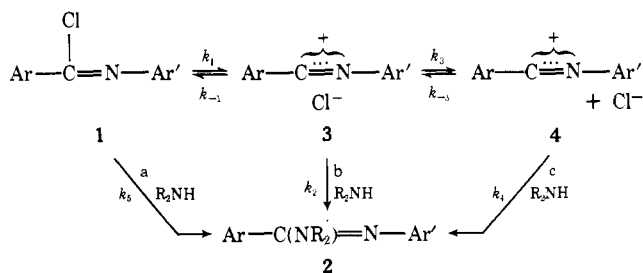
The multiplicity of mechanistic routes in the nucleophilic substitution at the carbon–nitrogen double bond of imidoyl chlorides by amines in benzene was presented in the preceding

papers of this series.<sup>1,13</sup> Amine-catalyzed routes were common in this low-dielectric solvent ( $\epsilon = 2.28$ ),<sup>19</sup> and while an intermediate ion pair was formed in one of the routes its further dissociation to a free ion was not observed kinetically.

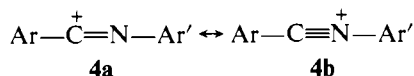
It is expected that in a higher dielectric solvent such as acetonitrile ( $\epsilon = 37.5$ )<sup>19</sup> the importance of the catalyzed routes will decrease, while the increased stability of charged intermediates will result in a greater importance of reactions via cationoid species. This was indeed observed as discussed below.

**Multiplicity of Mechanistic Routes.** The various types of mechanistic behavior can fit a unified reaction scheme

Scheme I



(Scheme I) which involves three routes for formation of the amidines: (a) a bimolecular, second-order reaction which is either an associative  $\text{S}_{\text{N}}2$  or a nucleophilic addition-elimination route, with a rate constant  $k_5$ ; (b) a reaction via the ion pair **3** which is formed in the ionization ( $k_1$ ); (c) a reaction via the free nitrilium ion **4** which is formed in the dissociation ( $k_3$ ) of **3**. Both **4** and the cationoid part of **3** are resonance hybrids of the canonical structures **4a** and **4b**. Routes a and b are



identical with those suggested for systems **1** in benzene,<sup>1</sup> but there are three important differences in the reactions in the two solvents.

First, reaction via the free nitrilium ion **4** was never observed in benzene, but was observed now for some systems in acetonitrile. Second, amine-catalyzed routes contributed to the overall substitution in benzene,<sup>1</sup> but kinetic terms higher than first order in the amine were not found in acetonitrile. Precedents of similar solvent effect are known in the reactions of activated vinyl<sup>20</sup> and aryl<sup>21</sup> chlorides with anilines. Third, the second-order uncatalyzed route with negative Hammett's  $\rho$  value in benzene was ascribed to reaction via an ion pair whose return to covalent  $\text{RCl}$  is faster than its capture rate by the amine.<sup>1</sup> In acetonitrile this condition is not fulfilled and the opposite is sometimes true. All these differences are accounted for by the higher ionizing power of acetonitrile and by its ability to stabilize the dipole formed in the heterolysis, the ion pair and the free ion. In the absence of stereochemical information the nature of the ion pair is not clear, but it is likely that it is more advanced along the ionization-dissociation route than that in benzene. Route b may therefore involve reactions of both an "intimate"<sup>9</sup> and a "solvent separated"<sup>9</sup> ion pair.

Applying the steady-state treatment to Scheme I gives a

$$k_{\text{obsd}} = \frac{k_1[\text{R}_2\text{NH}]\{k_2(k_{-3}[\text{Cl}^-] + k_4[\text{R}_2\text{NH}]) + k_3k_4\}}{(k_{-1} + k_2[\text{R}_2\text{NH}])(k_{-3}[\text{Cl}^-] + k_4[\text{R}_2\text{NH}]) + k_3k_4[\text{R}_2\text{NH}] + k_5[\text{R}_2\text{NH}]} \quad (4)$$

complex equation (eq 4) for  $k_{\text{obsd}}$ . Fortunately, it was found that the sensitivity of the reaction to the nature of both the imidoyl chloride and the amine resulted in a preferential reaction route for each system, thus simplifying eq 4. We will discuss the expected relationship between the structural parameters and the predicted  $k_{\text{obsd}}$  for limiting cases, and we will compare these predictions with the observed four kinetic behaviors i-iv.

**Route b. Kinetic Behavior i.** With a strong, sterically unhindered nucleophile such as piperidine or morpholine, and at the low chloride ion concentrations formed during the reaction, capture of the free diarylnitrilium ion **4** by the amine will be faster than its reversal to the ion pair **3**, i.e.,  $k_4[\text{R}_2\text{NH}] \gg k_{-3}[\text{Cl}^-]$ . Common ion rate depression will not be observed, and eq 4 will be reduced to:

$$k_{\text{obsd}} = \frac{k_1(k_2[\text{R}_2\text{NH}] + k_3)}{k_{-1} + k_2[\text{R}_2\text{NH}] + k_3} + k_5[\text{R}_2\text{NH}] \quad (5)$$

The first term of eq 5 represents reaction routes via initial ionization (routes b and c) while its second term represents reaction which involves initial C-nucleophile bond formation (route a). Routes b and c will be assisted by electron donation and route a by electron withdrawal. For moderate electron withdrawing Y's such as *m*-Cl and *p*-Cl (compounds **1d** and **1e**), the contribution of the bimolecular route a should be relatively negligible as judged by the fact that even in a solvent with a low ionizing power such as benzene, it contributes at most 55% to the overall reaction.<sup>1</sup>

When the second term in eq 5 is neglected, the kinetic behavior will be described by eq 6 which calls for a convex  $k_{\text{obsd}}$  vs. [amine] dependence, i.e., for kinetic behavior i. At high amine concentrations,  $k_2[\text{R}_2\text{NH}] \gg k_{-1}, k_3$ , the heterolysis of the C-Cl bond will be rate determining (eq 7) and the value

$$k_{\text{obsd}} = \frac{k_1(k_2[\text{R}_2\text{NH}] + k_3)}{k_{-1} + k_2[\text{R}_2\text{NH}] + k_3} \quad (6)$$

$$k_{\text{obsd}} = k_1 \quad (7)$$

of  $k_{\text{obsd}}$  at the plateau should be independent of the nature of the amine. Figure 1 shows that this expectation is fulfilled for the reactions of compounds **1d** and **1e**. The  $k_{\text{obsd}}$  values at the plateau for the reactions of **1e** with morpholine and piperidine are almost identical, although the morpholine concentration is four times higher than that of the piperidine. In the faster reaction of **1d** sufficiently high amine concentrations could not be studied, but approach to a plateau and convergence of the  $k_{\text{obsd}}$  values for the two amines to a similar  $k_{\text{obsd}}$  (plateau) value is clearly indicated.

A priori, the product could be formed both from **3** [the  $\text{S}_{\text{N}}2(\text{IP})$  route]<sup>14</sup> and from **4**, but if it is formed mainly from the free ion, i.e.,  $k_3 > k_2[\text{R}_2\text{NH}]$ , the reaction will be independent of the amine concentration, excluding the unlikely possibility that capture of **4** by the amine is involved in the rate-determining step. On the other hand, if dissociation of the ion pairs formed from **1d** and **1e** to the free ions is small compared with their capture by the amine, i.e.,  $k_2[\text{R}_2\text{NH}] \gg k_3$ , then by neglecting  $k_3$  in eq 6 and rearranging we obtain the following equation:

$$1/k_{\text{obsd}} = 1/k_1 + k_{-1}/k_1k_2(1/[\text{R}_2\text{NH}]) \quad (8)$$

A plot of  $1/k_{\text{obsd}}$  vs.  $1/[\text{R}_2\text{NH}]$  should then be linear with an intercept of  $1/k_1$  and a slope of  $k_{-1}/k_1k_2$ . Indeed, by using the data of Figure 1 it was found that such plots are linear (Figure 4) with correlation coefficients of  $>0.99$ . The  $k_1$  and  $k_2/k_{-1}$  values which were obtained from the slopes and the intercepts of these plots are given in Table VI. These values were applied for calculating the lines of Figure 1, and the fit between these calculated lines and the experimental points substantiate the assumptions involved in the derivation of eq 8.

Table VI and Figure 4 demonstrate again the constancy of  $k_1$  [=  $k_{\text{obsd}}$  (plateau)] values for each pair of amines. The ionization rate constant is ca. four times higher for **1d** than for **1e**, in line with an ionization process (see below).<sup>22</sup> As expected, the  $k_2/k_{-1}$  values which are the competition ratios for attack of the nucleophile on the ion pair vs. its return to  $\text{RCl}$ , increase with the amine basicity. Since  $k_{-1}$  should be independent of the nature of the amine, the ratios of these ratios for piperidine and morpholine are identical with the  $k_2(\text{piperidine})/k_2(\text{morpholine})$  ratios which are 2.47 for **1d** and 2.43 for **1e**. The derived "Bronsted  $\beta$ " values for **1d** and **1e** for the two amines are 0.14, a value lower than the values of 0.22 and 0.34 obtained in benzene.<sup>1</sup> This difference is reasonable since the values in benzene involve appreciable contribution from the

Table VI. Kinetic Parameters Derived from Eq 8

Compd	Amine	Intercept, s <sup>a</sup>	Slope, M s <sup>a</sup>	10 <sup>3</sup> k <sub>1</sub> , s <sup>-1</sup>	k <sub>2</sub> /k <sub>-1</sub> , M <sup>-1</sup>
1d	Morpholine	98 ± 3	0.322 ± 0.007	10.2 ± 0.3	300 ± 10
	Piperidine	89 ± 3	0.121 ± 0.005	11.2 ± 0.4	740 ± 30
1e	Morpholine	420 ± 10	1.10 ± 0.05	2.4 ± 0.1	380 ± 10
	Piperidine	380 ± 10	0.41 ± 0.01	2.6 ± 0.1	925 ± 30

<sup>a</sup> From the 1/k<sub>obsd</sub> vs. 1/[R<sub>2</sub>NH] plot.

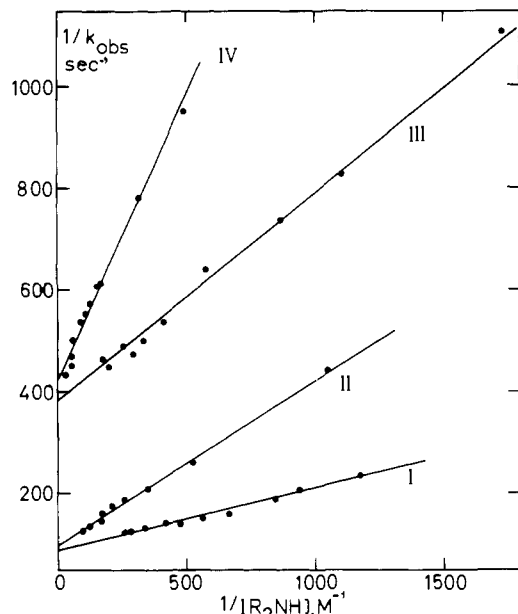


Figure 4. 1/k<sub>obsd</sub> vs. 1/[R<sub>2</sub>NH] plots for the reactions of: (I) 1d with piperidine; (II) 1d with morpholine; (III) 1e with piperidine; (IV) 1e with morpholine.

nucleophilic addition-elimination route, which is more sensitive to the effect of the nucleophile.

**Routes a and c. Kinetic Behavior ii.** The k<sub>2</sub>/k<sub>-1</sub> ratios (Table VI) are high even for systems with moderately electron-attracting substituents. Increase in the electron-withdrawal ability of Y is expected to result in several changes. The stability of the cationoid intermediates will decrease, and the condition k<sub>2</sub>[R<sub>2</sub>NH] > k<sub>3</sub> will be fulfilled at low amine concentrations. Both k<sub>2</sub> and k<sub>-1</sub> will increase, but judged by the higher k<sub>2</sub>/k<sub>-1</sub> ratios for 1e compared with 1d, these ratios will increase with the increase of σ<sub>Y</sub> and at amine concentrations ≥ 10<sup>-2</sup>-10<sup>-3</sup> M the condition k<sub>2</sub>[R<sub>2</sub>NH] > k<sub>-1</sub> will be fulfilled. Simultaneously the rate of the bimolecular reaction will also increase, so that its contribution to the overall process cannot be neglected anymore. Under these conditions eq 5 is reduced to eq 9, which is identical with the kinetic behavior ii observed for the reaction of 1f, 1g, and 1j with relatively un-

$$k_{\text{obsd}} = k_1 + k_5[\text{R}_2\text{NH}] \quad (9)$$

hindered amines (eq 2). The intercept of this dependence (k<sup>0</sup>) should then be again the ionization rate constant k<sub>1</sub>, while the slope (k') is identical with k<sub>5</sub>—the rate constant for the bimolecular reaction.

A downward drift from the linear k<sub>obsd</sub> vs. [amine] plot was observed in the reaction of 1f with morpholine for points when [morpholine] < 10<sup>-2</sup> M. Since a change from k<sub>2</sub>[R<sub>2</sub>NH] ≫ k<sub>-1</sub> to k<sub>2</sub>[R<sub>2</sub>NH] ≈ k<sub>-1</sub> would be observed in a reaction system when Y is not extremely strong electron withdrawing, and when the concentrations of not too highly nucleophilic amine are low, this may be an example for such a change.

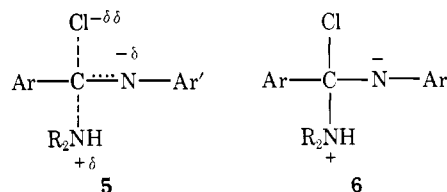
The k<sub>5</sub> values should be dependent on the nature of the amine while the k<sup>0</sup> = k<sub>1</sub> values should be independent of the amine. Table IV shows that this is indeed the case, although the dispersion of the k<sup>0</sup> values for 1g at 30 °C is relatively large. The constancy of the k<sup>0</sup> values contrasts the large variation in the k' values, which decrease with the decreased nucleophilicity of the amine due to steric and electronic effects. An apparent contradiction is a similarity of the k<sub>5</sub> values for morpholine [pK<sub>a</sub>(H<sub>2</sub>O) = 8.33]<sup>23</sup> and imidazole [pK<sub>a</sub>(H<sub>2</sub>O) = 6.95]<sup>23</sup> in their reaction with 1g.

**Route a. Kinetic Behavior iii.** Further increase in the electron-withdrawal ability of the substituents will result in an increased importance of route a over routes b and c, and in the extreme case when the second term of eq 5 will be much larger than the first term, the bimolecular reaction will take over

$$k_{\text{obsd}} = k_5[\text{R}_2\text{NH}] \quad (10)$$

(eq 10). The reaction of compound II (where X = Y = p-NO<sub>2</sub>) with piperidine is of pure second order (kinetic behavior iii), and it is very likely that route a is the exclusive substitution pathway.

As discussed for the corresponding reactions in benzene<sup>1</sup> the bimolecular reaction may be either an associative S<sub>N</sub>2 (with transition state 5) or an addition-elimination process via the zwitterion 6. In the more polar acetonitrile the addition-



elimination route is more likely, and two variants of it are possible: first, a rate-determining addition where k<sub>5</sub> is the rate constant for the nucleophilic attack, and second, a rate-determining elimination where k<sub>5</sub> is a product of the equilibrium constant for the formation of the tetrahedral intermediate 6 and the rate constant for the elimination step. Both variants have precedents in the substitution of activated vinyl halides by amines<sup>20,24,25</sup> and are not unequivocally distinguishable by the present data.

The k' values of systems 1f, 1g, and 1j in acetonitrile are 40-100-fold higher than those in benzene. This rate increase parallels the rate increase found on changing the solvent from toluene to dimethyl sulfoxide in the substitution of 2-chloroquinoline by piperidine,<sup>26</sup> which was ascribed to a rate-determining nucleophilic addition.

**Substituent Effects on Routes a and b.** By using the average k<sup>0</sup> values for the reactions with the various amines, the Hammett's ρ values were calculated for substitution via routes a and b. For route b ρ = -4.05 (r = 1.000) when using σ values,<sup>27</sup> while a less satisfactory correlation (ρ = -3.4; r = 0.989) was obtained by using σ<sup>+</sup> values.<sup>28</sup> The high negative value fits the ionization mechanism. It is more negative than the ρ values for the reactions of the imidoyl chlorides with amines in benzene<sup>1</sup> or in their hydrolysis in 75% aqueous dioxane.<sup>8</sup>

Table VII. Activation Parameters for the Reaction of  $\text{XC}_6\text{H}_4\text{C}(\text{Cl})=\text{NC}_6\text{H}_4\text{Y}$  with Amines in Acetonitrile

X	Y	Amine	Process	$k$	$\Delta H^\ddagger$ , kcal/mol <sup>a</sup>	$\Delta S^\ddagger$ , eu <sup>a</sup>
H	<i>p</i> -NO <sub>2</sub>	R <sub>2</sub> NH	Ionization	$k_1$	11 ± 4 <sup>b</sup>	-44 ± 13 <sup>b</sup>
H	<i>p</i> -NO <sub>2</sub>	Piperidine	Bimolecular	$k_5$	14 ± 0.7	-20 ± 2
H	<i>p</i> -NO <sub>2</sub>	Morpholine	Bimolecular	$k_5$	7 ± 1	-48 ± 4
<i>p</i> -NO <sub>2</sub>	H	Piperidine	Ionization	$k_1$	8 ± 0.3	-50 ± 2
<i>p</i> -NO <sub>2</sub>	H	Piperidine	Bimolecular	$k_5$	16 ± 0.8	-16 ± 3
<i>p</i> -NO <sub>2</sub>	<i>p</i> -NO <sub>2</sub>	Piperidine	Bimolecular	$k_5$	6.5 ± 0.9	-41 ± 3

<sup>a</sup> The errors in  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  are the maximum errors which were calculated according to R. C. Peterson, J. H. Markgraf, and S. D. Ross, *J. Am. Chem. Soc.*, **83**, 3819 (1961). <sup>b</sup> The activation parameters were calculated from the average  $k^0$  values for piperidine, morpholine, diethylamine, and imidazole at 30 °C and those for piperidine and morpholine at 45 °C.

The  $\rho$  values for route a are +2.75 and +1.5 for the reactions with piperidine and morpholine, respectively, and resemble those in benzene.<sup>1</sup> With the reservation that such  $\rho$  values which are based only on the two compounds **1f** and **1g** should be cautiously treated, the lower value for morpholine fits an addition-elimination route where stronger internal hydrogen bonding in **6**, R<sub>2</sub>NH<sup>+</sup> = morpholinium, reduces the demand for electron withdrawal from the C=N bond at the transition state. A higher  $\rho$  value for morpholine, the weaker nucleophile, would be expected for an associative S<sub>N</sub>2 reaction, provided that the reactivity-selectivity principle is applicable for our system.

The substituent effects in both routes are more pronounced when the substituent is in the aniline ring. For route a at 30 °C a two-point  $\rho$  for the X substituent is 1.0 when Y = *p*-NO<sub>2</sub>. Estimation of the  $|\rho(\text{Y}) - \rho(\text{X})|$  value for route b gives a value of 0.6. A lower sensitivity to changes in the carbon-substituted ring for reactions at the C=N bond was previously observed for the same reaction in benzene,<sup>1</sup> in the hydrolysis of imidoyl chlorides,<sup>7,8</sup> and in the addition of HCN to benzalanilines.<sup>29</sup> Reasons for this were discussed.<sup>1</sup>

The activation parameters which were calculated from the data of Table IV for the two processes (Table VII) show an extensive variation. Comparison with the bimolecular reactions of **1g** and **1j** with piperidine in benzene may indicate that the enhancement of the bimolecular rate in acetonitrile is entropy controlled. However, the comparison is not valid since the rate-determining step may differ in the two solvents. Indeed, a change from a rate-determining addition to a rate-determining elimination in nucleophilic vinylic substitution<sup>20,24,30</sup> is accompanied by a large decrease in  $\Delta S^\ddagger$ .

The bimolecular reaction of **1g** with morpholine is slower than that with piperidine since the higher  $\Delta S^\ddagger$  term more than compensates the lower  $\Delta H^\ddagger$  term (Table VII). The differences between these terms for the two amines are large and suggest an appreciable error in them.<sup>31</sup> Nevertheless, the trend is similar to that observed in benzene,<sup>1</sup> which was ascribed to stronger hydrogen bonds in the zwitterionic transition state with morpholine. This is probably also true in acetonitrile and argues against an S<sub>N</sub>2 reaction where the  $\Delta H^\ddagger$  values are usually higher for the weaker nucleophile.<sup>32</sup> Comparison of the reactions of piperidine with **1g**, **1j**, and **1i** show a decreasing  $\Delta H^\ddagger$  and a more negative  $\Delta S^\ddagger$  for the more reactive system. A similar trend in  $\Delta H^\ddagger$  was also found for the addition of morpholine and pyrrolidine to activated double bonds<sup>33</sup> and in the S<sub>N</sub>2 reaction of anilines with arylsulfonyl chlorides.<sup>32</sup> The trend in the  $\Delta S^\ddagger$  values probably reflects an enhanced solvation of a more positively charged transition state with a stronger bonds to the nucleophile.

The  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  values which are based on  $k_1$  are lower than the values for the hydrolysis of **1i** in aqueous acetone.<sup>7</sup> Rogne ascribes the similar behavior in the reaction of imidazole with benzenesulfonyl chloride in acetonitrile and in 95% EtOH to dispersion and dipole effects in acetonitrile which stabilize

the partially charged transition state more than the hydrogen bonding in the protic solvent.<sup>34</sup>

**Route c. Kinetic Behavior iv.** When the nucleophilicity of the amine is lowered,  $k_2$ ,  $k_4$ , and  $k_5$  will be reduced and the inequality  $k_4[\text{R}_2\text{NH}] \leq k_{-3}[\text{Cl}^-]$  may hold even in the absence of added chloride ion. The build-up of the chloride ion concentration during the reaction will result in an external ion return<sup>9</sup> and in common ion rate depression during the kinetic run<sup>17,35</sup> (kinetic behavior iv). This was found for the reactions of **1c** and **1g** with diisopropylamine, whose nucleophilicity is reduced due to steric hindrance. As expected from eq 4 the common ion rate depression is more pronounced at the low amine concentrations and it disappears at higher  $[\text{R}_2\text{NH}]$ , where apparently  $k_4[\text{R}_2\text{NH}] > k_{-3}[\text{Cl}^-]$ . In the small range of overlap in the amine concentrations used, the rate decrease is higher for **1g** than for **1c**.

The complexity of the reaction and the evidence below that route b cannot be neglected even at low amine concentrations prevented the conversion of eq 4 to a linear form which will enable the evaluation of the various rate constants. Comparison of the computer simulated reaction profiles, which were calculated by using assumed values of the rate constants  $k_1$ - $k_5$  with the observed profiles, failed to give only one set of rate coefficients for each amine, probably due to the large number of independent parameters. Hence, a graphical extrapolation of  $k_{\text{obsd}}^0$  values to zero reaction time was used to obtain the  $k_{\text{obsd}}^0$  values. Assuming that with the hindered amine  $k_5 = 0$ ,  $k_{\text{obsd}}^0$  is given by eq 11. Indeed, the  $k_{\text{obsd}}^0$  vs.  $[i\text{-Pr}_2\text{NH}]$  plot

$$k_{\text{obsd}}^0 = \frac{k_1(k_2[\text{R}_2\text{NH}] + k_3)}{k_{-1} + k_3 + k_2[\text{R}_2\text{NH}]} \quad (11)$$

for **1g** (Figure 3) resembles the nonlinear curves (Figure 1) found for **1d** and **1e** with morpholine and piperidine (cf. eq 6). The common ion rate depression disappears at the same amine concentrations where the plateau starts and consequently (cf. eq 4) both inequalities  $k_2[\text{R}_2\text{NH}] \gg k_3 + k_{-1}$  and  $k_4[\text{R}_2\text{NH}] \gg k_{-3}[\text{Cl}^-]$  hold simultaneously. That the  $k_{\text{obsd}}^0$  value at the plateau is  $(5.9 \pm 0.1) \cdot 10^{-5} \text{ s}^{-1}$ , in very good agreement with the average  $k^0$  value obtained with the stronger amines, is a strong evidence for Scheme I.

The reaction of **1c** with diisopropylamine is much faster, and the amine concentrations studied were low (0.00007-0.0005 M). This fact, together with the expected lower  $k_2$  and higher  $k_3$  values as compared with those for systems with stronger electron-attracting substituents result in the inequality  $k_{-1} + k_3 \gg k_2[\text{R}_2\text{NH}]$ . Equation 11 is reduced to eq 12, and the predicted linearity of  $k_{\text{obsd}}^0$  vs.  $[\text{R}_2\text{NH}]$  plot was indeed observed (kinetic behavior iv).

$$k_{\text{obsd}}^0 = \frac{k_1 k_3}{k_{-1} + k_3} + \frac{k_1 k_2}{k_{-1} + k_3} [\text{R}_2\text{NH}] \quad (12)$$

From the linear log  $k_1$  vs.  $\sigma$  correlation of compounds **1d-g** a  $k_1$  value of  $(8.6 \pm 0.5) \cdot 10^{-2} \text{ s}^{-1}$  was calculated for **1c**. By using this value and the slope and intercept of eq 12 we ob-

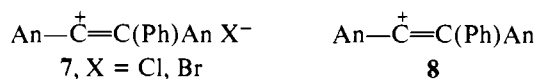
Table VIII. Analytical Data for the Amidines C<sub>6</sub>H<sub>5</sub>C(Z)=NC<sub>6</sub>H<sub>4</sub>Y

Y	Z	Mp, °C	Crystalline form	$\lambda_{\max}^{\text{MeCN}}$ , nm ( $\epsilon$ )	Analysis						
					Calcd, %			Formula	Found, %		
					C	H	N		C	H	N
H	<i>i</i> -Pr <sub>2</sub> N <sup>a</sup>	3	Rhombic plates <sup>b</sup>	247 (12 600)	81.50	8.57	10.00	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub>	80.94	8.90	10.29
<i>p</i> -NO <sub>2</sub>	<i>i</i> -Pr <sub>2</sub> N <sup>c</sup>	161	Rhombic plates <sup>b</sup>	370 (16 100)	70.20	7.08	12.91	C <sub>19</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub>	70.00	7.28	13.03
<i>p</i> -NO <sub>2</sub>	C <sub>3</sub> H <sub>3</sub> N <sub>2</sub> <sup>d</sup>	139	Yellow plates <sup>e</sup>	320 (13 500)	65.75	4.11	19.18	C <sub>16</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub>	66.05	4.38	18.73

<sup>a</sup>  $\delta$  (CDCl<sub>3</sub>) 1.42 (12 H, d, Me), 3.52 (2 H, septet, CH), 6.35–7.18 (10 H, m, Ar). <sup>b</sup> From EtOH. <sup>c</sup>  $\delta$  (CDCl<sub>3</sub>) 1.39 (12 H, d, Me), 3.68 (2 H, septet, CH), 7.05 (5 H, m, Ph), 6.37, 7.70 (4 H, AA'BB' q, C<sub>6</sub>H<sub>4</sub>Y). <sup>d</sup> Imidazolyl.  $\delta$ (CDCl<sub>3</sub>) 6.87, 8.09 (4 H, AA'BB' q, N-C<sub>6</sub>H<sub>4</sub>Y), 7.41 (7 H, m, C-Ar + imidazolyl), 7.88 (1 H, m, C-Ar or imidazolyl). <sup>e</sup> From MeCN-H<sub>2</sub>O.

tained the following ratios:  $k_2/k_3 = 1130 \pm 60 \text{ M}^{-1}$  and  $k_{-1}/k_3 = 100 \pm 5$ . The high  $k_2/k_3$  ratio found in the reaction of a weak nucleophile (expected low  $k_2$ ) for a system which gives a relatively stable nitrilium ion (expected high  $k_3$ ) justifies the neglect of  $k_3$  in the reactions of **1d**, **1e**, **1g**, and **1j** with reactive amines, as discussed above.

The  $k_{-1}/k_3$  value of 100 for the ion pair **3** is much higher than the return/dissociation ratios of 0.65–1.25 found for the ion pair **7**, which is formed in the solvolysis of 1,2-dianisyl-2-phenylvinyl chloride and bromide.<sup>17</sup> The difference is

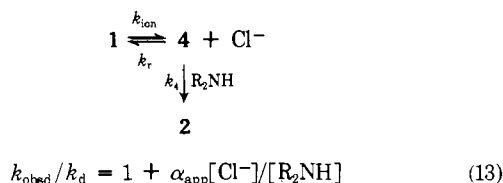


probably due to the more electrophilic solvent in the latter case, since the nitrilium ion **4** is probably more stable than the vinyl cation **8**, as judged by its higher rate of formation.

Table V shows that the depressed rate constant ( $k_d = k_{\text{obsd}}$  in the presence of added Cl<sup>-</sup>) depends on the nature of the substrate and the salt and on the amine concentration. The rate decrease with *i*-Pr<sub>2</sub>NH<sub>2</sub><sup>+</sup>Cl<sup>-</sup> is lower than with Et<sub>4</sub>N<sup>+</sup>Cl<sup>-</sup>, while the positive salt effect of *i*-Pr<sub>2</sub>NH<sub>2</sub><sup>+</sup>Br<sup>-</sup> on the reaction of **1g** is much higher than that of NaClO<sub>4</sub>, suggesting an electrophilic assistance by the ammonium ion to the C-Cl bond cleavage. With the noncatalytic salt, Et<sub>4</sub>N<sup>+</sup>Cl<sup>-</sup> and at amine concentration of 0.0012 M, the lowest  $k_d$  value for **1c** is only 2% of  $k_{\text{obsd}}$ . If correction for the normal salt effect is introduced by using NaClO<sub>4</sub> as a model, then  $k_{\text{obsd}}/k_d = 75$ –100. Hence  $\geq 98.7\%$  of the product is formed from the free ion **4**,<sup>9</sup> and route b is negligible for this substrate. The rate decrease is lower for **1g** where  $\geq 91\%$  of the product is formed from **4** when the amine concentration is 0.02 M. Comparison of the  $k_{\text{obsd}}/k_d$  ratios for **1c** and **1g** is not possible, since at different amine concentration a different fraction of the product will be obtained from the ion pair **3**.

When the simplified Ingold's scheme (Scheme II), which

Scheme II



neglects the intermediacy of ion pairs,<sup>35</sup> is applied to these substrates, the extent of rate depression is given by eq 13, where  $\alpha_{\text{app}} = k_r/k_4$ .<sup>36</sup> The  $\alpha_{\text{app}}$  values are 10–50 at our amine concentrations, indicating that the nitrilium ions are relatively selective and stable.

## Conclusions

The substitution of diarylimidoyl chlorides by amines in acetonitrile follows several mechanistic routes. With good nucleophiles the reaction proceeds exclusively via the nucleo-

philic addition-elimination route when the system is substituted by strong electron-attracting substituents. When the electron withdrawal from the azomethine bond is reduced, both the addition-elimination route and substitution via an intermediate ion pair occur simultaneously, while when it is further reduced the reaction via the ion pair is the exclusive one. When hindered nucleophile is used the reaction proceeds mainly or exclusively via the free nitrilium ion.

## Experimental Section

Melting points were determined with a Beckman apparatus and are uncorrected. UV spectra were measured with a Unicam 800 spectrophotometer and NMR spectra with a Varian T-60 instrument, and the signal positions are given in ppm downfield from internal tetramethylsilane.

Dry acetonitrile was prepared from an analytical grade solvent (Baker) by drying over phosphorus pentoxide and then over calcium hydride, according to Coetzee.<sup>37</sup> The dry solvent was distilled and kept at argon atmosphere.

The imidoyl chlorides were those described in the previous publication.<sup>1</sup> The amines were distilled twice from potassium hydroxide before use. The new substituted benzamidines were prepared from the reagents as described previously.<sup>1</sup> Their analytical and spectral properties are given in Table VIII.

**Kinetic Measurements.** Stock solutions of the reagents were prepared daily, mixed at the reaction temperature, and transferred to a thermostated chamber of a Gilford 2400 S spectrophotometer. The change of the optical density of the mixture was followed at a wavelength where the difference between the absorptions of the imidoyl chloride and the amidine has the highest value.

**Supplementary Material Available.** Tables I–III, rate constants for compounds **1c**–**1g**, **1j**–**1l** (4 pages). Ordering information is given on any current masthead page.

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## Kinetic Studies of the Reduction of Hemoglobin and Myoglobin by Chromium(II)

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**Abstract:** Kinetic studies of the reduction of methemoglobin and metmyoglobin by chromium(II) have been performed, giving rate constants of  $3.6 \times 10^4$  (pH 6.00,  $\mu = 0.167$ , 30.5 °C) and  $5.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$  (pH 6.00,  $\mu = 0.167$ , 30.5 °C), respectively. The reduction of hemoglobin in the presence of thiocyanate gave a third-order rate constant of  $4.0 \times 10^6 \text{ M}^{-2} \text{ s}^{-1}$  (pH 6.00,  $\mu = 0.167$ , 30.5 °C). The pseudo-first-order rate plots for hemoglobin were linear and showed no evidence for cooperativity. The kinetic products in the absence of thiocyanate contained protein-bound Cr(III) with a Cr(III)/protein ratio of 1.0 for myoglobin and 4.0 for hemoglobin. Kinetic products retained their respective CO and O<sub>2</sub> binding capacity and showed no spectral changes from their Cr(III)-free analogues. The results of the kinetic and product studies suggest possible pathways for electron transfer in this system which lend support to pathways previously deduced for electron transfer in the reduction of ferricytochrome *c*.

This paper is a continuation of our research of electron-transfer reactions in metalloproteins and metalloporphyrins.<sup>1</sup> The kinetics and product study of the reduction of metmyoglobin and methemoglobin with chromous are presented in this paper. Although these heme proteins are primarily reversible oxygen carriers without being involved in redox chemistry in their primary biological function and despite the elaborate safeguards to maintain the hemoglobin in the Fe(II) state, autoxidation does indeed take place. The biological oxidant, or oxidants for the unwanted reaction, is still unknown.

The amount of methemoglobin in cells is the result of the two opposing processes—a continuing oxidation of hemoglobin balanced by the reduction process. The erythrocyte requires some reductive system to keep the hemoglobin sufficiently reduced to function properly as an oxygen carrier. Such enzyme systems have been discovered and studied and these methemoglobin and metmyoglobin reductases are enzymes that keep the iron in the hemoglobin and myoglobin in the divalent state.<sup>2-12</sup>

This paper uses a model system to gain insight into the

physiological reduction of methemoglobin and metmyoglobin. Chromium(III) is substitutionally inert;<sup>13</sup> thus, the product of the reaction between metmyoglobin and chromous ions yields a product which is relatively stable and amenable to chemical structural studies. Recent kinetic and mechanistic studies<sup>14-16</sup> of the chromous ion reduction of ferricytochrome *c* have suggested that electron transfer may proceed via the heme crevice. Chromium(III) is bound to the cytochrome molecule<sup>15</sup> in the area of the heme crevices, and electron transfer involving tyrosine-67 was suggested.<sup>16</sup> This paper reports data indicating the probable location of the inert Cr(III) in the Cr(III)-myoglobin complex and, with kinetic data, considers mechanisms of electron transfer in hemoglobin and myoglobin and the relationship of these mechanisms to those suggested for the chromous ion reduction of ferricytochrome *c*.

### Experimental Section

Sigma equine skeletal muscle myoglobin (type I) and Miles horse hemoglobin, twice crystallized, were used without further purification.