= 6 Hz); ^{19}F NMR -186.5 ppm (m); MS, *m/e* 173 [(M - CH_2O - *i*-Pr)$^+$]. Anal. Calcd for $C_{15}H_{31}FO$: C, 73.17; H, 12.60. Found: C, 73.05; H, 12.62. Similar results were obtained when trifluoroethanol was used, producing the β-fluorododecyl β,β,β-trifluoroethyl ether (**54**): oil; 55% yield (75% conversion); ^{1}H NMR δ 4.65 (CHF, 1 H, dm, J_{HF} = 49 Hz), 3.95 (OCH_2CF_3, 2 H, q, J_{HF} = 12 Hz), 3.5-4.0 (CH_2O, 2 H, m) 0.85-1.80 (21 H, m); ^{19}F NMR -75 (CH_3, 3 F, t, J_{HF} = 12 Hz), -186.5 ppm (CHF, 1 F, m); MS, *m/e* 173 [(M - $CH_2OCH_2CF_3$)$^+$]. Anal. Calcd for $C_{14}H_{26}F_4O$: C, 59.74; H, 9.09. Found: C, 60.43, H, 9.52. The ethyl ether **55** was also synthesized by this method in 60% yield (60% conversion): ^{1}H NMR δ 4.62 (CHF, 1 H, dm, J_{HF} = 49 Hz), 3.33-3.70 (CH_2O, 4 H, m), 0.81-1.65 (24 H, m); ^{19}F NMR -186.5 ppm (m); MS, *m/e* 173 [(M - CH_2OEt)$^+$]. Anal. Calcd for $C_{14}H_{29}FO$: C, 72.41; H, 12.50. Found: C, 71.60; H, 12.05. This compound could also be prepared by refluxing **4** and NaOEt for 16 h in 85% yield. The methyl ether **56** (oil) could also be prepared from **4** and BrF in similar conditions as described above in 70% yield: ^{1}H NMR δ 4.62 (CHF, 1 H, dm, J_{HF} = 48 Hz), 3.51 (CH_2O, 2 H, dd, $^3J_{HF}$ = 20 Hz, J_{HH} = 4.5 Hz), 3.4 (OCH_3, 3 H, s), 0.85-1.80 (21 H, m); ^{19}F NMR -186 ppm (m); MS, *m/e* 173 [(M - CH_2OCH_3)$^+$]. Anal. Calcd for $C_{13}H_{27}FO$: C, 71.56; H, 12.39. Found: C, 71.37; H, 12.79.

Acknowledgment. We thank the Fund for Basic Research, administrated by The Israel Academy of Science and Humanities, for supporting this research.

Registry No. **1**, 111-66-0; **2**, 112-41-4; *dl*-**3**, 97211-45-5; *dl*-**4**, 97211-46-6; *dl*-**5**, 26489-02-1; **6**, 97211-47-7; **7**, 110-83-8; *dl*-**8**, 97211-48-8; *dl*-**9**, 1195-31-9; *dl*-**10**, 97211-49-9; **11**, 604-35-3; **12**, 2560-88-5; **13**, 57-83-0; **14**, 97211-50-2; **15**, 103-30-0; *meso*-**16**, 14090-31-4; *dl*-**17**, 52795-54-7; **18**, 645-49-8; **19**, 833-81-8; *dl*-**20**, 97211-51-3; *dl*-**21**, 97211-52-4; **22**, 20488-42-0; *dl*-**23**, 97211-53-5; *dl*-**24**, 97234-64-5; **25**, 628-92-2; **26**, 77517-69-2; **27**, 97211-54-6; **28**, 97211-55-7; **29**, 97211-56-8; *dl*-**30**, 97211-57-9; *dl*-**31**, 60886-86-4; *dl*-**32**, 97211-58-0; *dl*-**33**, 97211-59-1; **34**, 3724-55-8; *dl*-**35**, 97211-60-4; *dl*-**36**, 97211-61-5; *dl*-**37**, 59982-09-1; *dl*-**38**, 59974-31-1; **39**, 91-64-5; **40**, 82470-30-2; **41**, 82470-31-3; **42**, 82451-75-0; **43**, 939-18-4; **44**, 930-30-3; **45**, 82470-32-4; **46**, 10481-34-2; **47**, 55106-05-3; **48**, 84983-52-8; **49**, 97211-62-6; **50**, 97211-63-7; **51**, 97211-64-8; *dl*-**52**, 97211-65-9; *dl*-**53**, 97211-66-0; *dl*-**54**, 97211-67-1; *dl*-**55**, 97234-65-6; *dl*-**56**, 97234-66-7; IF, 13873-84-2; I_2, 7553-56-2; F_2, 7782-41-4; BrF, 13863-59-7; Br_2, 7726-95-6; *t*-BuOH, 75-65-0; EtOH, 64-17-5; *i*-PrOH, 67-63-0; CF_3CF_2OH, 75-89-8; NaOEt, 141-52-6; MeOH, 67-56-1.

Mechanism of Amine and Amide Ion Substitution Reactions at the Carbon-Nitrogen Double Bond

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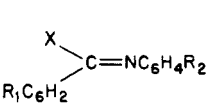
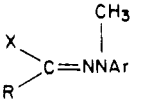
Received January 28, 1985

Reactions of the (*Z*)-hydroximoyl chlorides **3a-e** with secondary amines without solvent at 32 °C for 24 h give high yields of (*Z*)-benzamidoximes **7a-f**. Although the amidoximes **7a-f** do not isomerize under the reaction conditions, they isomerize to the *E* isomers (**8a-f**) by refluxing them in dioxane. Under the same reaction conditions, the (*E*)-hydroximoyl chlorides **4a** or **4b** give no detectable product with secondary amines even after 2 days at 32 °C. In benzene solution the reactions of pyrrolidine with (*Z*)-hydroximoyl chlorides **3a-d** contain both first- and second-order terms in amine. The amine-catalyzed process gives a Hammett correlation with σ with a ρ value of +1.06. The uncatalyzed process is insensitive to changes in para substituents in **3** ($\rho \simeq 0$). The reaction of pyrrolidine with the hydroximoyl bromide **3g** gives an element effect (k_{Br}/k_{Cl}) of 10.1 for the catalyzed process and 26.9 for the uncatalyzed pathway. Lithium pyrrolidide in a benzene-hexane solution reacts rapidly with both **3a** and **4a** (relative reaction rate of **3a**/**4a** = 6 at 21 °C). The reaction of **3a** gives only the (*Z*)-amidoxime **7a** whereas the (*E*)-hydroximoyl chloride **4a** gives a 57:43 mixture of the (*Z*)- and (*E*)-amidoximes (**7a** and **8a**). These results are consistent with a stereoelectronically controlled nucleophilic addition-elimination mechanism for the reaction of **3a** or **4a** with secondary amines and their conjugate bases.

Extensive studies have been carried out on the mechanisms of bimolecular nucleophilic reactions at the C=O and activated C=C bonds, but there are relatively few studies on bimolecular nucleophilic reactions at the C=N bond. A detailed kinetic study on bimolecular substitution at the C=N bond has been carried out by Ta-Shma and Rappoport[1-3] on the reactions of diaryl imidoyl chlorides (**1a**) with secondary amines in benzene[3] or acetonitrile.[2] Depending on the solvent and the nature of the substituents on the aromatic ring attached to carbon, they suggested a pathway involving a nitrilium ion intermediate or a nucleophilic addition-elimination mechanism. The stereochemistry of the imidoyl chloride reactions could not be determined because the *Z* and *E* isomers of these compounds and their substitution products are not known.



1a, X = Cl
b, X = CN



2a, X = Cl
b, X = Br
c, X = OCH_3
d, X = SAr
e, X = OAr

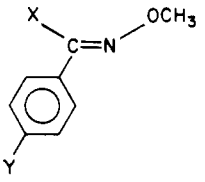
Besides our work,[5,6] two other full reports have appeared on the stereochemistry of bimolecular substitution at the

(1) Ta-Shma, R.; Rappoport, Z. *Tetrahedron Lett.* **1971**, 3813-3816.
(2) Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1976**, *98*, 8460-8467.
(3) Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1977**, *99*, 1845-1858.
(4) Ta-Shma, R.; Rappoport, Z. *J. Chem. Soc., Perkin Trans. 2* **1977**, 659-667.
(5) Johnson, J. E.; Nalley, E. A.; Weidig, C. *J. Am. Chem. Soc.* **1973**, *95*, 2051-2052.
(6) Johnson, J. E.; Nalley, E. A.; Weidig, C.; Arfan, M. *J. Org. Chem.* **1981**, *46*, 3623-3629.

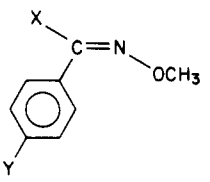
0022-3263/85/1950-3348$01.50/0

C=N bond. Hegarty et al.[7,8] found that (*Z*)-hydrazonyl halides **2a** and **2b** react with methoxide ion to give only (*Z*)-hydrazonate **2c**. Unfortunately, (*E*)-hydrazonyl halides are not configurationally stable; consequently, it has not been possible to study the stereochemistry and kinetics of the reaction of methoxide ion with the *E* isomers of **2a**. In a recent study Rowe and Hegarty[9] have investigated the stereochemistry and kinetics of methoxide ion substitution in both the *Z* and *E* isomers of aryl thiohydrazonates (**2d**), the *Z* isomers of hydrazonyl chlorides (**2a**), and the *Z* isomer of an aryl hydrazonate (**2e**). Their results are similar to ours[5,6] although the reactions of (*Z*)-**2d** and (*Z*)-**2e** were not as highly stereospecific as the reactions we have reported.

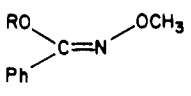
Our recent report[6] concerned the stereochemistry and mechanism of bimolecular substitution reactions of the *Z* and *E* isomers of *O*-methylbenzohydroximoyl chloride (**3a** and **4a**) and ethyl *O*-methylbenzohydroximate (**5a** and **6a**) with methoxide ion in a 90% dimethyl sulfoxide–10% methanol solution. A dramatic difference was observed in the *Z*/*E* ratios for the two systems (**3a**/**4a** = 0.87; **5a**/**6a** = 290). The reaction of the (*Z*)-hydroximoyl chloride **3a** with methoxide ion gave almost exclusive formation of the (*Z*)-hydroximate **5b**. The (*E*)-hydroximoyl chloride **4a**, however, gave a mixture of the (*Z*)- and (*E*)-hydroximates **5b** and **6b** with **6b** predominating (**5b**:**6b** = 27:73). Reaction of methoxide ion with ethyl (*Z*)-*O*-methylbenzohydroximate (**5a**) gave only the *Z* isomer of the methyl hydroximate (**5b**). The slow reaction of methoxide ion with the (*E*)-hydroximate **6a** initially gave **5b** which slowly isomerized to **6b** during the course of the reaction. We have applied Deslongchamps' theory of stereoelectronic control[10] to explain the stereochemistry and the large difference in *Z*/*E* rate ratios between the two systems.



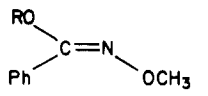
3a X = Cl; Y = H
b, X = Cl; Y = NO_2
c, X = Cl; Y = CH_3
d, X = Y = Cl
e, X = Cl; Y = OCH_3
f, X = Br; Y = H
g, X = Br; Y = NO_2



4a, X = Cl; Y = H
b, X = Cl; Y = NO_2



5a, R = C_2H_5
b, R = CH_3

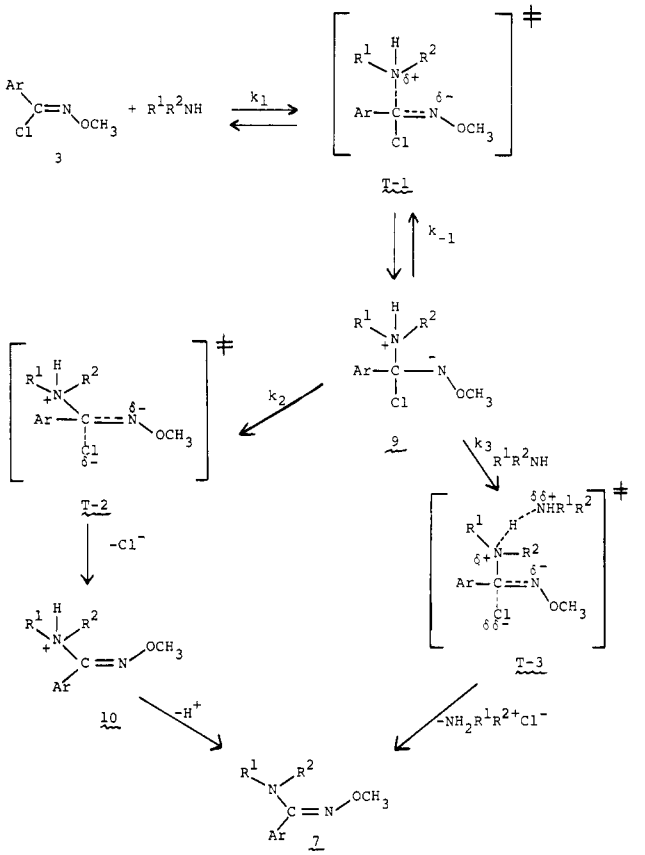


6a, R = C_2H_5
b, R = CH_3

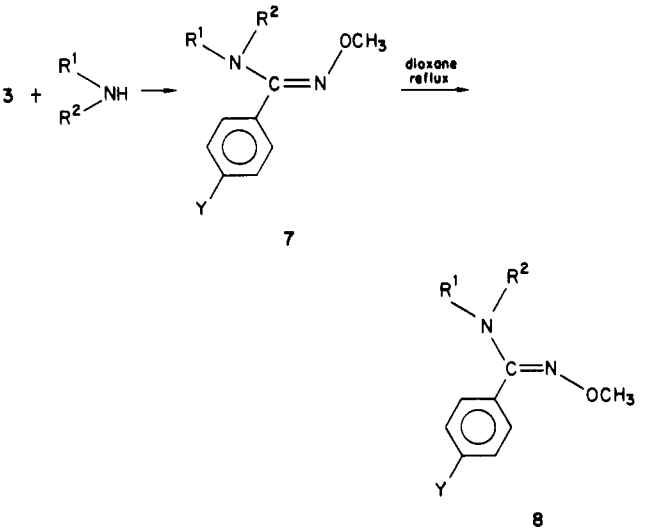
Results

In a continuation of our investigations on the stereochemistry and mechanisms of nucleophilic substitution at the carbon–nitrogen double bond, we now report on the reactions of amines and their conjugate bases (amide ions) with the *Z* and *E* isomers of *O*-methylbenzohydroximoyl chlorides (**3** and **4**). Reactions of the (*Z*)-hydroximoyl

Scheme I



chlorides (**3**) with secondary amines (mole ratio of **3**:amine = 1:20) without solvent[11] at 32 °C for 24 h give high yields (>85%) of (*Z*)-benzamidoximes **7a–f**. Although **7a–f** do not isomerize under the reaction conditions, they isomerize completely (or nearly completely) to the *E* isomers (**8a–f**) by refluxing them in dioxane from 8 to 48 h.[12–14]



7

8

(7) McCormack, M. T.; Hegarty, A. F. *Tetrahedron Lett.* **1976**, 395–396.
(8) Hegarty, A. F.; McCormack, M. T.; Hathaway, B. J.; Hulett, L. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1136–1141.
(9) Rowe, J. E.; Hegarty, A. F. *J. Org. Chem.* **1984**, *49*, 3083–3087.
(10) (a) Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon: Elmford, NY, 1983. (b) For an alternate viewpoint see: Hosie, L.; Marshall, P. J.; Sinnott, M. L. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1121–1131.
(11) The reactions of **3a** and **3b** with amines to give **7** have also been carried out in solvents (dimethyl sulfoxide, benzene, or anhydrous ether). The (*E*)-hydroximoyl chlorides **4a** and **4b** do not react with amines in any of these solvents.
(12) Equilibrium mixtures of *Z* and *E* isomers were obtained in many of the isomerizations: **7c**:**8c** = 12.88; **7d**:**8d** = 13:87; **7e**:**8e** = 12:88; **7f**:**8f** = 12:88. The (*Z*)-amidoxime **7f** slowly isomerizes in the solid state to the *E* isomer **8f**. After more than one year at room temperature, **7f** had isomerized completely to **8f**.
(13) Similar isomerizations have been reported: Dignam, K. J.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1437–1443.

	R^1	R^2	Y
7 or 8a	$-(CH_2)_4-$		H
7 or 8b	$-(CH_2)_4-$		NO_2
7 or 8c	$-(CH_2)_4-$		CH_3
7 or 8d	$-(CH_2)_4-$		Cl
7 or 8e	$-(CH_2)_4-$		OCH_3
7 or 8f	$-(CH_2)_5-$		NO_2
7g	CH_3	H	H
7h	CH_3	H	NO_2
7i	n-C_4H_9	H	NO_2

Primarily amines also react with **3a** or **3b** to give (*Z*)-amidoximes[17] (**7g–i**), but in these cases the (*Z*)-amidoximes do not thermally isomerize to the *E* isomers. Under the same reaction conditions the (*E*)-hydroximoyl chlorides **4a** or **4b** give no detectable product with primary or secondary amines even after two days at 32 °C. These results are remarkabe considering that **3a** and **4a** react at almost identical rates with methoxide ion.[6]

In our initial kinetic work on these reactions, the pyrrolidine substitution reactions of **3a–e** were carried out with no added solvent and were followed by ^{1}H NMR spectroscopy. The pseudo-first-order rate constants (Table I) for substitution of **3a–e** with pyrrolidine were measured and a good correlation (ρ = +1.13, r = 0.999) of log k_{obsd} was obtained with σ. A substantial element effect was observed for the reactions of the *p*-nitro derivatives **3b** and **3g** with pyrrolidine [k(**3g**)/k(**3b**) = 11.3].

In benzene solution (by a spectrophotometric method) with excess pyrrolidine, the pseudo-first-order rate constants (k'_{obsd}, Table II) increase with amine concentration according to the following equation:

$$k'_{obsd} = k''[\text{pyrrolidine}] + k'''[\text{pyrrolidine}]^2$$

The derived second-order (k″) and third-order (k‴) rate constants (Table III) were obtained from plots of the observed second-order rate constants k''_{obsd} (k''_{obsd} = k'_{obsd}/[pyrrolidine]) vs. pyrrolidine concentration. The second-order rate constant (k'') is insensitive to changes in para substituents ($\rho \simeq 0$), whereas the third-order rate constants (k''') give a ρ value of +1.06 (r = 0.983) with σ.[18] Both the second-order (k'') and third-order (k''') rate constants for the *p*-nitro derivatives **3b** and **3g** show an element effect, but the element effect on the second-order process is 2.7 times larger than on the third-order term [k''(**3g**)/k''(**3b**) = 26.9; k'''(**3g**)/k'''(**3b**) = 10.1].

It is clear from the magnitude of the third-order terms (Table III), that the pseudo-first-order rate constants measured in pure pyrrolidine (Table I) represent only the third-order term. It is gratifying that the element effect and the Hammett ρ value for the third-order process (k''') are, within experimental error, identical with the values obtained in pure pyrrolidine.

It is possible that the third-order term in our kinetics is due only to an increase in the dielectric constant of the medium as the concentration of pyrrolidine is increased. In order to investigate this possibility, rates of pyrrolidine

Table I. Pseudo-First-Order Rate Constants k_{obsd} for the Reaction of (*Z*)-*O*-Methylbenzohydroximoyl Chlorides with Pyrrolidine in the Absence of Solvent at 32.0 °C

no.	10^4k, s^{-1}	no.	10^4k, s^{-1}	no.	10^4k, s^{-1}
3b	14.8	**3a**	1.80	**3e**	0.970
3d	3.63	**3c**	1.22	**3g**	20.3

Table II. Pseudo-First-Order Rate Constants k'_{obsd} and Second-Order Rate Constants k''_{obsd} for the Reactions of (*Z*)-*O*-Methylbenzohydroximoyl Halides with Pyrrolidine in Benzene at 32.0 °C

no.[a]	10^2[pyrrolidine], M	$10^6k'_{obsd}$, s^{-1}	$10^6k''_{obsd}$, M^{-1} s^{-1}
3b	0.305	0.992	3.25
3b	0.500	1.75	3.50
3b	0.889	5.03	5.66
3b	1.14	7.89	6.92
3b	1.34	10.6	7.91
3b	1.54	14.1	9.22
3b	1.81	18.8	10.5
3b	2.09	24.9	11.9
3b	2.24	28.6	12.8
3d	0.500	1.17	2.34
3d	0.615	1.64	2.67
3d	0.876	2.68	3.06
3d	1.10	3.94	3.63
3d	1.34	5.19	3.87
3d	1.70	8.14	4.79
3d	1.86	9.65	5.19
3d	2.26	12.8	5.66
3a	1.38	2.79	2.02
3a	1.54	3.30	2.14
3a	1.83	4.23	2.31
3a	1.89	4.48	2.37
3a	2.24	5.81	2.59
3a	2.64	7.10	3.06
3a	3.62	12.6	3.48
3c	1.00	1.59	1.59
3c	1.30	2.28	1.75
3c	1.71	3.32	1.95
3c	2.40	5.70	2.38
3c	2.60	6.55	2.52
3c	2.90	7.80	2.69
3g	0.156	0.647	4.12
3g	0.306	1.54	5.03
3g	0.495	2.97	6.00
3g	0.710	4.73	6.66
3g	0.876	6.85	7.81
3g	1.15	10.8	9.39
3g	1.30	12.7	9.77
3g	1.54	17.7	11.5

[a] Concentration varied from 8 × 10^{-3} M to 2 × 10^{-2} M. The pseudo-first-order rate constants k'_{obsd} were independent of hydroximoyl halide concentration.

Table III. Second-Order (k') and Third-Order (k'') Rate Constants for the Reaction of (*Z*)-*O*-Methylbenzohydroximoyl Chlorides with Pyrrolidine in Benzene at 32.0 °C

no.	$10^6k''$, M^{-1} s^{-1}	$10^6k'''$, M^{-2} s^{-1}	k'''/k'', M^{-1}	correl coef[a]
3b	1.23	5.13	4.17	0.998
3d	1.42	1.93	1.12	0.996
3a	1.10	0.668	0.607	0.989
3c	0.982	0.586	0.596	0.999
3e		0.41[b]		
3g	33.1	51.7	1.56	0.997

[a] Correlation coefficients for the plot of k''_{obsd} vs. pyrrolidine concentration. [b] Estimated from the kinetic data in Table I (see ref 18).

(14) The configurations of the amidoximes **7a–f** and **8a–f** were assigned on the basis of their ^{1}H NMR spectra, i.e., the methoxy singlet and the NCH_2 absorptions are farther downfield on the *Z* isomer than in the *E* isomer (ref 9, 13, 15, and 16).

(15) Johnson, J. E.; Springfield, J. R.; Hwang, J. S.; Hayes, L. J.; Cunningham, W. C.; McClaugherty, D. L. *J. Org. Chem.* **1971**, *36*, 284–294.

(16) Johnson, J. E.; Nalley, E. A.; Kunz, Y. K.; Springfield, J. R. *J. Org. Chem.* **1976**, *41*, 252–259. The stereochemical assignments for the (*Z*)- and (*E*)-hydroximoyl chlorides should be reversed in this paper.

(17) The configurations of **7g–i** are assumed to be *Z* in analogy with *p*-nitrobenzamidoxime which exists in the *Z* configuration: Arte, E.; Declerq, J. P.; Germain, G.; Van Meersche, M. *Bull. Soc. Chem. Belg.* **1978**, *87*, 573–578.

(18) Because the rate of the *p*-methoxy compound (**3e**) was too slow to follow in benzene solution, the k''' value for **3e** in benzene (Table III) was estimated by using the rate constant measured in pure pyrrolidine. The ratio of the first-order rate constant in the absence of solvent (k_{obsd} in Table I) and the derived third-order rate constant k''' (Table III) are approximately constant ($k_{obsd}/k''' = 238$) for compounds **3a–d**. The value of k''' for **3e** was estimated from this ratio.

Table IV. Dielectric Constant Effect on k''_{obsd} in the Reaction of Pyrrolidine with (*Z*)-*O*-Methyl-*p*-nitrobenzohydroximoyl Chloride (3b) in Benzene at 32.0 °C

[pyrrolidine], M	[C_6H_5Cl], M	$10^6 k''_{obsd}$, M^{-1} s^{-1}
1.14	0	6.92
1.14	0.674	7.43
1.14	0.953	7.55
1.14	1.10	7.72

substitution were measured for **3b** with added chlorobenzene which has a dielectric constant ($\epsilon = 5.71$)[19] close to cyclic secondary amines[20] (Table IV). The value of k''_{obsd} increased with increasing chlorobenzene concentration, but the increase due to the change in dielectric constant of the medium is only about 13% of the effect observed when the concentration of pyrrolidine was increased. Furthermore, it should be pointed out that k''' is greatest in the case of **3b** where the lowest concentrations of pyrrolidine were used in the rate measurements (compare **3b** to **3a** for example). This observation is inconsistent with dimerization of the pyrrolidine or some other association phenomenon as an explanation for the second-order term in pyrrolidine. We, therefore, conclude that a significant portion of the third-order term is due to amine catalysis.

To gain further insight into the mechanism of these reactions, we examined the reactivity of **3a** and **4a** with the conjugate bases of pyrrolidine and methylamine. Lithium pyrrolidide in a benzene–hexane mixture reacts rapidly with both the (*Z*)- and (*E*)-hydroximoyl chlorides (relative reaction rate of **3a**/**4a** = 6 at 21 °C). The reaction with the (*Z*)-hydroximoyl chloride **3a** gives only the (*Z*)-amidoxime **7a** whereas the (*E*)-hydroximoyl chloride **4a** gives a mixture of the (*Z*)- and (*E*)-amidoximes (**7a**:**8a** = 57:43). Similarly, **3a** and **4a** react rapidly with lithium methylamide (relative reaction rate of **3a**/**4a** = 4 at 21 °C) to give **7g**. No (*E*)-amidoxime is formed in the reaction of lithium methylamide with **4a**, but this result is probably due to a rapid isomerization of the (*E*)-amidoxime formed during the reaction.

Discussion

The kinetic results reported herein are consistent with a mechanism in which the (*Z*)-hydroximoyl chlorides (**3**) react with pyrrolidine through an addition–elimination process (Scheme I).[21] The initially formed dipolar tetrahedral addition product **9**, which is expected to be very unstable,[22a] expels chloride ion in either an uncatalyzed process (k_2) or in a process in which a pyrrolidine molecule assists by removing a proton from the positive nitrogen (k_3). The amine-catalyzed pathway plays an important mechanistic role in liberating an electron pair on nitrogen to facilitate leaving group expulsion and by avoidance of the unstable N-protonated amidoxime **10** and the unstable transition state **T-2** leading to its formation.[22]

Because of the instability of **10**, we suggest that the transition state **T-2** is approximately halfway between **9** and **10** with an equal negative charge on the chlorine and nitrogen atoms (both **9** and **10** are unstable intermediates). In the amine-catalyzed route, the transition state **T-3** should resemble the dipolar intermediate **9** more than the stable amidoxime **7**, i.e., **T-3** is an early transition state.

Assuming a steady-state concentration of the dipolar intermediate **9**, the rate equation for this mechanism is as follows:

$$\frac{d[7]}{dt} = \frac{k_1k_2[3][R^1R^2NH]}{k_{-1} + k_2 + k_3[R^1R^2NH]} + \frac{k_1k_3[3][R^1R^2NH]^2}{k_{-1} + k_2 + k_3[R^1R^2NH]}$$

If the rate constant for the reverse reaction is much larger than either k_2 or k_3 ($k_{-1} \gg k_2 + k_3[R^1R^2NH]$) the rate equation becomes:

$$\frac{d[7]}{dt} = \frac{k_1k_2[3][R^1R^2NH]}{k_{-1}} + \frac{k_1k_3[3][R^1R^2NH]^2}{k_{-1}}$$

Thus, the derived second-order (k'') and third-order (k''') rate constants are equal to:

$$k'' = \frac{k_1k_2}{k_{-1}}$$

$$k''' = \frac{k_1k_3}{k_{-1}}$$

The element effect observed on the derived second-order rate constant k'' of the *p*-nitro derivative ($k''_{3g}/k''_{3b} = 26.9$) is similar to that reported by Bender and Jones[23] for the reactions of morpholine with benzoyl halides in cyclohexane ($k_{Br}/k_{Cl} = 25$). Bender and Jones attributed this element effect to differences in rates of carbon–halogen bond breaking in the tetrahedral intermediate. In the mechanism outlined in Scheme I, only k_2 and k_3 should be subject to a significant element effect. If one assumes the ratio k_1/k_{-1} is approximately the same for the hydroximoyl chloride **3b** and the corresponding bromide **3g**, then the difference in the element effect between the second- and third-order processes should be due to differences in the sensitivity of k_2 and k_3 to the element effect.

The lower value for the element effect in the third-order process is consistent with an early transition state (**T-3**) with less carbon–halogen bond cleavage than in the second-order process (**T-2**). The second-order process, with a transition state (**T-2**) intermediate between **9** and **10**, should show a larger element effect than the amine-catalyzed pathway where the transition state (**T-3**) resembles reactants.

The substituent effects on the second- and third-order processes are also consistent with the addition–elimination mechanism shown in Scheme I. It would be expected that k_1 would not be affected much by substituents since the transition state for this step (**T-1**) has both a negative and positive charge approximately equidistant from the aromatic ring. For the same reasons the reverse process k_{-1} also should not be affected significantly by changes in substituents. It also seems reasonable that the value of ρ would be close to zero for the elimination process k_2 because the charge distribution in the transition state **T-2** is similar to that of intermediate **9**. Although the negative charge in transition state **T-2** is dispersed more than in intermediate **9**, the total negative charge and the positive

(19) Weissberger, A., Ed. "Techniques of Organic Chemistry, Vol. VII: Organic Solvents", 2nd ed.; Interscience: New York, 1955.

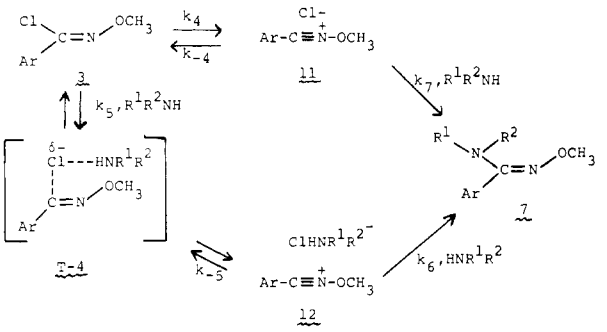
(20) The dielectric constant of pyrrolidine has not been reported, but the dielectric constants of piperidine ($\epsilon = 5.8$) and morpholine ($\epsilon = 7.33$) are known (ref 19).

(21) The addition–elimination mechanism in Scheme I is similar to the mechanism proposed by Ta-Shma and Rappoport (ref 3) to account for the second- and third-order terms found in the reactions of diaryl imidoyl chlorides with secondary amines in benzene solution.

(22) (a) Page, M. I.; Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 8828–8838. (b) Page, M. I.; Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 8818–8827.

(23) Bender, M. L.; Jones, J. M. *J. Am. Chem. Soc.* **1962**, *27*, 3771–3774.

Scheme II



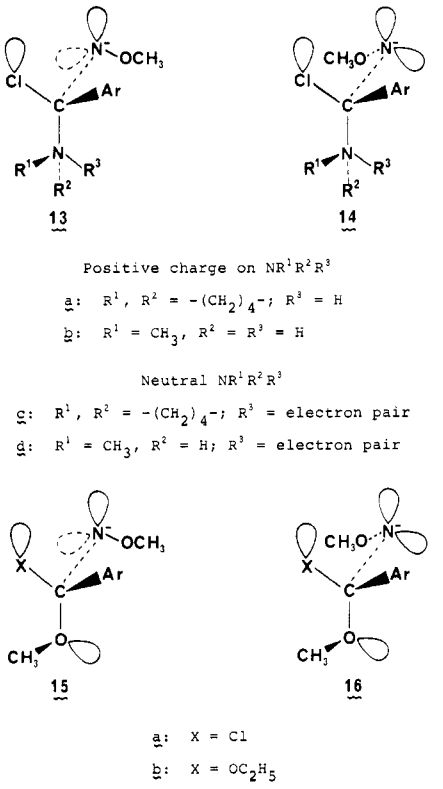
charge in **T-2** are approximately equidistant from the aromatic ring. Thus, one would expect a ρ value of approximately zero for the second-order process where $k'' = k_1k_2/k_{-1}$.

The elimination step k_3 in the third-order process, however, should have a positive ρ value since some of the positive charge in the transition state **T-3** is further removed from the aromatic ring than in intermediate **9**. It is likely that the relatively low positive ρ value for the amine-catalyzed pathway is a reflection of the early transition state **T-3** where only a small part of the positive charge is transferred to the second amine molecule.

It is possible that the reactions of (*Z*)-hydroximoyl chlorides (**3**) with amines are proceeding by an S_N2 (IP) mechanism[24] (Scheme II). If one invokes pyrrolidine assistance in the ionization process (**T-4**) to account for the third-order term, the overall process takes on the same kinetic form as the addition–elimination mechanism in Scheme I. It has been shown by us[25] that the rate of ionization of the (*Z*)-hydroximoyl chloride **3a** is at least 470 times[26] faster than the ionization of the *E* isomer **4a** which could explain the substantially lower reactivity of the (*E*)-hydroximoyl chlorides with amines. Furthermore, additions of nucleophiles to nitrilium ions are known to proceed so that the nucleophile and the electron pair on nitrogen are anti to each other;[25,27] this could account for the stereochemistry of the reaction of (*Z*)-hydroximoyl chlorides with secondary amines. The primary reason why the S_{N^2} (IP) mechanism is unlikely for the reactions of (*Z*)-hydroximoyl chlorides with amines is that such a process should give a negative ρ value in the Hammett correlation with σ.[3,25]

One possible explanation for the lack of reactivity of the (*E*)-hydroximoyl chlorides (**4**) with primary and secondary amines is that the extremely unstable dipolar tetrahedral addition intermediate reverts to starting materials by explusion of the attacking amine faster than it breaks down to products. Alternatively, it is possible that the difference in reactivity of **3** and **4** with amines is due to a steric approach problem in the *E* isomer, i.e., the rate of nucleophilic attack by the amine on the *E* isomer **4** is much less than the rate of nucleophilic attack on the *Z* isomer **3**. Recent X-ray crystallographic results[28a] have shown that the phenyl group in the (*E*)-hydroximoyl chloride **4b** is twisted by 52° from the C=NO plane while the analogous dihedral angle in the *Z* isomer **3b** is only 14°.[28b] If the conformations of these isomers in solution are similar in a general way to those found in the solid state, it is conceivable that the twisted phenyl in **4b** could block nucleophilic attack perpendicular to the OC=NO plane. Although this explanation could be valid for most of the amines investigated in this work, it seems unlikely in the case of methylamine, which is approximately the same size as methoxide ion, but is unreactive toward the (*E*)-hydroximoyl chlorides **3a** and **3b** at 32 °C.

Scheme III

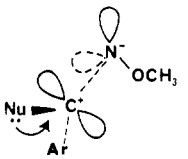


The observations reported herein with amines and amide ions, along with out earlier work,[6] suggest the following stereoelectronic[10] explanations for the reactions of nucleophiles with **3–6** (tetrahedral intermediates **13–16** in Scheme III).

(1) Only one antiperiplanar electron pair is necessary for stereoelectronically controlled elimination of chloride ion from a tetrahedral intermediate (**4a** + CH_3O^- → **15a** → **5b** + **6b**; **4a** + pyrrolidide → **13c** → **7a** + **8a**; **4a** + CH_3NH^- → **13d** → **7h**; **3a** + pyrrolidine → **14a** → **7a**; **3a** + CH_3NH_2 → **14b** → **7g**). In the reactions of (*E*)-hydroximoyl chlorides (**4**) with methoxide ion or pyrrolidide ion we suggest that the tetrahedral carbons in **13c** and **15a** eliminate chloride ion with assistance only from an electron pair on the nucleophile, i.e., the elimination of chloride ion occurs before carbon–nitrogen bond rotation brings an electron pair on the hydroxylamine nitrogen into an antiperiplanar position with respect to the leaving chloride ion. In the limiting case this would produce the dipolar intermediate **16**. Rehybridization of nitrogen in **16** from sp^3 to sp^2 and C–N bond rotation could produce a mixture of the *Z* and *E* substitution products. It is possible, of course, that the elimination of chloride ion, the rehybridization of nitrogen, and C–N bond rotation are concerted processes.

(2) Two antiperiplanar electron pairs are necessary for stereoelectronically controlled elimination of ethoxide ion (**5a** + CH_3O^- ⇌ **16b** → **5b**; **6a** + CH_3O^- ⇌ **15b** $\xrightarrow{\text{slow}}$ **16b**

(24) Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46–53.
(25) Johnson, J. E.; Cornell, S. C. *J. Org. Chem.* **1980**, *45*, 4144–4148.
(26) The ionization rate factor **3a**/**4a** = 470 represents a lower limit since the hydrolysis rate constant measured for **4a** could be due to ionization of **3a** formed by the slow thermal isomerization of **4a**.
(27) (a) McCormack, M. T.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2*, **1976**, 1701–1709. (b) Hegarty, A. F. *Acc. Chem. Res.* **1980**, *13*, 448–454.
(28) (a) Johnson, J. E.; Ghafouripour, A.; Haug, Y. K.; Cordes, A. W.; Pennington, W. T.; Exner, O. *J. Org. Chem.* **1985**, *50*, 993–997. (b) Bertolasi, V.; Sacerdoti, M.; Tossi, D. *Cryst. Struct. Commun.* **1977**, *6*, 335–341.



16a: Nu = CH_3O
b: Nu = C_4H_6N

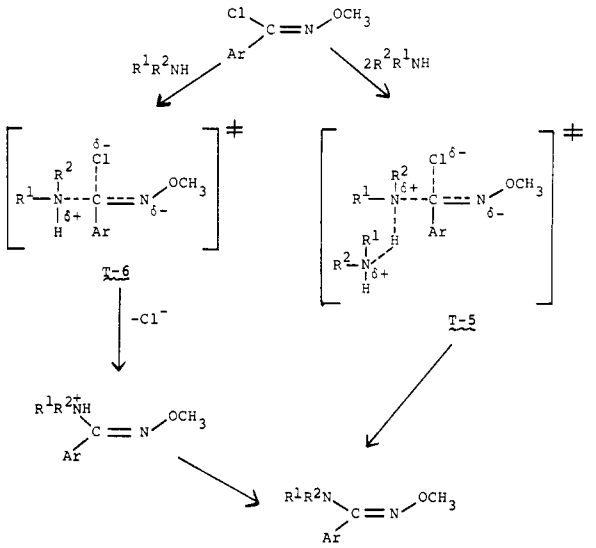
→ **5b**). In the elimination of ethoxide ion, which is a much poorer nucleofuge than chloride ion, two electron pairs are required for rapid elimination. In the reaction of the (*E*)-hydroximate **6a** with methoxide ion, only the reverse reaction is stereoelectronically controlled; this accounts for its lower reactivity in comparison to **5a**. The slow reaction of **6a** with methoxide ion to give **5b** is probably due to stereomutation of **15b** to give **16a**. As discussed above, we suggest that with the better nucleofuge chloride ion, the elimination proceeds directly from the tetrahedral intermediate **15a**, possibly through intermediate **16**, to give a mixture of products. The two different mechanistic processes for the reaction of methoxide ion with (*E*)-hydroximoyl chlorides (**4**) and (*E*)-hydroximates (**6**) account for the difference in the rate ratios (**3a**/**4a** = 0.87; **5a**/**6a** = 290) as well as the difference in the substitution product distributions (**4a** + CH_3O^- → **5b** + **6b**; **6b** + CH_3O^- → **5b**).

(3) In the reaction of primary and secondary amines with **4a**, deprotonation of the amino nitrogen in the tetrahedral intermediates does not compete with the stereoelectronically controlled reverse reaction to form starting materials (**4a** + pyrrolidine ⇌ **13a** ⇌ **13c** → **7a** + **8a**; **4a** + CH_3NH_2 ⇌ **13b** ⇌ **13d** → **7g**).

Although an addition–elimination mechanism seems to be the most likely explanation for our kinetic and stereochemical results, there are some questions concerning this mechanism that need further clarification. First of all, in order for the tetrahedral intermediate to maintain its stereochemical integrity, C–N bond rotation in the tetrahedral intermediate must be slower than elimination of either the attacking amine (k_{-1}) or the leaving group (k_2 and k_3). It has been estimated that C–N bond rotation in such an intermediate may have a rate constant $\leq 10^6$ s^{-1} (a barrier of ≥10 kcal/mol).[29] This means that k_{-1} in Scheme I would have to be greater than 10^6 s^{-1} in order to maintain the stereochemical integrity of the tetrahedral intermediate. This may not be an unreasonable value for k_{-1} since amines are good nucleofuges,[30] and rate constants in the range of 10^7–10^8 have been estimated for amine departure from tetrahedral intermediates.[22a,31,32]

Another question regarding the proposed addition–elimination mechanism concerns the rate of deprotonation of the positive nitrogen in the tetrahedral intermediate. Rate limiting deprotonation of amine addition intermediates in nucleophilic aromatic substitutions (S_NAr) were originally proposed in aprotic solvents, but this has been discounted primarily because it has been shown that proton transfer in aprotic media occurs very rapidly.[32] In protic solvents, however, it has been suggested that diffusion-controlled deprotonation of the intermediate is rate limiting.[32] Our explanation for the lack of reactivity of the (*E*)-hydroximoyl chlorides (**4**) with amines, which requires

Scheme IV



that deprotonation be slower than explusion of the attacking amine (k_{-1}), seems extraordinary and requires further substantiation.

The amine catalyzed elimination in Scheme I (transition state **T-3**) bears a formal resemblance to a concerted breaking of the N–H and C–X bonds in the dipolar intermediate formed in amine substitution reactions with aryl halides (S_NAr reactions). Although convincing arguments have been presented against the concerted mechanism in S_NAr reactions,[33] it has been readvocated.[34] We favor a concerted elimination from **12**, primarily because it seems unlikely that the tetrahedral intermediate could maintain its stereochemical integrity through a two-step process (deprotonation followed by chloride ion elimination).

The possibility of synchronous displacement, without the formation of a tetrahedral intermediate in nucleophilic substitution reactions at acyl or imine carbon atoms, has been discussed by several investigators.[3,22a,29,35] A concerted mechanism for the reactions of **3** and **4** with amines and amide ions (Scheme IV for **3** with amines) is consistent with the observed kinetics, the Hammett ρ values, and the element effect. The major difficulty with the concerted mechanism is that it does not provide an obvious explanation for the stereochemistry of these reactions, especially when the reaction is not highly stereospecific as is the case when methoxide ion reacts with (*Z*)-arylthio hydrazonates,[9] (*Z*)-aryl hydrazonates,[9] (*E*)-arylthio hydrazonates,[9] and (*E*)-hydroximoyl chlorides (methoxide ion[6] and pyrrolidide ion). Furthermore, the concerted mechanism would require a termolecular step for the third-order process (**T-5** in Scheme IV) and assuming that this is less likely than a two-step process, we prefer the addition–elimination pathway in Scheme I.

In summary, we suggest that the reactions of primary and secondary amines with (*Z*)-hydroximoyl chlorides proceed by a stereoelectronically controlled addition–elimination mechanism. The (*E*)-hydroximoyl chlorides do not give substitution products with amines because the initially formed dipolar tetrahedral intermediate ejects the

(29) Miller, S. I. *Tetrahedron* **1977**, *33*, 1211–1217.
(30) Stirling, C. J. *Acc. Chem. Res.* **1979**, *12*, 198–203.
(31) Barnett, R. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 2358–2369.
(32) Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147–152.
(33) (a) Orvik, J. A.; Bunnett, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 2417–2427. (b) Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3217–3224.
(34) Brewis, D. M.; Chapman, N. B.; Paine, J. S.; Shorter, J.; Wright, D. J. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1787–1801.
(35) Kevill, D. N.; Daum, P. H.; Sapre, R. *J. Chem. Soc., Perkin Trans. 2* **1975**, 963–965.

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

no.	mp or [bp], °C	NMR, δ ($CDCl_3$) α-CH_2	NMR, δ ($CDCl_3$) β- and γ-CH_2	NMR, δ ($CDCl_3$) Ar	NMR, δ ($CDCl_3$) OCH_3	IR principal absorptions,[b] cm^{-1}	UV_{max}, nm (log ε)[c]
7a	*e*	3.47 (t)	1.80 (m)	7.40	3.82 (s)	1585, 1610	215[d] (4.10), 273 (3.52)
8a	[99 (0.4 torr)]	3.16 (t)	1.85 (m)	7.36	3.67 (s)	1582, 1592	215[d] (4.08), 260[d] (3.46)
7b	69–71.5 (ether–hexane)	3.50 (t)	1.82 (m)	7.66, 8.34[f]	3.83 (s)	1590	259 (4.06), 355 (3.17)
8b	78–80 (ether–hexane)	3.18 (t)	1.90 (m)	7.60, 8.40[f]	3.70 (s)	1580, 1605	257 (4.11), 346 (2.96)
7c	*e*	3.48 (t)	1.80 (m)	7.24,7.39[f]	3.81 (s) 2.37 (s)[j]	1575, 1605	222 (4.19), 267 (3.53)
8c	*g*, *k*	3.15 (t)	1.82 (m)	7.27	3.65 (s) 2.37 (s)[j]	1600, 1630	
7d	*e*	3.46 (t)	1.81 (m)	7.42	3.80 (s)	1570, 1605	226 (4.22), 282 (3.39)
8d	*h*, *k*	3.13 (t)	1.83 (m)	7.42	3.63 (s)	1600, 1620	
7e	*i*	3.43 (t)	1.78 (m)	7.32, 7.86[f]	3.76 (s), 3.80 (s)		
8e	63–64 (hexane)[g]	3.14 (t)	1.83 (m)	6.92, 7.27[f]	3.64 (s), 3.82 (s)	1590, 1618	
7f	61.5–63 (hexane)	3.23 (m)	1.65 (m)	7.77, 8.28[f]	3.85 (s)	1585, 1600	262 (4.06), 354 (3.43)
8f	58.5–60 (hexane)	3.03 (m)	1.60 (m)	7.58, 8.33[f]	3.65 (s)	1585, 1608	263 (4.07), 340 (3.04)
7g	[70 (0.02 torr)]	2.77 (d, CH_3), 5.23 (NH)	7.53	7.53	3.92 (s)	1580, 1635, 3430	
7h	78–79 (ethanol–water)	2.78 (d, CH_3), 5.22 (NH)	7.79, 8.39[f]	7.79, 8.39[f]	3.92 (s)	1602, 1628, 3330	
7i	58.5–60.0 (ethanol–water)	3.03 (q, NCH_2), 1.43 (m, CH_2CH_2), 0.87 (m, CH_3)	7.78, 8.38[f]	7.78, 8.38[f]	3.95 (s)	1592, 1620, 3400	

[a] Satisfactory elementary analysis (C, H, and N) were reported for all compounds listed in this table. [b] The IR spectra were determined on thin films of the neat liquids or as KBr pellets of the solids. [c] The UV spectra were determined on 95% ethanol solutions. [d] Inflection. [e] A liquid or low melting solid that isomerizes to the *E* isomer on vacuum distillation. The microanalysis and spectroscopic measurements were carried out on the undistilled reaction product. [f] Centers of each doublet of an AA'BB' quartet. [g] An equilibrium mixture of *E*:*Z* = 88:12. [h] An equilibrium mixture of *E*:*Z* = 87:13. [i] The *Z* isomer isomerizes to an equilibrium mixture of *Z* and *E* isomers on standing at room temperature. The ^1H NMR of the *Z* isomer was determined on the reaction product immediately after workup. [j] $ArCH_3$. [k] Purified by preparative GLC.

amine to reform starting material much faster than it ejects chloride ion to form product.

Experimental Section

General Methods. The benzene was spectrophotometric grade and was stored over 4A molecular sieves. The hydroximoyl halides (**3a–e**) were prepared according to published procedures.[15,16,25] The hydroximoyl bromide **3g** has not been reported previously and its synthesis is described in this section. The pyrrolidine was freshly distilled before each kinetic run. Ultraviolet spectra of the benzamidoximes were determined on a Cary 15 and optical density measurements in the kinetic work were carried out on a Cary 17D. Infrared spectra were determined with a Pye Unicam SP-1100 and ^1H NMR spectra were obtained on a Varian EM-390 NMR spectrometer. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. The gas-liquid chromatography (GLC, analytical and preparative) was carried out with a column (30 ft × 0.375 in.) consisting of 20% silicon gum rubber (SE-30) on 45–60 mesh Chromosorb W. Elemental analyses were performed at Atlantic Microlab. The ultraviolet, infrared, and ^1H NMR spectra, along with melting points or boiling points for all the compounds prepared in this study, are in Table V. One representative example of the reaction of a (*Z*)-hydroximoyl chloride with an amine is described in this section.

(*Z*)-*O*-Methyl-*p*-nitrobenzohydroximoyl Bromide (3g). Phosphorus tribromide (16.3) was added dropwise over a period of 5 min to a stirred suspension of methyl *p*-nitrobenzohydroxamate[15] in benzene (150 mL). A benzene (20 mL) solution of bromine (10.2 g) was then added dropwise to the mixture. After the addition of the bromine was complete, the reaction mixture was refluxed for 3 h. The resulting solution was cooled to room temperature and washed with saturated aqueous sodium bicarbonate solutions until the benzene solution no longer reacted with the sodium bicarbonate. The benzene solution was dried over anhydrous magnesium sulfate; the benzene was evaporated at aspirator pressure, and the solid residue was recrystallized from methanol to give **3g** (9.84g, 76%) as light yellow crystals: mp 115–116.5 °C; IR (KBr) 1602, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.24 (s, 3 H), 8.12 (d, 2 H), 8.37 (d, 2 H).

Anal. Calcd for $C_8H_7N_2O_3Br$: C, 37.09; H, 2.72; N, 10.81; Br, 30.85. Found: C, 37.13; H, 2.77; N, 10.82; Br, 30.76.

(*Z*)-*O*-Methylpyrrolidino-*p*-nitrobenzamidoxime (7b). (*Z*)-*O*-Methyl-*p*-nitrobenzohydroximoyl chloride chloride (**3b**, 1.00 g) and freshly distilled pyrrolidine (6.50 g) were mixed at 0 °C. The solution was stirred at 32 °C for 24 h, after which time ice (100 g) was added with stirring to the solution. The orange precipitate that formed was filtered and washed several times with cold water. The precipitate was dried at room temperature and recrystallized from ether–hexane to give **7b** (1.03g, 90%) as orange crystals, mp 69–71.5 °C.

Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.88; H, 6.11; N, 16.79.

Thermal Isomerization of 7b to 8b. A dioxane (10 mL) solution of **7b** (0.20 g) was refluxed for 24 h. The dioxane was removed by evaporation at aspirator pressure and the residual solid was recrystallized from ether–hexane to give **8b** (0.15g, 75%) as yellow crystals, mp 78–80 °C.

Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.93; H, 6.11; N, 16.79.

Kinetic Methods. Method A (rate constants for the reaction of **3** with pyrrolidine in benzene). Amidoxime formation was followed by monitoring the increase in absorbance at a wavelength where the hydroximoyl halide had a lower absorptivity than the amidoxime (320 nm for **3a**, **3c**, and **3d**; 410 nm for **3b** and **3g**).

Method B (rate constants for reaction of **3** with pyrrolidine in the absence of solvent). Approximately 10% solutions of the hydroximoyl halides (**3**) in pyrrolidine were made up in NMR spin tubes and thermostated in a constant temperature bath at 32.0 °C (±0.1 °C). At various intervals the spin tubes were removed from the bath and the ^1H NMR spectra were determined in the region of the methoxy absorptions. The rates of the substitution reactions were determined from integration of the methoxy signals of starting material (**3**) and product (**7**).

Method C (relative reaction rates of **3a** and **4a** with lithium pyrrolidide and lithium methylamide). A hexane solution of *n*-butyllithium (18 mL of 1.55 M, Aldrich Chemical Co.) was added to freshly distilled pyrrolidine (2.0 g) dissolved in benzene (50 mL) under a nitrogen atmosphere. A small portion (0.25 mL)

of this solution was transferred under a nitrogen atmosphere to a mixture of **3a** (0.0156 g) and **4b** (0.0156 g) which had been cooled to 0 °C in an ice bath. The reaction was stirred for several minutes, ice was added, and the reaction mixture was extracted with benzene (3 × 5 mL). The combined benzene extracts were dried over anhydrous magnesium sulfate, and dodecane (0.012 g) was added to the solution. The amounts of unreacted **3a** and **4a** were determined by GLC analysis by using the dodecane as an internal standard. The relative reaction rates of **3a** and **4a** with lithium methylamide were determined in a similar manner. The product distributions (**7a** and **8a**) in the reaction of **3a** and **4b** with lithium pyrrolidide were determined by reacting pure **3a** or **4b** with an equimolar amount of lithium pyrrolidide, working up the reaction as described above, evaporating the benzene, and analyzing the product by ^1H NMR spectroscopy.

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Registry No. **3a**, 41071-35-6; **3b**, 41071-37-8; **3c**, 57139-33-0; **3d**, 57139-34-1; **3e**, 57139-36-3; **3f**, 57139-40-9; **3g**, 97315-84-9; **4a**, 41071-34-5; **4b**, 41071-36-7; **7a**, 97315-85-0; **7b**, 97315-86-1; **7c**, 97315-87-2; **7d**, 97315-88-3; **7e**, 97315-89-4; **7f**, 97315-90-7; **7g**, 97315-97-4; **7h**, 97315-98-5; **7i**, 97315-99-6; **8a**, 97315-91-8; **8b**, 97315-92-9; **8c**, 97315-93-0; **8d**, 97315-94-1; **8e**, 97315-95-2; **8f**, 97315-96-3; piperidine, 110-89-4; lithium pyrrolidide, 4439-90-1; pyrrolidine, 123-75-1; lithium methylamide, 67601-96-1; methyl *p*-nitrobenzohydroxamate, 1613-79-2.

Supplementary Material Available: Analytical data for benzamidoximes (1 page). Ordering information is given on any current masthead page.

Annulation Reactions Leading to Naphthalene Derivatives. New Syntheses of Natural 1,2- and 1,4-Naphthoquinones

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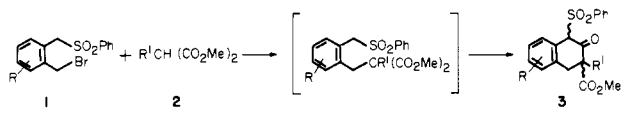
1-(Phenylsulfonyl)-2-oxo-3-(methoxycarbonyl)-1,2,3,4-tetrahydronaphthalene derivatives with various C-3 substituents were effectively prepared by a one-step cyclization involving 1-[(phenylsulfonyl)methyl]-2-(bromomethyl)benzene derivatives and monosubstituted malonic esters. A high yield one-step decarboxylation–desulfonylation of the above products by lithium iodide led to C-3-substituted 2-naphthalenols **7a–g** whereas prior C-1 alkylation of the cyclization products provided 1,3-dialkylated 2-naphthalenols **6a,b**. Oxidations of compounds **7** to *o*-naphthoquinones **8a–f** and further oxidations of the above products to substituted 2-hydroxy-1,4-naphthoquinones provided a new pathway to naturally occuring naphthoquinones like phthiocol (**9**), droserone methyl ether (**10**), and lapachol (**15**).

Regioselective annulation methodology for the formation of carbocycles fused to aromatic and heteroaromatic rings is a research area of utmost importance in providing new pathways for the construction of polycyclic natural compounds. Apart from the sequential Friedel–Crafts cyclization, there has been, during recent years, extensive utilization of one-step processes ensuring the formation of two carbon–carbon bonds, namely Diels–Alder reactions of *o*-quinodimethane species[1] and Michael-induced ring closure (MIRC) reactions,[2] to give new rings fused to aromatics. In the MIRC reactions a variety of aromatic derivatives have been used as 1,4-dipole synthons, supplying four carbons to the newly formed cyclohexane ring.

We recently initiated an annulation pathway, similar to the above in purpose but conceptually different, in which bifunctional aromatic or heteroaromatic compounds, having both electrophilic and nucleophilic centers, can function as versatile 1,4-dipole synthons in a substitution–acylation scheme. The success of such a regioselective annulation route depended on the choice of the two functions on the annulating reagents, to ensure

Scheme I



effective intermolecular reactivity instead of self-annihilation and byproduct formation under the reaction conditions. Furthermore, the problem of a regioselective bifunctionalization leading to the required annulating reagents had to be solved. We have found that activation of vicinal benzylic centers by Br and SO_2Ph groups provides a fulfillment of these requirements. Thus, 1-(bromomethyl)-2-[(phenylsulfonyl)methyl]-substituted aromatic[3] or heteroaromatic[4] derivatives, obtained via regioselective radical bromination of the unsubstituted methyl group in the presence of a vicinal (phenylsulfonyl)methyl group,[5] react with various substrates to provide new and effective pathways for the generation of bicyclic and tricyclic systems.

We report on the annulation reactions leading to functionalized naphthalene derivatives and on the potentialities of the latter as versatile synthetic intermediates to afford, inter alia, naturally occurring naphthoquinones.

(1) For leading references on cyclization via *o*-quinodimethane species, see: Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609. Oppolzer, W. *Pure Appl. Chem.* **1981**, *53*, 1181.

(2) For leading references, see, e.g.: Eisenhut, W.; Renfroe, H. B.; Schmid, H. *Helv. Chim. Acta* **1965**, *48*, 375. Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. Broom, N. J.; Sammes P. G. *J. Chem. Soc., Chem. Commun.* **1978**, 162. Kraus, G. A.; Sugimoti, H. *Tetrahedron Lett.* **1978**, 2263. Li, T.; Wu, Y. L. *J. Am. Chem. Soc.* **1981**, *103*, 7007. Dodd, J. H.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, 3593. Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 318.

(3) Ghera, E.; Ben-David, Y. *Tetrahedron Lett.* **1983**, 3533.

(4) Ghera, E.; Ben-David, Y.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 774.

(5) Ghera, E.; Plemenitas, A.; Ben-David, Y. *Synthesis* **1984**, 504. Alternative pathways, via bromination of corresponding benzyl alcohols, have been also utilized for the preparation of annulation reagents (see Experimental Section).

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