Reactivity of 1,3-Dipoles in Aqueous Solution. 2. Stereospecific Reactions of Benzonitrile Oxides with Oxygen, Carbon, and Nitrogen Nucleophiles

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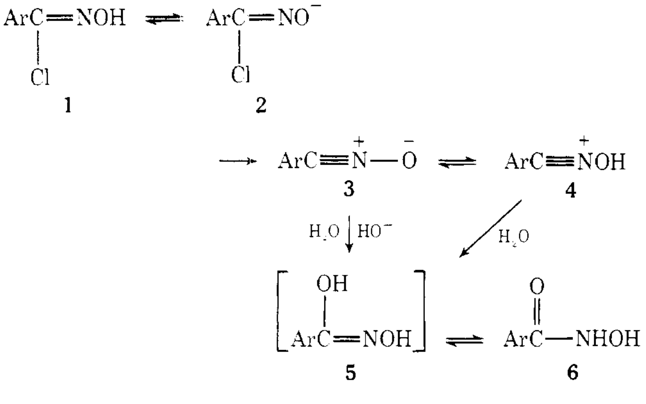
The reactivities of substituted benzonitrile oxides **3** (generated in situ from the corresponding chlorides **1**) have been examined in aqueous solution; simple second-order reactions were observed with nucleophiles and with acrylonitrile. Substituent variation in Ar gave the following Hammett ρ values: +0.57 (H_2O), +0.80 (HO^-), and +0.75 ($CH_3CO_2^-$). With alkoxide ions as nucleophiles, only the (*Z*)-*O*-alkylhydroxamic acid **10** is formed. Evidence is also presented that only *Z* isomers (in which the entering nucleophile at carbon and forming lone pair on nitrogen are trans) are also formed with the nucleophiles $CH_3CO_2^-$, N_3^-, Cl^-, and carbanions. Cycloaddition of acrylonitrile to **3** is characterized by a similar low sensitivity to substituents in the benzonitrile oxide ($\rho = +0.36$). Both cycloaddition of benzonitrile oxides to alkenes and reaction of nucleophiles at carbon are therefore characterized by similar transition states, and the key role of carbon-nucleophile bond formation in determining stereospecificity is discussed.

In the previous paper in this series,[1] we reported on the reactivity of benzonitrile oxides with primary and secondary amines and the stereospecific formation of (*Z*)-amidoximes. We have now extended this to a kinetic study involving oxygen nucleophiles (HO^-, H_2O, $CH_3CO_2^-$) and report on the unique stereochemistry both of these reactions and the reaction of nitrile oxides with other nucleophiles. Since nucleophilic attack at the carbon of the nitrile oxide is a possible model for the first step in the alternative two-step mechanism of 1,3-dipolar cycloaddition to alkenes, the relevance of the observed stereospecificity of the first step is also considered.

Results and Discussion

Neutral Hydrolysis. The required benzonitrile oxides **3** were prepared in aqueous solution by rapid dehydrohalogenation of the corresponding hydroxamoyl chlorides.[1] The conversion of **1** to **3** is base catalyzed and rapid ($t_{1/2} < 1$ s) at pH >4 in water at 25 °C. The subsequent reaction of **3** with water is surprisingly slow and could be conveniently measured. At pH <8, the reaction with **3** (Ar = *p*-$MeOC_6H_4$) is independent of pH, consistent with H_2O as the nucleophile in this region.



Buffer catalysis (by acetate ion) was noted in the presence of acetate buffers (see below); the rates of reaction of substituted benzonitrile oxides with water were therefore measured (at 61 °C) by extrapolation of k_{obsd} vs. buffer concentration plots to zero buffer concentration. The results (at pH 4.65) are summarized in Table I. The low sensitivity of the reaction to substituents in the nitrile oxide is obvious from the Hammett ρ value of +0.57 (r = 0.998) calculated from these data.

The products of hydrolysis under neutral conditions are the corresponding benzohydroxamic acids **6** (which were also prepared by independent synthesis from the ethyl benzoate and hydroxylamine[2]). Under the conditions used to study the kinetics, no detectable further hydrolysis of the benzohydroxamic acids occurs (although it is well established that in concentrated acid or base **6** hydrolyse to benzoic acids and hydroxylamine).[3] The formation of **6** contrasts with previous reports of complex products,[4,5] although Edwards and Tremaine[6] also observed the quantitative formation of benzohydroxamic acids **6** on hydrolysis of chlorides **1** under mild conditions (aqueous sodium bicarbonate).

Base-Catalyzed Hydrolysis. The reaction of **3** with hydroxide ion was also examined; the products formed were the corresponding benzohydroxamic acids **6**. The rate of reaction was proportional to [HO^-] over a wide range (Table II). Again electron-withdrawing substituents enhanced reactivity to a small extent; the rate constants for reaction with HO^- at 25 °C at pH 11.15 are summarized in Table III. The Hammett ρ value calculated from these data is +0.80 (r = 0.998).

Acid-Catalyzed Hydrolysis. Since the dehydrohalogenation of **1** occurs at a rate comparable to that of acid-catalyzed hydrolysis of **3** at low pH, the latter reaction was examined using the following sequence. The chloride (**1**, Ar = *p*-ClC_6H_4) was added to water (μ = 1.0, $NaClO_4$, 25 °C) at pH ca. 4. The solution was then acidified to the desired pH with concentrated perchloric acid.

Over the pH range 1.0 to 0, the logarithm of the rate of hydrolysis of **3** was inversely proportional to pH ($k_{obsd} = 2.4 \times 10^{-2}$ s^{-1} at pH 0). The observation of acid catalysis is interesting, since it implies a mechanism involving rate-determining attack by water on the nitrilium ion **4**; this is the first demonstration of the existence of this species on a reaction pathway.[7] The dehydrohalogenation of **1** might by analogy with the hydrazonoyl halides system **7** occur via an uncatalyzed pathway (involving **4**); however, in spite of a careful examination no evidence for this was found even in 1.0 M acid (where the dehydrohalogenation of **1** remained base catalyzed). The difficulty of formation of **4** by unimolecular solvolysis of **1** was confirmed when *O*-phenylbenzohydroxamoyl chloride **8** was examined in 7:3 water–dioxane at 60 °C in neutral solution and in the presence of 0.1 M sodium hydroxide. No spectral change was observed over a 24 h period. The difficulty of formation of **9** by this route is explicable in terms of the destabilization of the nitrilium ion by the electronegative phenoxy group.

$$\underset{\mathbf{7}}{\mathrm{ArCCl{=}NNHAr'}} \qquad \underset{\mathbf{8}}{\mathrm{ArCCl{=}NOPh}} \nrightarrow \underset{\mathbf{9}}{\mathrm{ArC{\equiv}NOPh}}$$

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Table I. Observed Rate Constants for the Hydrolysis of Benzonitrile Oxides (3, Ar = XC_6H_4) at 61 °C in Water at pH 4.65

Substituent X	Registry no.	$10^4 k_{obsd}$, s^{-1} Total acetate buffer concn, M[b] 1×10^{-2}	5×10^{-3}	1×10^{-3}	$10^4 k_{H_2O}$, s^{-1} [a]
p-MeO	15500-73-9	4.68	3.50	2.73	2.25
H	873-67-6	7.90	5.33	3.65	3.10
p-Cl	15500-74-0	12.0	8.45	5.18	4.52
m-Cl	13820-15-0	14.8	10.2	5.83	4.98
m-NO_2	7007-35-4	22.3	15.7	9.17	7.83
p-NO_2	2574-03-0	25.2	16.7	10.8	8.98
o-Cl	49660-38-0	3.65	2.62	1.65	1.45

[a] Obtained by extrapolation to zero buffer concentration. [b] $\mu = 1.0$ ($NaClO_4$).

Table II. Observed Rate Constants for the Hydrolysis of Benzonitrile Oxides (3, Ar = XC_6H_4) at 25 °C in 1:4 Dioxane–Water as a Function of Hydroxide Ion Concentration

$[HO^-]$, M	$10^3 k_{obsd}$, s^{-1} X = p-Cl	X = p-MeO	X = p-NO_2
0.25		120	
0.125		66	
0.062	86.8	33	
0.031	42.1	17	132
0.016	21.4	8.0	64
0.0078	11.1	3.5	27.2
0.0039	5.40		12.0
0.0020	2.60		

Table III. Observed Rate Constants for Hydroxide-Catalyzed Hydrolysis of 3 (Ar = XC_6H_4) in Water at pH 11.15 at 25 °C

Substituent X	λ, nm[a]	$10^3 k_{obsd}$, s^{-1}
p-MeO	270	4.89
H	250	7.37
p-Cl	265	11.8
m-Cl	255	14.4
p-NO_2	310	33.2
m-NO_2	294	40.7

[a] Wavelength used to follow course of reaction.

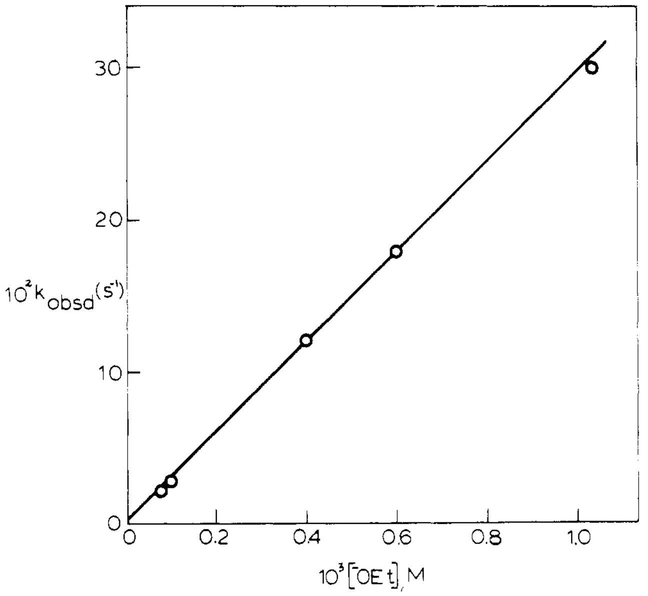
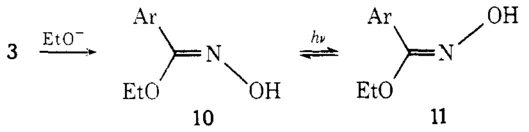


Figure 1. Plot of observed rate (s^{-1}) of reaction of 3 (Ar = p-$NO_2C_6H_4$) with sodium ethoxide in ethanol at 25 °C.

Stereochemistry of Addition: (a) Ethoxide Ion. Addition of hydroxide ion to nitrile oxides 3 initially gives 5 which tautomerizes to the more stable benzohydroxamic acid 6. The intermediates 5 are potentially isolable in two forms which differ in the configuration about the C=N bond; the rapid tautomerism via 6 would ensure equilibration of these isomers. The stereochemistry of the original addition was therefore probed using alkoxide in place of hydroxide.

Preliminary experiments showed (Figure 1) that the rate of reaction of p-nitrobenzonitrile oxide (3, Ar = p-$NO_2C_6H_4$) with sodium ethoxide in ethanol was overall second order, first order in ethoxide ion and the nitrile oxide over a wide concentration range. The product isolated on neutralization of the solution was a single isomer to which we assign the Z-configuration 10. The assignment was based on literature data,[9,10] and on comparison with authentic samples of 10 and 11 (Ar = Ph). The assignment was confirmed by isomerization of 10 (Ar = p-$NO_2C_6H_4$) on irradiation at 70 °C for 2 h in benzene to a mixture of 10 and 11. The NMR spectrum of the E isomer 11 showed an upfield shift of 0.25 ppm for the methylene proton quartet (similar to that observed for 10 and 11, Ar = Ph). In Me_2SO the =NOH protons gave a sharp NMR signal, that in the E form 11 being 0.9-ppm upfield from that in the Z isomer 10. A similar upfield shift was also noted with Z/E isomer mixtures of amidoximes also measured in Me_2SO.[11]



10 11

A single Z isomer was also formed on reaction of 3 (Ar = p-$NO_2C_6H_4$) with methoxide ion (see Experimental Section).

(b) Acetate. The rates of reaction of p-nitrobenzonitrile oxide (3, Ar = p-$NO_2C_6H_4$) in the presence of different concentrations of acetate buffers were measured in water at pH 4.65 at 50 °C (Figure 2, see also Table I). Clearly, acetate ion is the reactive species since no significant catalysis is observed at pH 3 where acetate is converted almost entirely to its conjugate acid. From these data, a second-order rate constant for the reaction of acetate ion with the nitrile oxide of 0.30 M^{-1} s^{-1} was calculated. Examination of other substituted benzonitrile oxides gave (Figure 3) a ρ value of +0.75 (r = 0.996), very similar to that reported above for the reaction of the other negatively charged nucleophile, HO^-.

Repetitive scans of the ultraviolet spectrum during the reaction of 3 with acetate ion showed tight isosbestic points, indicating the absence of relatively long-lived intermediates during reaction. The product of reaction was not the O′-acetyl benzohydroxamic acid 12 as expected by analogy with the reaction product from other nucleophiles, but the isomeric O-acetylbenzohydroxamic acid 13. The latter was prepared independently by acetylation of p-nitrobenzohydroxamic

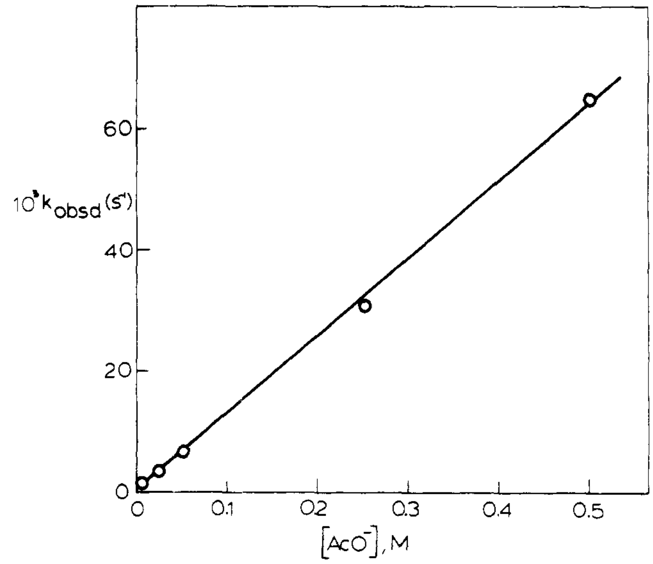
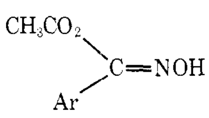


Figure 2. Plot of observed rate constants (s^{-1}) for the reaction of 3 (Ar = p-$NO_2C_6H_4$) with acetate ion in water at pH 4.6 in H_2O at 50 °C.

acid, and its structure, although controversial, follows from the work of Just and Dahl.[12-15]



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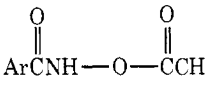
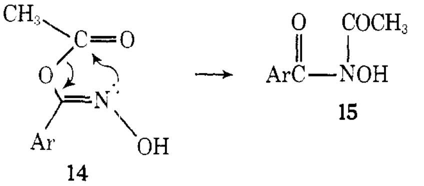


$$\mathrm{Ar\overset{O}{\overset{\|}{C}}NH{-}O{-}\overset{O}{\overset{\|}{C}}CH_3}$$

13

The quantitative formation of 13 can be related as follows to the configuration of the original product 12 formed on reaction of 3 with acetate ion. Thus, the E-isomer 14, if formed, would either be isolated as such (without rearrangement) or as the isomeric N-acyl material 15. This follows from recent work[16] on the corresponding O-alkyl derivatives of 14, which are relatively stable at ambient temperatures but undergo isomerization to O-alkylated 15 at ca. 70 °C. However, if the initial products are of the Z-configuration 16 then rapid O′ → O acyl group migration via a five-membered ring gives the observed O-acyl products 13. Since oximes undergo extremely slow EZ isomerization, 14 and 16 are not interconvertible; therefore, the quantitative isolation of 13 provides good evidence that 16 was initially formed.



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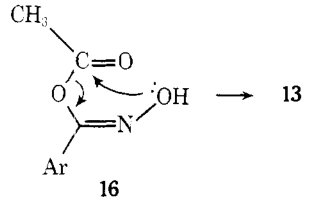

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(c) Azide Ion. Open-chain hydroxamoyl azides 17 are formed on reaction of nitrile oxides 3 with azide ion, although in general imidoyl azides are unstable relative to cyclization to isomeric tetrazoles.[19] Recent theoretical studies have emphasized the importance of the cis arrangement of the azido group and the long pair on the imine nitrogen.[20] We therefore conclude that the imidoyl azides have the Z-configuration 17.

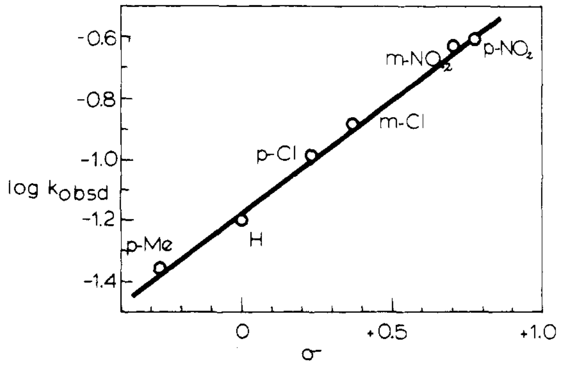
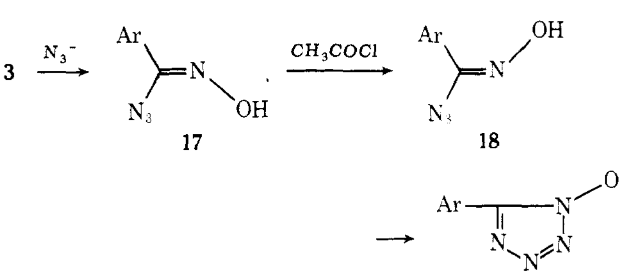
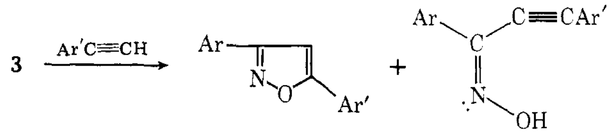


Figure 3. Plot of log k_2 [k_2 is the second-order rate constant ($M^{-1}\,s^{-1}$) for the reaction of acetate ion with nitrile oxides (3, Ar = XC_6H_4)] vs. Hammett σ values (at 50 °C, μ = 1.0, $NaClO_4$); ρ = +0.75.

Interestingly, it has recently been shown[21] that treatment of the azides 17 with acetyl chloride at reflux catalyzes the cyclization of 18 to the isomeric N-hydroxytetrazole 19. These are conditions known to promote EZ equilibration of oximes;[22] presumably, the E isomer 18 formed by this route spontaneously cyclizes to the more stable 19.



(d) Carbanions. Reaction of nitrile oxides with arylacetylenes gives in addition to the normal cycloadduct 20 the open-chain acetylenic oxime 21.[23-25] Higher yields of the oxime are obtained when the acetylide ion is used.[26] The configuration of the oxime 21 formed has not been unequivocally established but it is most likely Z (as shown), since (a) cyclization of the oxime to 20 is facile and quantitative in base[25] (conditions unlikely to promote EZ isomerization of oximes[27]) and (b) reduction of the acetylene followed by Beckmann rearrangement also indicates the Z configuration for 21.[24]



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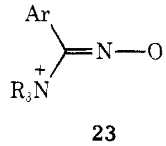
(e) Polymerization. It has been shown recently[28] that polymerization of nitrile oxides 3 is catalyzed by tertiary amines. The proposed mechanism involves the equilibrium formation of a small concentration of the zwitterion 23 which then acts as a nucleophile toward further nitrile oxide, ultimately giving polymers and macrocycles of general formula 24. Crystallographic studies[29] have shown that in the macrocycle 24 (n = 8) all of the C═N linkages have the Z configuration, implying stereospecific reaction of 23 with 3.



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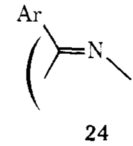

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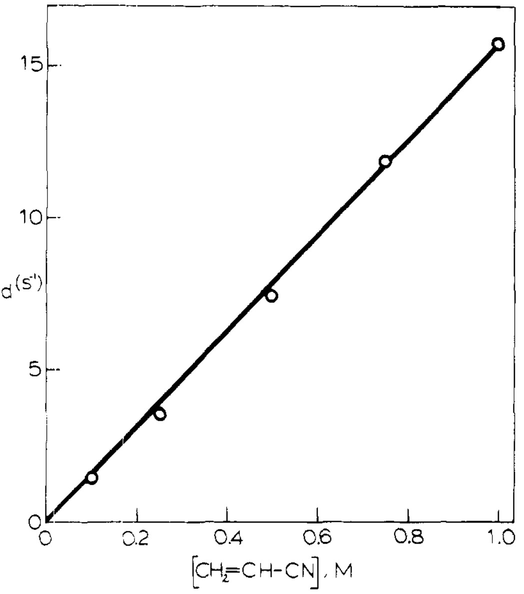
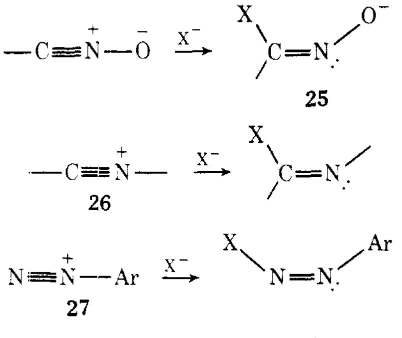


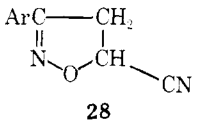
Figure 4. Observed rate constants (in s^{-1}) for the reaction of **3** (Ar = p-$NO_2C_6H_4$) at 25 °C as a function of added acrylonitrile.

(f) Chloride Ion. When the nitrile oxide **3** is treated with concentrated hydrochloric acid, the equilibrium is reversed and the hydroxamoyl chloride **1** is re-formed.[30] The configuration of **1** formed by this route has been established (by x-ray crystallography) as *Z*.[31] However, in this case the corresponding *E* isomer has not been reported, so the assignment of (*Z*)-**1** as the kinetic product is not unequivocal [e.g., (*E*)-**1** may be formed which rapidly isomerizes to a thermodynamically more stable (*Z*)-**1**].

In summary, in each case in which an unequivocal assignment of structure can be made, it is shown that on reaction of the 1,3-dipole **3** with nucleophiles only the product with the *Z* configuration is formed. In several other cases there is good evidence that the same stereospecificity exists. In the products formed, the entering nucleophile and the forming lone pair on the adjacent nitrogen are mutually *trans*-**25**, and this appears to be the critical factor which determines the stereochemistry of the product. The nitrile oxides are therefore directly analogous to nitrilium ions[32] **26** and aryl diazonium ions[33] **27** which show just the same type of stereospecificity.



Cycloaddition. In order to compare the charge distributions in the transition states for nucleophilic attack on the 1,3-dipole with 1,3-dipolar cycloaddition, the reaction with acrylonitrile in aqueous solution was also examined. The rate of cycloaddition is proportional to acrylonitrile concentration (see Figure 4) and the formation of **28** under these conditions was confirmed by TLC and actual isolation using an authentic sample.



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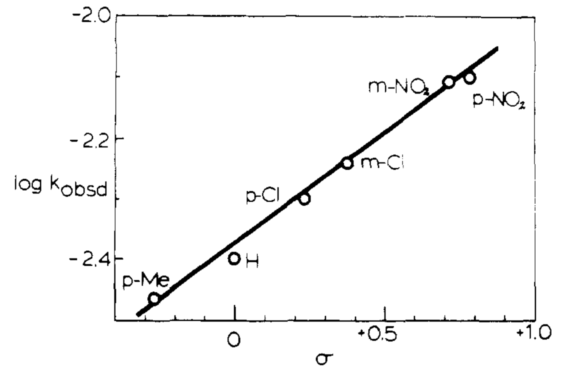


Figure 5. Plot of log k_{obsd} [k_{obsd} is the observed rate of reaction of **3** (Ar = XC_6H_4) with acrylonitrile (0.25 M) in water at 25 °C] vs. Hammett σ values; $\rho = +0.36$.

Table IV. Second-Order Rate Constants for the Reaction of 3 (Ar = p-$NO_2C_6H_4$) (a) in Water and (b) in 1:1 Dioxane–Water at 25 °C

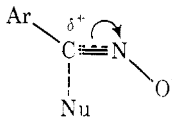
Dipolarophile	(a) 10^3k, $M^{-1}\,s^{-1}$	(b) $10^3\,k$, $M^{-1}\,s^{-1}$
Ethyl acrylate	145	75.6
Dimethyl fumarate		58.4
Methyl methacrylate		56.4
Ethyl propiolate		26.8
Acrylonitrile	29.3	
Dimethyl maleate	5.0	3.48
Methyl crotonate		2.50

[a] $\mu = 1.0$, $NaClO_4$; pH maintained at 4.65 by 5×10^{-3} M acetate buffer; the solubility of the other dipolarophiles was too low to permit measurements in H_2O. [b] $\mu = 0.25$, $NaClO_4$; pH = 4.0 (2×10^{-3} M acetate).

The effect of substituents in the 1,3-dipole was investigated in water at 25 °C using 0.25 M acrylonitrile. A plot of log k_{obsd} vs. Hammett σ values gave a ρ value of +0.36 ($r = 0.995$) (see Figure 5). The small positive ρ value obtained in aqueous solution is consistent with previous values of +0.79 (styrene as dipolarophile in carbon tetrachloride)[34] and +0.60 (phenylacetylene)[35] reported for substituents in nitrile oxides.

The order of reactivity of various 1,3-dipolarophiles in aqueous solution and in 1:1 dioxane–water (Table IV) is the same as that observed by Huisgen from competitive experiments in diethyl ether,[36] although the spread of reactivity is slightly less (e.g., $k_{\text{ethyl acrylate}}/k_{\text{dimethyl maleate}}$ is 38 in diethyl ether).[36] These results extend and confirm the remarkable insensitivity to solvent shown by the rates of cycloaddition even in solvents as disparate as diethyl ether and water.

The similarity in the magnitude and sign of the ρ values obtained for reaction of **3** with water, hydroxide ion, acetate ion, and with amines[1] to that for cycloaddition to an alkene measured under the same conditions indicates like charge distributions in the transition states for both reactions. There is convincing evidence[37] that cycloaddition to **3** occurs via an early transition state, which is reached while there is still little C–C or C–O bond formation (the low solvent effect observed on the rate of cycloaddition confirms this). Nucleophilic attack at the carbon of **3** is also characterized by an early transition state with little C–nucleophile bond formation.[1] However, in spite of the early transition state in the latter reaction, the stereochemistry of the kinetic product implies that the interaction of the initially linear nitrile oxide **3** with the nucleophile in the transition state is sufficient to bend the dipole so that the oxygen is adjacent to the incoming nucleophile **29**.



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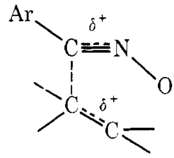

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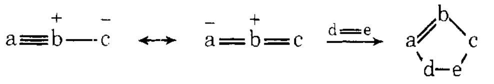
It is interesting that recent ab initio molecular-orbital studies of the reaction pathway for the addition of simple nitrile oxides to alkenes and alkynes show[38] that the only significant geometry change in passing from reactants to transition state is a marked bending of the —C≡N$^+$—O$^-$ skeleton (**30**), the C–C and C–O bonds remaining long. This bending of the C–N–O group from 180° to 144° in the transition state (all the atoms are coplanar) requires the major portion (55 kJ mol^{-1} relative to 89 kJ mol^{-1}) of the energy required to bring the reactants to the transition state. Once this bending of the 1,3-dipole has occurred, the alkene carbon and nitrile oxide oxygen are correctly placed (**30**) to allow ring closure to occur in a rapid subsequent step. Clearly then the factors which determine the stereospecificity of reactions of nucleophiles with nitrile oxides (and also with nitrilium ions and diazonium ions) can also be invoked in cycloadditions to alkenes without implying any C–O bond formation in the transition state **30**.

These observations may have wide generality for 1,3-dipolar cycloadditions, since in each of the propargyl–allenyl type 1,3-dipoles **31** (which like **3** are linear) a pair of electrons originally involved in the π system of the 1,3-dipole becomes localized on the central atom of the original 1,3-dipole (b) in the product **32**. The most important factor in the transition state for the formation of **32** may be the nucleophilic character of the alkene (d=e), the small amount of a–d bond formation being sufficient to induce the required bending of the 1,3-dipole.



31a **31b** **32**

Experimental Section

General. Melting points were determined on an electrothermal apparatus and are uncorrected. uv spectra for product analysis were run on a Unicam SP-800 B spectrophotometer. A Perkin Elmer Model R20A was used for NMR spectra. All inorganic salts were Analar grade. Aqueous sodium hydroxide solutions were made up from Volucon (M & B) standard ampules and the perchloric acid from 60–62% Analar perchloric acid. Dioxane was Analar grade and was used without further purification.

Substrates. All hydroxamoyl chlorides were prepared as previously described.[1] The following were made by standard literature methods: *O*-phenylbenzohydroxamoyl chloride (**8**, Ar = Ph), mp 35–36 °C (lit.[39] 35–36 °C); benzohydroxamic acid (**6**, Ar = Ph), mp 125–128 °C (lit.[2] 125–128 °C); *p*-nitrobenzohydroxamic acid (**6**, Ar = *p*-$NO_2C_6H_4$), mp 182–184 °C (lit.[40] 177 °C, 186 °C dec); *O*-acetylbenzohydroxamic acid (**13**, Ar = Ph), mp 123 °C (lit.[12] 125 °C).

Product Analysis. (*Z*)-Ethyl *p*-Nitrobenzohydroximate (10, Ar = *p*-$NO_2C_6H_4$). Sodium ethoxide (5 equiv) was added to *p*-nitrobenzohydroxamoyl chloride (1 equiv) in ethanol and stirred for 10 min. The solution was diluted fivefold with water and neutralized by bubbling carbon dioxide through the solution. The mixture was extracted with chloroform, and the combined extracts were dried over sodium sulfate and evaporated to leave a light yellow solid which, on recrystallization from cyclohexane, had mp 94–95 °C (lit.[9] 95 °C): NMR (Me_2SO-d_6) δ 1.36 (t, 3, *J* = 7 Hz, OCH_2CH_3), 4.46 (q, 2, *J* = 7 Hz, OCH_2CH_3), 7.9–8.5 (m, 4, aromatic H), 11.21 (s, 1, OH). Irradiation of a sample of **10** (Ar = *p*-$NO_2C_6H_4$) in dry benzene for 2 h at 70 °C with a Hanovia 100-W medium-pressure lamp in a quartz apparatus gave a 50:50 mixture of *ZE* isomers. For **11** (Ar = *p*-$NO_2C_6H_4$): NMR (Me_2SO-d_6) δ 1.36 (t, 3, *J* = 7 Hz, OCH_2CH_3), 4.22 (q, *J* = 7 Hz), 4.46 (q, *J* = 7 Hz) (*Z*, OCH_2CH_3), 7.9–8.5 (m, 4, aromatic H), 10.44, 11.21 (s, 1, OH).

(*Z*)-Methyl *p*-Nitrobenzohydroximate. Sodium methoxide (5 equiv) was added to *p*-nitrobenzohydroxamoyl chloride (1 equiv) in methanol and stirred for 10 min. The solution was diluted fivefold with water and neutralized by bubbling carbon dioxide through the solution. The mixture was extracted with chloroform and the combined extracts were dried over sodium sulfate and evaporated to leave a light yellow solid which, on recrystallization from cyclohexane, had mp 128–129 °C: NMR (Me_2SO-d_6) δ 4.09 (s, 3, OCH_3), 7.9–8.6 (m, 4, aromatic H), 11.18 (s, 1, OH). Anal. Calcd for $C_8H_8N_2O_4$: C, 4 .98; H, 4.11; N, 14.28. Found: C, 48.98; H, 4.03; N, 14.37. Irradiation as above gave a 40:60 mixture of *ZE* isomers: NMR (Me_2SO-d_6) δ 3.84 (s), 4.08 (s) (3, OCH_3), 7.9–8.6 (m, 4, aromatic H), 10.51, 11.18 (s, 1, OH).

Reaction of *p*-Nitrobenzohydroxamoyl Chloride with Acrylontrile in 50% Dioxane–Water. Sodium acetate (2 equiv) and perchloric acid (1 equiv) were added to 50% dioxane–water containing acrylonitrile (10 equiv). To this solution was added *p*-nitrobenzohydroxamoyl chloride (0.1 equiv), and the solution was stirred at room temperature for 24 h. It was then extracted with ether (three times) and the combined ether extracts were extracted in turn with water (two times). The ether extract was then dried with sodium sulfate and evaporated to dryness under reduced pressure at room temperature. TLC indicated that the yellow solid which remained was principally the oxadiazole **28** together with a small amount of unreacted starting material. Preparative TLC (silica gel with ether) gave pure 3-*p*-nitrophenyl-5-cyano-1,2,4-oxadiazole (**28**, Ar = *p*-$NO_2C_6H_4$) (79%), mp 157–158 °C. Anal. Calcd for $C_{10}H_7N_3O_3$: C, 55.29; H, 3.23; N, 19.35. Found: C, 55.01; H, 3.25; N, 19.20.

Kinetic Method. All rate data were measured on a Unicam SP-800 B spectrophotometer fitted with a scale expansion accessory at previously described wavelengths.[1] Substrates were made up 10^{-2} M in dioxane (Analar). pHs were measured using a Radiometer Model PHM 26 pH meter fitted with a Metrohm EA-125U glass electrode. The techniques used for following the kinetics have already been fully described.[41]

The products formed during a kinetic experiment were determined spectrophotometrically using authentic samples and confirmed using TLC analysis. When the product had a pK_a in the accessible region (e.g., the benzohydroxamic acids, **6**) as an addition, check the pK_a was determined in situ using the combined pH–stat spectrophotometer. The difference in absorbance between the acidic and basic forms of the product was also used to show that the formation of the hydroxamic acid was quantitative.

Attempted Reaction of *O*-Phenylbenzohydroxamoyl Chloride (8). The chloride was dissolved (10^{-4} M) in 3:7 dioxane–water at neutral pH and maintained (a) at neutral pH for 1 week at 25 °C and (b) for 24 h at 60 °C in the presence of 0.1 M sodium hydroxide. In neither case did a detectable reaction occur. Since the starting chloride **8** and the expected product *O*-phenylbenzohydroxamic acid have similar UV spectra in basic solution [λ_{max} 282 nm (ε 7800), 268 nm (ε 8500), and 272 nm (ε 7600), respectively], the solution was acidified at the end of the reaction period. The spectrum of *O*-phenylbenzohydroximate changed under these conditions [λ_{max} 272 nm (ε 1900), 268 nm (ε 2200)], whereas that of the chloride **8** was unaltered; any conversion to the hydroxamic acid would therefore have been detectable. The chloride **8**, mp 35–36 °C, (lit.[42] 35–36 °C), was also recovered unchanged when attempted reaction was carried out on a preparative scale.

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Registry No.—**1** (Ar = *p*-$NO_2C_6H_4$), 1011-84-3; **10** (Ar = *p*-$NO_2C_6H_4$), 7340-18-3; **11** (Ar = *p*-no$_2C_6H_4$), 64011-07-0; **28**, 64011-09-2; (*Z*)-methyl-*p*-nitrobenzohydroximate, 64011-08-1; (*E*)-methyl *p*-nitrobenzohydroximate, 64025-03-2; sodium ethoxide, 141-52-6; sodium methoxide, 124-41-4; acrylonitrile, 107-13-1.

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Neighboring Group Interaction in Ortho-Substituted Aminopyridines. Pyridopyrimidines and Related Systems[1]

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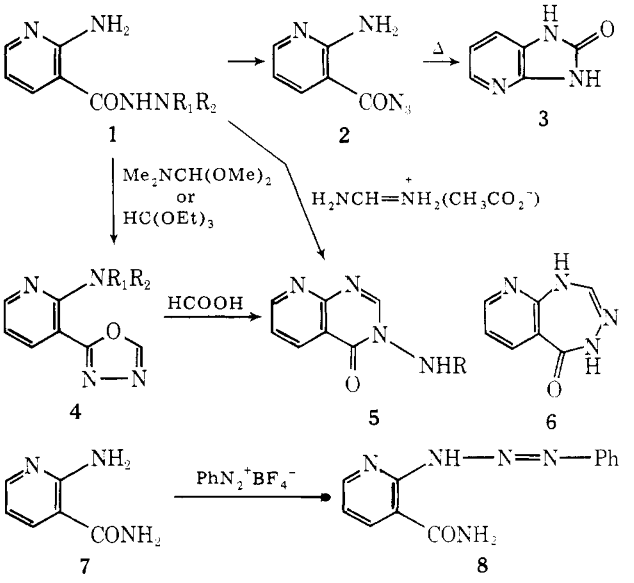
Hydrazides of isomeric *o*-aminopyridinecarboxylic acids have been used for syntheses of various bicyclic heterocycles. Derivatives of pyrido[2,3-*d*]-, pyrido[3,2-*d*]- or pyrido[3,4-*d*]pyrimidine, pyrido[3,2-*d*]- or pyrido[3,4-*d*]-*v*-triazine, and pyrazolo[1,5-*a*]pyrido[2,3-*d*]pyrimidine have been prepared. Some other transformations are also described.

Our recent interest in pyridopyrimidines[2,3] and related systems prompted us to investigate these systems and, in particular, some aspects of their preparation. Many synthetic approaches have been reported,[4] but in view of our recent findings it seemed worthwile to explore the possibilities of application of either *N,N*-dimethylaminomethylene derivatives[5-9] or participation of diazo or azido groups[10-19] in the construction of these bicyclic heterocycles. *N,N*-Dimethylformamide dimethyl acetal has been frequently used as a methine group source for various ring closures.



As starting material we have used hydrazides of 2-aminonicotinic acid, 3-aminopicolinic acid, and 3-aminoisonicotinic acid. 2-Aminopyridine-3-carboxylic acid hydrazide (**1**, $R_1 = R_2 = H$) was transformed with either isoamyl nitrite or benzenediazonium tetrafluoroborate under the conditions for azo-transfer reaction[13] into the acyl azide **2**, which was thermally converted into imidazo[4,5-*b*]pyridin-2-one (**3**). This transformation is an example of a Curtius rearrangement with subsequent intramolecular cyclization involving the isocyanato and *o*-amino groups. By monitoring this rearrangement in a NMR probe, the reaction is shown to be completed in 40 min at 80 °C. The hydrazide, when heated with either *N,N*-dimethylformamide dimethyl acetal or triethyl orthoformate, was transformed into an oxadiazolylpyridine (**4**, $R_1 = R_2 = H$). In the IR spectrum there was no evidence for a carbonyl group, and the NMR spectrum also revealed, in addition to three vicinal pyridine protons, a signal at δ 9.35, arising apparently from a CH group. In the literature, chemical shifts of few 1,3,4-oxadiazoles[20,21] and pyridopyrimidones[4] are recorded, and a differentiation between a H_2 of the oxadiazole system or a H_2 of the pyridopyrimidinone system is not reliable. On the basis of theoretical considerations and the determined molecular weight (162 g), besides the oxadiazole derivative (**4**), two other structures, i.e., the pyrido[2,3-*d*]pyrimidine (**5**,

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