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Supplementary Material Available: Details of the AM1-CI calculations, consisting of the points used to define the potential energy surfaces and the functions used to interpolate between the points (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Mechanisms and Stereochemistry of Amine Substitution Reactions at the Carbon-Nitrogen Double Bond

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The reaction of (*Z*)-*O*-methyl-*p*-nitrobenzohydroximoyl chloride [4-$NO_2C_6H_4C(Cl)$=$NOCH_3$] with morpholine, piperidine, pyrrolidine, and azetidine gives the corresponding (*Z*)-amidoximes [4-$NO_2C_6H_4C(NR_1R_2)$=$NOCH_3$]. The rate equations for these reactions in benzene solution contain both first-order and second-order terms in amine. The rates of these reactions increase with increasing basicity [k(pyrrolidine > k(morpholine)] and decreasing size of the amine [k(azetidine) > k(pyrrolidine) > k(piperidine)]. The approximate Hammett ρ-values for the reaction of (*Z*)-hydroximoyl chlorides with azetidine are +1.0 for the amine-catalyzed process and 0 for the uncatalyzed pathway. The element effect, k(*p*-nitrobenzohydroximoyl bromide)/k(*p*-nitrobenzohydroximoyl chloride), is 11.9 for the amine-catalyzed reaction and 8.16 for the uncatalyzed reaction. These results suggest that the reactions proceed by an addition-elimination mechanism ($A_N + D_N$) in which the amine is deprotonating the zwitterionic tetrahedral intermediate in the amine-catalyzed process. The slow reaction of azetidine in benzene solution with (*E*)-*O*-methyl-*p*-nitrobenzohydroximoyl chloride gives a mixture of the (*Z*)- and (*E*)-amidoxime with the *E* isomer predominating ($E/Z \cong 98:2$). The rate equation for this reaction contains first-order and third-order terms in azetidine. It is suggested that the amine-catalyzed route involves nucleophilic attack by an amine monomer to form a tetrahedral intermediate which breaks down with the assistance of an amine dimer (or the homoconjugate acid of the amine). The difference in the observed rate equations for (*Z*)- and (*E*)-hydroximoyl chlorides with azetidine is attributed to stereoelectronic effects.

Introduction

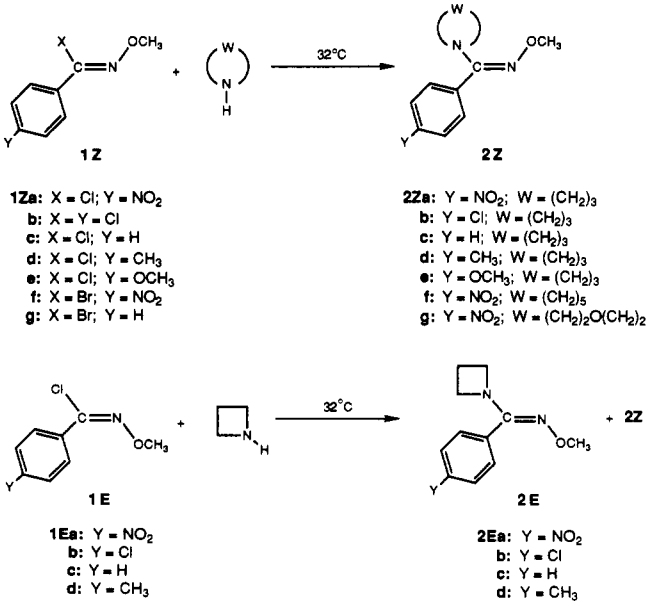
The kinetics and stereochemistry of pyrrolidine substitution in (*Z*)-*O*-methylbenzohydroximoyl chlorides (**1Z**) in benzene solution has been reported by us.[1] These substitution reactions gave the (*Z*)-amidoxime **2Z** as the only product. Under pseudo-first-order conditions (excess pyrrolidine) the kinetic equation followed by these reactions contained both first-order and second-order terms in pyrrolidine:

$$k'_{obs} = k'[\text{amine}] + k''[\text{amine}]^2 \quad (1)$$

The derived second-order (k') and third-order (k'') rate constants were obtained from plots of the second-order rate constants (k''_{obs}) vs pyrrolidine concentration:

$$\frac{k'_{obs}}{[\text{amine}]} = k''_{obs} = k' + k''[\text{amine}] \quad (2)$$

The third-order rate constants (k'') gave a Hammett ρ-value of +1.06 with σ while the second-order rate constants (k') showed no systematic substituent effect ($\rho \cong 0$). The positive ρ-value on k'' and the relatively small element effect ($k''_{Br}/k''_{Cl} = 26.9$ and $k''_{Br}/k''_{Cl} = 10.1$ for **1Za** and **1Zf**) suggested that this reaction proceeds by an addition-elimination mechanism ($A_N + D_N$, Scheme I). It was suggested that the positive ρ-value for the amine-catalyzed pathway was due to the transition state for k_3 (TS-3 in Scheme I) where the second molecule of amine assists the reaction by deprotonating the amino nitrogen. The deprotonation of the amino nitrogen moves some of the positive charge to the second amine molecule, leaving a disproportionate amount of negative charge near the aromatic ring.



Results and Discussion

In an attempt to learn more about the factors that determine the reactivity of amines in nucleophilic substitu-

(1) Johnson, J. E.; Ghafouripour, A.; Arfan, M.; Todd, S. L.; Sitz, D. A. *J. Org. Chem.* **1985**, *50*, 3348-3355.
(2) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworth: London, 1965.
(3) Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1977**, *99*, 1845-1858.

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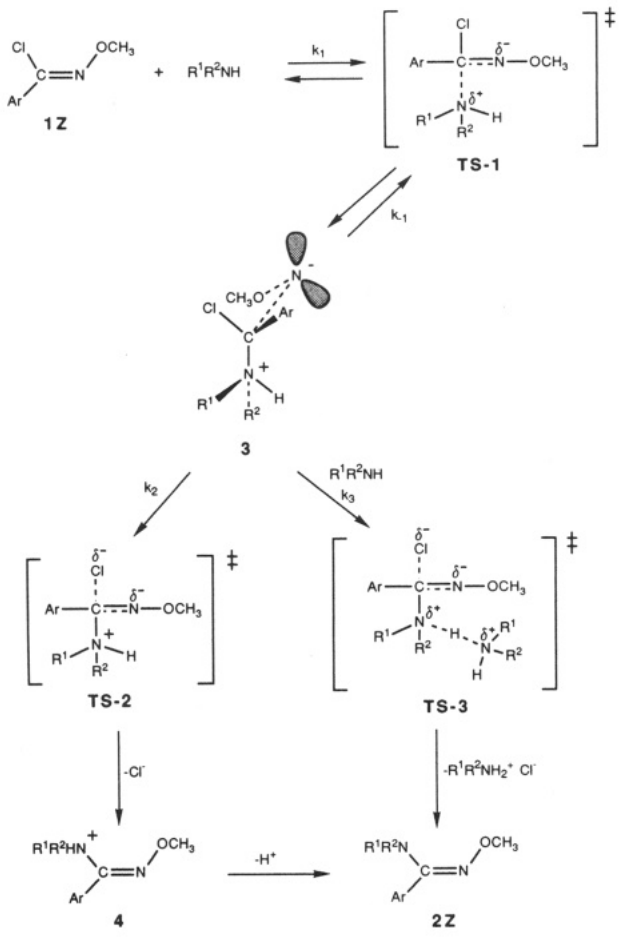
Scheme I



tion reactions on hydroximoyl chlorides, we have carried out kinetic measurements on the reactions of (*Z*)-*O*-methyl-*p*-nitrobenzohydroximoyl chloride (**1Za**) with several cyclic amines in benzene solution (Tables I and II). All of these reactions gave exclusively the (*Z*)-amidoxime **2Z** as the substitution product and followed kinetic equation 1. When the (*Z*)-amidoximes **2Za-d** were heated in diphenyl ether solution at 100 °C for approximately 10 h they underwent isomerization to an equilibrium mixture of *Z* and *E* isomers with the *Z* isomer predominating (Table III). This demonstrates that these reactions, and the reactions of the (*E*)-hydroximoyl chlorides **1E** described later, are kinetically controlled.

An increase in the bascity of the amine appears to enhance the rate of the substitution reaction as evidenced by the greater reactivity of piperidine [$pK_a(H_2O)$ of 11.12][2] as compared to morpholine [$pK_a(H_2O)$ of 8.33].[2] These two amines should have about the same steric approach requirements but differ in rate by a factor of 12 at 2.00 M amine concentration.

The estimated Bronsted β values based on rate constants for morpholine and piperidine are 0.35 for k'' and 0.38 for k'''. These results are in agreement with those obtained by Ta-Shma and Rappoport[3] on reactions of morpholine and piperidine in benzene solution with imidoyl chlorides [Ar(Cl)C=NAr] that contained electron-withdrawing substituents (β = 0.22 – 0.78). Ta-Shma and Rappoport favored a nucleophilic addition–elimination mechanism for these reactions. Imidoyl chlorides containing electron-donating substituents gave β values <0.1 and these reactions were suggested to proceed by a dissociative pathway with an nitrilium ion (as an ion pair) intermediate [$D_N + A_N$; S_N2(IP)].

Table I. Pseudo-First-Order Rate Constants k'_{obsd} and Second-Order Rate Constants k''_{obsd} for the Reactions of (*Z*)- and (*E*)-*O*-Methylbenzohydroximoyl Chlorides with 2° Cyclic Amines in Benzene at 32.0 °C

no.	amine	[amine], M	$10^5k'_{obsd}$, s^{-1}	$10^5k''_{obsd}$, M^{-1} s^{-1}
1Za	morpholine	1.00	0.0129	0.0129
		1.50	0.0269	0.0179
		2.00	0.0419	0.0210
		2.50	0.0666	0.0266
		3.00	0.0905	0.0302
1Za	piperidine	1.00	0.143	0.143
		1.50	0.288	0.192
		2.00	0.502	0.251
		2.50	0.725	0.290
		3.00	0.997	0.337
1Za	azetidine	0.300	0.656	2.19
		1.00	4.13	4.13
		1.50	9.15	6.10
		1.75	13.2	7.47
		2.00	16.3	8.13
		2.50	26.2	10.5
1Zb	azetidine	1.00	1.64	1.64
		1.25	2.38	1.91
		1.50	3.27	2.18
		1.75	4.47	2.55
		2.00	5.77	2.88
		2.25	7.24	3.22
1Zc	azetidine	1.00	0.937	0.937
		1.25	1.32	1.05
		1.50	1.81	1.20
		1.75	2.38	1.36
		2.00	3.03	1.51
		2.25	3.70	1.64
1Zf	azetidine	1.00	39.8	39.8
		1.25	58.8	47.4
		1.50	81.3	54.2
		1.75	109	62.3
		2.00	142	71.0
1Ea	azetidine	0.300	0.00392	0.0131
		1.00	0.0251	0.0251
		1.50	0.0527	0.0351
		2.00	0.0993	0.0497
		2.25	0.0130	0.0578
		2.50	0.172	0.0688
		3.00	0.271	0.0903
1Eb	azetidine	2.00	0.0474	0.0237
		2.25	0.0612	0.0272
		3.00	0.0126	0.0420

Table II. Derived Second-Order (k'), Third-Order (k'''), and Fourth-Order (k'''') Rate Constants for the Reaction of (*Z*)- and (*E*)-*O*-Methylbenzohydroximoyl Chlorides with 2° Cyclic Amines in Benzene at 32.0 °C

no.	amine	$10^6k''$, M^{-1} s^{-1}	$10^6k'''$, M^{-2} s^{-1}	$10^6k''''$, M^{-3} s^{-1}	k'''/k'', M^{-1}	correl coeff[a]
1Za	morpholine	0.0440	0.0866		1.97	0.997
1Za	piperidine	0.512	0.952		2.27	0.997
1Za	pyrrolidine[b]	1.23	5.13		4.17	0.998
1Za	azetidine	6.95	38.1		5.48	0.996
1Zb	azetidine	3.23	12.8		3.96	0.998
1Zc	azetidine	3.45	5.79		1.68	0.998
1Ze	azetidine	82.5	311		3.77	0.999
1Ea	azetidine[c]	0.151	0.0186	0.0776		1.000
1Eb	azetidine[d]	0.0876		0.0369		1.000

[a] Correlation coefficients for the plot of k''_{obsd} vs [amine]. [b] Data from ref 1. [c] Rate constants obtained by a nonlinear regression analysis of a plot of k'_{obsd} vs amine concentration. [d] Rate constants obtained from a plot of k''_{obsd} vs [amine]^2.

Table III. Equilibrium Distribution of (*Z*)- and (*E*)-Amidoximes Obtained by Thermal Isomerization of the (*Z*)-Amidoximes at 100 °C in Diphenyl Ether

(*E*)-amidoxime	% (*E*)-amidoxime at equilibrium
2Ea	20
2Eb	33
2Ec	29
2Ed	29

Table IV. Product Distributions in the Reactions of (*E*)-Hydroximoyl Chlorides 1E with Azetidine in the Absence of Solvent

(*E*)-hydroximoyl chloride	% (*E*)-amidoxime
1Ea	86
1Eb	67
1Ec	71
1Ed	74

Table V. Product Distributions in the Reaction of (*E*)-*O*-Methyl-*p*-nitrobenzohydroximoyl Chloride (1Ea) with Azetidine in Benzene Solution

[1Ea], M	% reaction	% (*E*)-amidoxime (2Ea)
5.0	25	96.4
3.0	50	98.7
5.0	90	99.7
3.0	>99	97.3

The three cyclic amines piperidine [p$K_a(H_2O)$ of 11.12],[2] pyrrolidine [p$K_a(H_2O)$ of 11.27],[2] and azetidine [p$K_a(H_2O)$ of 11.29][2] all have about the same bascity but the rate of substitution with the (*Z*)-hydroximoyl chloride **1Za** increases by a factor of over 32 at 2.00 M amine from piperidine to azetidine. Most of this increase is due to an increase in the third-order rate constant [k'''(azetidine)/k'''(piperidine) = 40.0 as compared to k''(azetidine)/k''(piperidine) = 13.6]. The amine-catalyzed pathway provides an important pathway for this reaction by freeing an electron pair on nitrogen, which facilitates nucleofuge expulsion and avoids the unstable N′-protonated amidoxime 4 (Scheme I). Since the amine-catalyzed route involves a rather congested transition state (TS-3), it appears that decreasing the size of the amine increases the importance of this process.

The substantial rate increase in the reaction of **1Za** with azetidine as compared to pyrrolidine prompted us to carry out the reaction of azetidine with the (*E*)-hydroximoyl chlorides. We observed that the (*E*)-hydroximoyl chlorides **1Ea–d** slowly reacted with azetidine in the absence of solvent to give mixtures of the (*Z*)- and (*E*)-amidoximes **2Z** and **2E** with the *E* isomer predominating (Table IV). When the reaction of azetidine with **2Ea** was carried out at 32 °C in benzene solution, HPLC analysis of the reaction product at various degrees of completion (Table V) showed that the (*E*)-amidoxime was formed almost exclusively (ca. 2% *Z*). It is not clear why the stereoselectivity is lower in neat azetidine, but it is not due to isomerization during the isolation of the reaction product since we used the same workup procedure for the (*Z*)-hydroximoyl chloride reactions and were able to obtain pure samples of the (*Z*)-amidoximes without any isomerization to the *E* isomers. One does need to use caution in the analysis of the *Z* and *E* isomers of amidoximes because they are very sensitive to acid-catalyzed isomerization. In fact, separation of the *Z* and *E* isomers of amidoximes by HPLC cannot be accomplished with silica-based columns, including reversed-phase columns, presumably because SiOH groups catalyze the isomerization. The HPLC analyses performed in this research were carried out on a polymer-based column.

Investigation of the kinetics of the reaction of azetidine with the (*Z*)-hydroximoyl chlorides **1Za**, **1Zb**, and **1Zc** showed that these reactions followed the same rate equation as the reactions with pyrrolidine (eq 2). As with pyrrolidine there appears to be a substituent effect on the third-order term (approximate ρ = 1.0 with σ) whereas there is no systematic substituent effect on the second-order term.

A small element effect was observed on both the derived second-order (k''_{1Zf}/k''_{1Za} = 11.9) and third-order (k'''_{1Zf}/k'''_{1Za} = 8.16) rate constants. Element effects have been important in determining the mechanism of nucleophilic substitution in vinyl halides where k_{Br}/k_{Cl} ratios for dissociative mechanisms with vinyl cation intermediates ($D_N + A_N$; S_N1) are substantially higher (k_{Br}/k_{Cl} rate ratios in the range of 5–42 in HOAC)[4a] than those observed for addition–elimination mechanisms ($k_{Br}/k_{Cl} \simeq 1$).[4b] Element effects for nucleophilic substitution reactions of imidoyl chlorides also appear to be useful. We have reported[5a] a k_{Br}/k_{Cl} ratio of 41 for the hydrolysis ($D_N + A_N$) of (*Z*)-*O*-methylbenzohydroximoyl halides (**1Zc** and **1Zg**). The k_{Br}/k_{Cl} ratio for hydrolysis reactions ($D_N + A_N$) of other imidoyl halides are in the range of 30–440.[3,7] An element effect of 2.2 was reported by us[5b] for methoxide ion substitution in **1Zg** and **1Zc**. This reaction proceeds by rate-limiting nucleophilic attack by methoxide ion to form a tetrahedral intermediate which rapidly loses halide ion. The reactions of **1Zf** and **1Za** with pyrrolidine in benzene solution gave element effects (k''_{1Zf}/k''_{1Za} = 26.9 and k'''_{1Zf}/k'''_{1Za} = 10.1)[1,8] that were considerably higher than the methoxide substitution reaction which indicates that k_2 and k_3 are the rate-limiting steps in the addition–elimination mechanism outlined in Scheme I.

Recent theoretical calculations[4b] indicate that ground-state stabilization of a carbon–carbon double bond by chlorine exceeds bromine stabilization by approximately 1.3 kcal/mol. Thus, one could observe an element effect in an addition–elimination mechanism on vinyl halides, even when the addition step is rate-limiting, because of greater ground-state stabilization of the vinyl chloride as compared to the vinyl bromide.

It is apparent that caution must be used in the interpretation of element effects especially when the values are greater than unity. Nevertheless, the relatively small element effects observed in this work along with the positive Hammett ρ-value is more consistent with an addition–elimination mechanism than a dissociative process.

Direct displacement (A_ND_N; S_N2), without the formation of a tetrahedral intermediate, has been proposed for nucleophilic substitution at acyl carbon atoms.[6] The element effect for this mechanism would be expected to be higher (k_{Br}/k_{Cl} = 425 for the reaction of methyl halide with chloride ion in acetone;[9a] k_{Br}/k_{Cl} = 63 for N_3^- + methyl halide in methanol;[9b] the "normal" value for k_{Br}/k_{Cl} is ca. 50 for A_ND_N reactions of alkyl halides[9c]) than the element effects we have observed in the reactions of secondary amines with hydroximoyl halides. An A_ND_N mechanism cannot be unequivocally ruled out since such a pathway should give a much smaller element effect if the carbon–

(4) (a) Rappoport, A.; Gal, A. *J. Chem. Soc., Perkin Trans. 2* **1973**, 301–310. (b) Hoz, S.; Basch, H.; Wolk, J. L.; Rappoport, Z.; Goldberg, M. *J. Org. Chem.* **1991**, *56*, 5424–5426. (c) Rappoport, Zvi; Rav-Acha, C. *Tetrahedron Lett.* **1984**, *25*, 117–120.

(5) (a) Johnson, J. E.; Cornell, S. C. *J. Org. Chem.* **1980**, *45*, 4144–4148. (b) Johnson, J. E.; Nalley, E. A.; Weidig, C.; Arfan, M. *J. Org. Chem.* **1981**, *46*, 3623–3629.

(6) Song, B. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 8470–8479, and references cited therein.

(7) Scott, F. L.; Cronin, D. A.; O'Halloran, J. K. *J. Chem. Soc. C.* **1971**, 2769–2775.

(8) Unfortunately there were several errors in our report (ref 1) on the element effect for pyrrolidine substitution reactions of hydroximoyl halides. In Table II of ref 1 the reported first-order and second-order rate constants for the (*Z*)-*O*-methyl-*p*-nitrobenzohydroximoyl bromide (**3g** in ref 1) should all be increased by a factor of 10. Furthermore, the element effect reported for the substitution in pyrrolidine in the absence of solvent was carried out on the (*Z*)-*O*-methylbenzohydroximoyl bromide (**3f** in ref 1) and the chloride (**3a** in ref 1) and not the *p*-nitro derivative (**3g**) as reported in the second paragraph on page 3350 and in Table I of ref 1 (in Table I, **3g** should be replaced by **3f**).

(9) (a) Hoffman, H. M. R. *J. Chem. Soc.* **1965**, 6753–6761. (b) Stirling, C. J. M. *Acc. Chem. Res.* **1979**, 198–203. (c) Klumpp, G. W. *Reactivity in Organic Chemistry*; Wiley: New York, 1982; p 189.

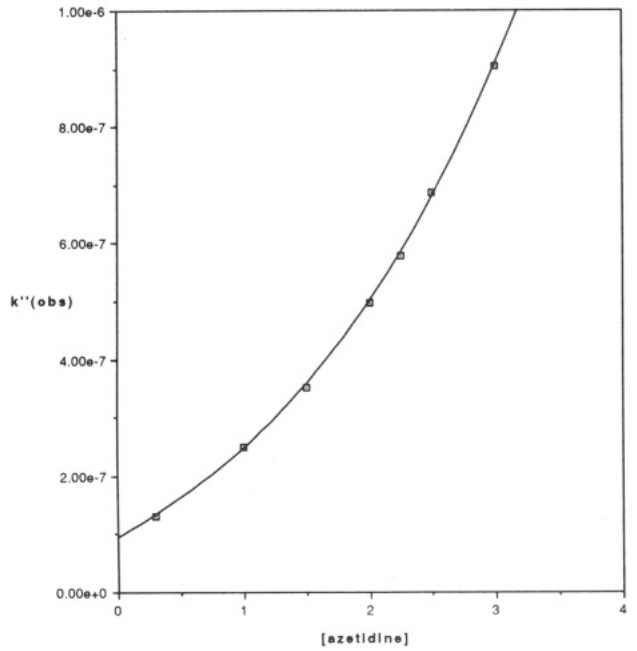


Figure 1. Plot of the second-order rate constants (k''_{obs}) vs [azetidine] for the reaction of (*E*)-*O*-methyl-*p*-nitrobenzohydroximoyl chloride (**2Ea**) with azetidine in benzene at 32.0 °C.

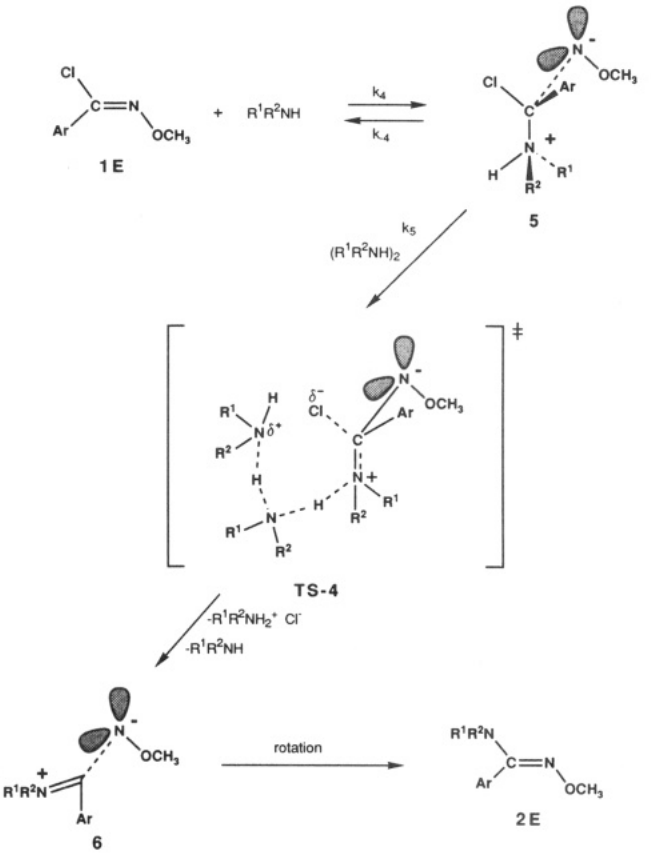
halogen bond were only slightly elongated in the transition state.[4c] In a direct displacement, however, the third-order process (TS-1 and TS-3 in Scheme I) becomes a termolecular step. Although the entropic disadvantage of a termolecular step could be overcome by prior association of the amine molecules with the hydroximoyl halide, we still prefer the addition–elimination mechanism shown in Scheme I.

The reactions of the (*E*)-hydroximoyl chlorides **1Ea** and **1Eb** with azetidine are considerably slower ($k_{1Za}/k_{1Ea} \cong 160$ and $k_{1Zb}/k_{1Eb} \cong 120$) than the reactions with the *Z* isomer. Furthermore, a plot of the second-order rate constants k''_{obs} vs. azetidine concentration for **1Ea** is curved upward (Figure 1). If one assumes that the curvature is due to a contribution from a fourth-order term, a plot of the first-order rate constants vs amine concentration for **1Ea** can be fitted by a nonlinear regression analysis to the experimental data. Using this analysis of the data the (*E*)-hydroximoyl chloride appears to be reacting mainly through a second-order and fourth-order pathway (Table II). The plot of k''_{obs} vs azetidine concentration for the (*E*)-*p*-chlorobenzohydroximoyl chloride (**1Eb**) reaction also appears to be upwardly curved. Although there is insufficient data for a complete analysis (only three points), a plot of k''_{obs} vs [azetidine]^2 is linear and the estimated second-order and fourth-order rate constants for this reaction are included in Table II.

Rate equations with a fourth-order term (third-order in amine) have been observed in some aromatic nucleophilic substitution reactions with amine nucleophiles in nonpolar solvents. Nudelman and her co-workers[10] have attributed this observation to the reaction of an amine dimer in the first step of the reaction (Scheme III, reaction pathway A where S = starting material, I(1) = an intermediate, and P = product) to form a zwitterionic intermediate (Meisenheimer complex). This intermediate then breaks down with the assistance of another amine molecule. The exact role of this third amine molecule in the breakdown of the intermediate has not been specified.

(10) Nudelman, N. S. *J. Phys. Org. Chem.* **1989**, *2*, 1–14.

Scheme II



Scheme III

Pathway A

$$2\ R^1R^2NH \rightleftharpoons (R^1R^2NH)_2 \quad \text{amine dimer}$$

$$S + (R^1R^2NH)_2 \rightleftharpoons I(1)$$

$$I(1) + R^1R^2NH \longrightarrow P$$

Pathway B

$$S + R^1R^2NH \rightleftharpoons I(2)$$

$$I(2) + 2\ R^1R^2NH \longrightarrow P$$

Pathway C

$$2\ R^1R^2NH \rightleftharpoons (R^1R^2NH)_2$$

$$S + R^1R^2NH \rightleftharpoons I(2)$$

$$I(2) + (R^1R^2NH)_2 \longrightarrow P$$

Banjoko and co-workers[11,12] have also observed this kinetic behavior in certain aromatic nucleophilic substitution reactions. Banjoko has argued, however, that at the relatively low amine concentrations used for these reactions, amine dimers should be in very low concentration and therefore should not be important. He proposes a

(11) Banjoko, O.; Ezeani, C. *J. Chem. Soc., Perkin Trans. 2* **1986**, 531–536.

(12) Banjoko, O.; Bayeroju, I. A. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1853–1857.

mechanism (pathway B in Scheme III) in which the intermediate reacts with two monomeric amine molecules. One of these amine molecules assists in deprotonating the ammonium ion nitrogen in the intermediate and the other assists in the departure of the nucleofuge. Banjoko has stated that the second step of this reaction is not a true termolecular process because the two amine molecules could be hydrogen bonded to the substrate prior to the nucleophilic attack.

Another possible interpretation of the observation of a fourth-order term in aromatic nucleophilic substitution involves nucleophilic attack by monomeric amine in the first step followed by reaction of an amine dimer with the zwitterionic intermediate (Scheme III, pathway C). Apparently this mechanism has never been proposed for aromatic nucleophilic substitution.[14]

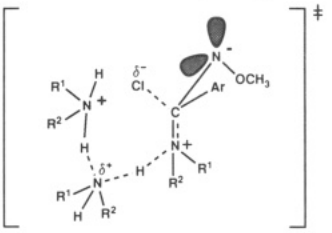
Nudelman[10] has recently reviewed these mechanistic proposals and has presented arguments in favor of the mechanism where an amine dimer undergoes nucleophilic attack in the first step (Scheme III, pathway A). Nudelman points out that quantitative measurements have shown that dimers are in relatively high concentration in nonpolar solutions of amines.

Hirst et. al[13,14] have given another explanation for the upward curvature of the plots of the observed second-order rate constants vs amine concentration (similar to our plot in Figure 1) in aromatic nucleophilic substitution reactions. They suggest that the curvature is due to electrophilic catalysis of the departure of the leaving group by the homoconjugate acid of the amine, $R^1R^2NH_2^+---HR^1R^2N$.

In our view, pathway A is flawed when it is applied to the reactions of hydroximoyl chlorides with amines. It is difficult to envision why nucleophilic attack by an amine dimer would be preferred in the reaction of the *E* isomer of a hydroximoyl chloride and not in the *Z* isomer.

For the reactions of (*E*)-hydroximoyl chlorides with amines, we prefer a mechanism where nucleophilic attack involves monomeric amine followed by reaction of an amine dimer with the tetrahedral intermediate. This seems reasonable because the tetrahedral intermediate from the (*E*)-hydroximoyl chloride is not in a conformation that would allow stereoelectronically assisted elimination of chloride ion, i.e., there is no electron pair in the tetrahedral intermediate **5** (Scheme II) that is antiperiplanar to the nucleofuge.[15-17] We suggest that the breakdown of the tetrahedral intermediate **5** in Scheme II is assisted by the amine dimer which can deprotonate the ammonium ion nitrogen of **5** and also assist in the departure of the nucleofuge (shown in TS-4). As one of the nitrogen atoms of the amine dimer is deprotonating the ammonium ion nitrogen, the second nitrogen atom of the dimer, which is becoming positively charged, assists in the departure of the chloride ion through electrostatic attraction (electrophilic assistance). This assistance should be especially important in a nonpolar solvent such as benzene where ionic species exist as ion pairs.[18] The ylide **6** produced by elimination of the elements of hydrogen chloride from the tetrahedral intermediate could then undergo rotation and rehybridization of the tetrahedral nitrogen to form the product **2E**.

Alternatively, the homoconjugate acid of the amine could deprotonate the ammonium ion nitrogen as well as provide assistance for nucleofuge departure (TS-5). In



TS-5

another possible mechanism[19] (Scheme IV) an amine dimer could trap the unstable zwitterionic intermediate **5** by transferring a proton from the ammonium ion nitrogen to the negatively charged nitrogen (TS-6) to give a neutral tetrahedral intermediate **7A**. Bond rotation followed by stereoelectronically assisted elimination of chloride ion would give the resonance-stabilized iminium ion **8**.

The tetrahedral intermediate **3** formed from the (*Z*)-hydroximoyl chloride differs from the intermediate **5** in the reaction of the *E* isomer in that **3** has an electron pair antiperiplanar to the nucleofuge. We suggest that the tetrahedral intermediate **3** does not require the extra assistance for nucleofuge expulsion given by an amine dimer (or the homoconjugate acid of the amine).

The results reported herein do not allow us to select among the mechanistic alternatives for the reaction of azetidine with **1E**. It seems reasonable, however, that the difference in stereochemistry, reaction rates, and the kinetic equations for the reaction of azetidine with **1Z** and **1E** should be attributed to different reaction mechanisms for the geometric isomers.

Although the reactions of **1Z** and **1E** with azetidine in benzene solution are stereospecific, the experimental evidence indicates that these reactions are proceeding by $A_N + D_N$ mechanisms with tetrahedral intermediates which could lose their stereochemical integrity by rotation about the carbon–nitrogen single bond. In order for the tetrahedral intermediates **3** and **5** to maintain their stereochemical integrity, nucleofuge expulsion must be faster than carbon–nitrogen bond rotation. It has been suggested previously[1] that the rate constants for loss of the attacking amine (k_{-1} for **3** and k_{-4} for **5**) from these tetrahedral intermediates could be as much as 2 orders of magnitude greater than the rate constants for carbon–nitrogen bond rotation.

The concentrations of amine used in the kinetic measurements reported in this work ranged from 0.300 to 3.00 M. These are relatively high concentrations of amine as compared to those typically used in kinetic studies on aromatic nucleophilic substitution reactions. Work is in progress to prepare systems that are more reactive toward nucleophilic substitution so that kinetic measurements can be made at lower amine concentrations.

Experimental Section

General Methods. The benzene was spectrophotometric grade and was stored over 4A molecular sieves. The hydroximoyl halides **1Za–e** and **1Ea–c** were prepared according to published procedures.[5a,20,21] The amidoximes were isolated by reaction of a (*Z*)-

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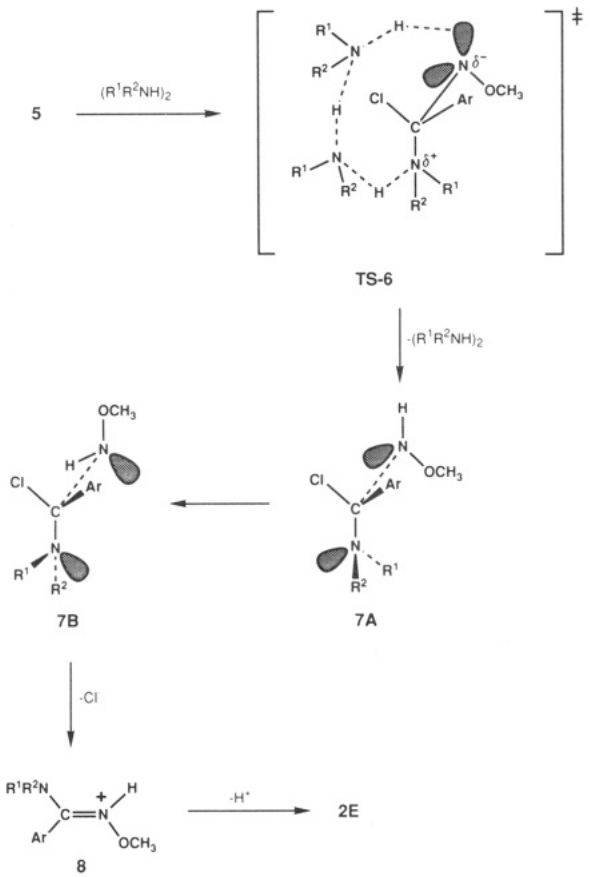
Table VI. Properties of Benzamidoximes $YC_6H_4C(NR^1R^2)=NOCH_3$[a]

no.	mp, °C	NMR, δ ($CDCl_3$)[b] α-CH_2	β- and σ-CH_2	Ar	OCH_3	IR principal absorptions,[c] cm^{-1}	UV max, nm (log ε)[d]
2Za	102–104[k] (ether–hexane)	4.16[f]	2.26[g]	7.58, 8.22[h]	3.81 (s)	1600, 1610, 1630	258 (4.07), 343 (3.29)
2Zb	51–53 (ether–hexane)	4.12[f]	2.20[g]	7.38	3.72 (s)	1580, 1620	224 (4.26), 266 (3.55)
2Zc	*e*	4.22[f]	2.26[g]	7.50	3.79 (s)	1580, 1610	218 (4.11), 264 (3.38)
2Zd	*e*	4.08[f]	2.12[g]	7.18, 7.30[h]	3.70 (s), 2.32 (s)[i]	1570, 1615	218 (4.15), 259 (3.66)
2Ze	*e*	4.14[f]	2.19[g]	6.86, 7.30[h]	3.79 (s), 3.70 (s)	1610	
2Zg	110–111[o] (methanol)	3.80[f]	3.38[f]	7.81, 8.40[h]	3.91 (s)	1580, 1595, 1611[j]	
2Ea	*k, l*	3.73[f]	2.26[g]	7.61, 8.25[h]	3.71 (s)		
2Eb	*m*	3.71[f]	2.20[g]	7.38	3.69 (s)		
2Ec	*n*	3.80[f]	2.26[g]	7.45	3.76 (s)		
2Ed	*o*	3.08[f]	2.12[g]	ca. 7.20	3.67 (s), 2.32[i]		

[a] Satisfactory elementary analyses (C, H, and N for all except **2Zb** and **2Eb** where C, H, N, and Cl were determined) were obtained for all compounds listed in this table. [b] Unless otherwise noted the ^{1}H-NMR spectra were determined on a Varian EM-390 spectrometer. [c] The IR spectra were determined on thin films of the neat liquids or as KBr pellets of the solids. [d] The UV spectra were determined on 95% ethanol solutions. [e] A liquid that isomerizes to a mixture of the *Z* and *E* isomers on vacuum distillation. The microanalyses and spectroscopic measurements were carried out on the undistilled product. [f] Triplet. [g] Quintet. [h] Centers of each doublet of an AA^1BB^1 quartet. [i] $ArCH_3$. [j] Mineral oil mull. [k] NMR spectrum determined with a General Electric GN500 NMR spectrometer. [l] NMR spectrum determined on a mixture of 42% and 58% Z. [m] NMR spectrum determined on a mixture of 76% *E* and 24% *Z*. [n] NMR spectrum determined on a mixture of 44% *E* and 56% *Z*. [o] NMR spectrum determined on a mixture of 25% *E* and 75% *Z*.

Scheme IV



or (*E*)-hydroximoyl chloride (**1Z** or **1E**) with the amine in the absence of solvent as previously described.[1] The amines used in this study were purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI) and were freshly distilled before each kinetic run. The kinetic measurements were made with a Gilford modified Beckman DU-2. Ultraviolet spectra were measured on a Cary 15 and infrared spectra were determined with a Pye Unicam SP-1100 spectrophotometer. Melting points were carried out on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. The HPLC analyses were carried out on an apparatus made up of a Spectra Physics IsoChrom pump, an ISCO μLC-10 variable wavelength UV/vis detector fitted with a 10-mm pathlength cell, a Rheodyne injector, and a Spectra Physics SP4270 integrator. Elemental analyses were performed at Atlantic Microlab. The ultraviolet, infrared, and ^{1}H-NMR spectra for all the new amidoximes prepared in this study are in Table VI. The properties of the amidoximes **2Zf** and **2Zh** have been reported previously.[1]

Product Analysis of the Reaction of (*Z*)-*O*-Methyl-*p*-nitrobenzohydroximoyl Chloride (1Ea) with Azetidine in Benzene. A benzene solution of **1Ea** (8.0×10^{-3} M) and azetidine (3.00–5.00 M) contained in a 2.00-mL volumetric flask was placed in a constant temperature bath at 32.0 °C. At appropriate times, approximately 1 mL of the solution was removed from the reaction vessel. The benzene and excess azetidine were evaporated from this sample on a rotary evaporator at aspirator pressure. The residue was dissolved in 73 μL of acetonitrile. Approximately 15 μL of this solution was injected into a Hamilton PRP column using 35:60:5 (v/v/v) acetonitrile, water, and concd ammonium hydroxide as the mobile phase. The HPLC normalization factor for the (*Z*)- and (*E*)-amidoximes (**2Za** and **2Ea**) was calculated from peak areas obtained by HPLC analysis of a sample of known *Z*/*E* ratio (from the ^{1}H-NMR spectrum). The samples were analyzed at a detector wavelength of 262 nm.

Kinetic Method. Separate benzene solutions of the hydroximoyl halide and the amine were kept in a constant temperature bath at 32.0 ± 0.1 °C. Three milliliters of the azetidine solution and 0.250 mL of the hydroximoyl halide were pipetted into a 1-cm quartz cell using a 3-mL volumetric pipette and a 0.250-mL fixed volume micropipettor, respectively. The quartz cell was stoppered with a round Teflon stopper. The quartz cell was then shaken and placed in a thermostated (32.0 ± 0.2 °C) cell chamber of the spectrophotometer. The temperature of the solution in the cell was monitored with a Cole-Parmer Model 8502-20 centrigrade thermometer which had been calibrated with a Hewlett Packard Model 2804A quartz thermometer. Amidoxime formation was followed by monitoring the increase in absorbance at 315 nm for **2Zb**, 320 nm for **2Zc**, 345 nm for **2Eb**, and 410 nm for **2Za**, **2Ea**, **2Zf**, and **2Zg**.

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Supplementary Material Available: Elemental analyses for the benzamidoximes (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(21) Johnson, J. E.; Nalley, E. A.; Kunz, Y. K.; Springfield, J. R. *J. Org. Chem.* **1976**, *41*, 252–259. The *Z*/*E* assignments for **1Z** and **1E** in this paper are incorrect and must be reversed.