Kinetics of Addition and Cycloaddition of Phenylacetylene to Benzonitrile *N*-Oxides. Competitive Concerted and Stepwise Mechanisms

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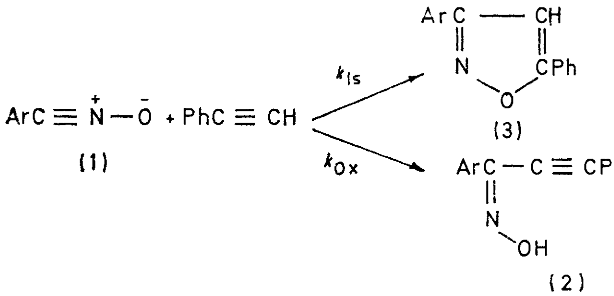
The kinetics of the concurrent processes leading to isoxazoles (1,3-cycloaddition) and acetylenic oximes (1,3-addition) in the reactions of substituted benzonitrile *N*-oxides with phenylacetylene have been examined under various conditions. The results supplement previous findings and are in accord with the occurrence of two independent pathways, a concerted 1,3-cycloaddition and a two-step 1,3-addition. For the latter reaction the rate-determining step is formation of an intermediate derived from the electrophilic addition of the nitrile oxide to the *p* electrons of the triple bond of phenylacetylene.

AFTER the first report[1] on the formation of acetylenic oximes as well as isoxazoles in the reactions of nitrile oxides with acetylenes, kinetic investigations[2] established that these products are formed through concurrent processes. However, the details of the mechanism are a matter of discussion. Firestone considered[3] that the formation of the acetylenic oximes, acyclic isomers of isoxazoles, provided evidence for his mechanistic interpretation of 1,3-dipolar cycloadditions[4] and two-step diradical mechanisms were indicated for both reactions. Moreover, kinetic data appeared[2b] to be consistent with the rate-determining formation of a diradical or dipolar intermediate common to both processes. These conclusions have been criticized[5] in several instances by Huisgen who recently outlined[5b] a scheme with two independent pathways wherein isoxazole formation occurs through a concerted mechanism according to the general process for 1,3-dipolar cycloadditions,[4] and the oxime through a two-step mechanism.



a ; Ar = *m* − ClC$_6$H$_4$
b ; Ar = *p* − ClC$_6$H$_4$
c ; Ar = Ph
d ; Ar = *p* − MeC$_6$H$_4$
e ; Ar = *p* − MeOC$_6$H$_4$
f ; Ar = 2,6 − Cl$_2$C$_6$H$_3$
g ; Ar = 2,4,6 − Me$_3$C$_6$H$_2$

We now report the results of a kinetic study of the competitive 1,3-cycloaddition and 1,3-addition of phenylacetylene to a series of benzonitrile *N*-oxides (1a—g) which support this mechanistic interpretation and allow new suggestions on the mechanism of formation of the acyclic products. A re-evaluation of rate constants previously reported[6] is also given.

RESULTS

The acetylenic oximes (2) and 3,5-diarylisoxazoles (3), obtained in small-scale preparations under conditions identical with those of the kinetic experiments, were characterized by analytical data and spectroscopic properties. By comparison of some oximes (2) with samples of known configuration[7] prepared by another route it seems likely that the hydroxyimino-group is *syn* to the phenylethynyl group in all cases. The product composition is kinetically controlled, since the molar ratio oxime : isoxazole ($C_{\text{Ox}} : C_{\text{Is}}$) is constant throughout the conversion range. Rate constants, determined in carbon tetrachloride as previously described,[2a] are listed in Table 1. The rates of monosubstituted benzonitrile *N*-oxides (1a—e) are correlated by linear Hammett plots and give ρ_{Ox} +1·04 (*r* 0·986) for 1,3-addition and ρ_{Is} +0·52 (*r* 0·969) for 1,3-cycloaddition.

TABLE 1

Rate constants (l mol^{-1} s^{-1}) for the reactions of substituted benzonitrile oxides (1) with phenylacetylene in CCl$_4$ at 25·0°

Nitrile oxide	Substituent	10^3k_{tot} [a]	10^3k_{Is} [b]	10^3k_{Ox} [c]	$k_{\text{Ox}}/k_{\text{Is}}$
(1a)	*m*-Cl	2·90	2·05	0·845	0·412
(1b)	*p*-Cl	2·76	1·96	0·743	0·379
(1c)	H	1·58	1·23	0·335	0·272
(1d)	*p*-Me	1·30	1·05	0·229	0·218
(1e)	*p*-OMe	1·26	1·05	0·210	0·200
(1f)	2,6-Cl$_2$	0·508	0·388	0·120	0·300
(1g)	2,4,6-Me$_3$	0·172	0·162	0·010	0·062

[a] Over-all rate constant; taken in part from ref. 6. [b] Rate constant for the formation of isoxazole. [c] Rate constant for the formation of the oxime.

The different sensitivity of the two concurrent reactions to substituent effects is reflected in the ratio $k_{\text{Ox}} : k_{\text{Is}}$ (or $C_{\text{Ox}} : C_{\text{Is}}$ †) which is increased by *para*- or *meta*-electron-withdrawing substituents. For *ortho*-disubstituted compounds where steric and electronic effects operate, the

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† $C_{\text{Ox}} : C_{\text{Is}}$ and $k_{\text{Ox}} : k_{\text{Is}}$ are equivalent[2a] and no distinction is made in their usage in this paper.

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$C_{Ox}:C_{Is}$ ratio is much lower for mesitonitrile *N*-oxide (1g) than for *p*-toluonitrile *N*-oxide (1d), but is almost identical for 2,6-dichlorobenzonitrile *N*-oxide (1f) and benzonitrile *N*-oxide (1c). Hence, in contrast to previous assumptions[3] the product distribution depends on the substituents in the benzonitrile oxide to an extent comparable with that reported for substitution in phenylacetylene.[2b]

TABLE 2

Effect of the solvent on the kinetics (k/l mol^{-1} s^{-1}) of the reaction of *p*-chlorobenzonitrile oxide (1b) with phenylacetylene at 25·0°

Solvent	ε [a]	10^3k_{tot}	10^3k_{Is}	10^3k_{Ox}	k_{Ox}/k_{Is}
CCl_4	2·24	2·76	1·96	0·743	0·379
$CHCl_3$	4·81	1·16	0·880	0·280	0·318
C_2H_5OH	25·7	1·79	1·45	0·341	0·235
Dioxan	2·21	1·20	1·01	0·190	0·186
DMF	37·6	1·00	0·91	0·09	0·099
THF					0·173

[a] Dielectric constants at 25° are from reference 8*b*.

Although some data on solvent effects have been reported,[2] we have examined this point in greater detail (Table 2). The observed variations of the product composition bear no relation to solvent polarity. The lowest values of the $C_{Ox}:C_{Is}$ ratio are observed in the basic aprotic solvents[8] dioxan, tetrahydrofuran (THF), and dimethylformamide (DMF). The variations of these ratios are mainly due to changes of k_{Ox} which in fact decreases eight times in going from carbon tetrachloride to DMF, whereas k_{Is} is reduced to one half only. The greater sensitivity of k_{Ox} than k_{Is} to solvent effects parallels the influence of substituents.

Table 3 gives rate constants measured at different temperatures and the activation parameters for two specimen reactions. The results confirm[2] the close similarity of the energies and entropies of activation for the two processes in carbon tetrachloride and dioxan and consequently the independence of the product composition from temperature.

Table 4 presents results aimed at providing evidence for an H/D primary isotope effect which is of major importance since the formation of oximes (2) involves a hydrogen shift. This point has been investigated[2b] using carbon tetrachloride as solvent by Beltrame and his co-workers who found no appreciable isotope effect. We have re-examined this question for dioxan as solvent since it was conceivable that in this basic medium proton transfer could be involved in the rate-determining step. The results of Table 4 show that the rate constants and product distribution were unchanged when phenylacetylene was replaced by phenyl[^{2}H]acetylene in the reactions with two nitrile oxides, thus proving the absence of an appreciable isotope effect for 1,3-addition in dioxan.

TABLE 3

Rate constants (l mol^{-1} s^{-1}) for reactions of nitrile oxides (1d) and (1b) with phenylacetylene as a function of temperature

p-Toluonitrile *N*-oxide (1d); solvent CCl_4

Temp. (°C)	15·0	25·0	35·0	50·0	E_a/kcal mol^{-1} [a]	$\Delta S^‡$/cal mol^{-1} K^{-1} [b]
10^3k_{tot}	0·520	1·30	3·01	9·97		
10^3k_{Is}	0·432	1·05	2·44	8·03	15·4	−23
10^3k_{Ox}	0·0883	0·229	0·572	1·95	16·3	−23

p-Chlorobenzonitrile *N*-oxide (1b); solvent dioxan

Temp. (°C)	25·0	40·0	50·0		
10^3k_{tot}	1·20	3·84	8·35		
10^3k_{Is}	1·01	3·24	7·04	14·8	−25
10^3k_{Ox}	0·190	0·600	1·31	14·7	−28

[a] Accurate to ±0·2 kcal mol^{-1}. [b] At 35°; accurate to ±2 cal mol^{-1} K^{-1}.

TABLE 4

Reactions (k/l mol^{-1} s^{-1}) of nitrile *N*-oxides (1b and d) with phenylacetylene (PA) and phenyl[^{2}H]acetylene ([^{2}H]PA) in dioxan

p-Chlorobenzonitrile *N*-oxide (1b); temp. 25°

Acetylene	PA	PA	[^{2}H]PA
10^3k_{tot}	1·22 [a]	1·22 [a]	1·26 [a]
10^3k_{Is}	1·03	1·01	1·04
10^3k_{Ox}	0·19	0·21	0·22
k_{Ox}/k_{Is}	0·186 [a]	0·205 [b]	0·210 [b]

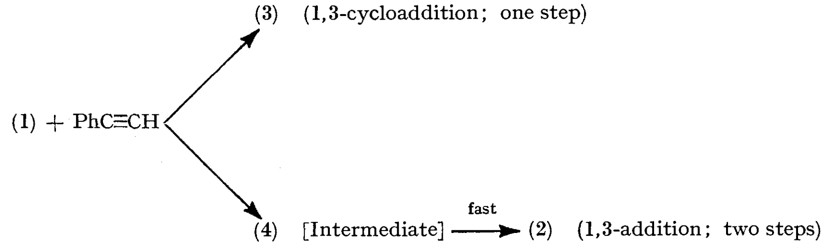
p-Toluonitrile *N*-oxide (1d); temp. 35°

Acetylene	PA	[^{2}H]PA
10^3k_{tot}	1·65 [a]	1·65 [a]
10^3k_{Is}	1·47	1·44
10^3k_{Ox}	0·18	0·21
k_{Ox}/k_{Is}	0·125 [b]	0·143 [b]

[a] From i.r. measurements. [b] From n.m.r. measurements; in triplicate experiments the standard deviation was ±0·013.

DISCUSSION

The results are in accord with previous reports[2] and support the existence[5b] of two independent pathways with different mechanisms (see Scheme). The substantial differences in the effects of substituents and solvents on the kinetics of the two reactions, as well as the absence of a primary isotope effect on the product



SCHEME

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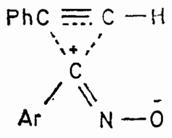
[8] (*a*) E. M. Arnett, *Progr. Phys. Org. Chem.*, 1963, **1**, 223; (*b*) R. Curci, R. A. Di Prete, J. O. Edwards, and G. Modena, *J. Org. Chem.*, 1970, **35**, 740.

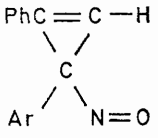
composition make the existence of a common intermediate unlikely.*

A concerted mechanism for 1,3-cycloaddition fits [4] the results so far reported including the kinetic (small substituent and solvent effects, low energy of activation, large and negative entropy of activation) and stereochemical data,† and meets the provisions based on current theoretical treatments [13] of cycloaddition reactions. As assumed for other cycloadditions of nitrile oxides,[14] there may in this case be differing extents of bond formation in the transition state which accounts for the reactivity pattern of Table 1.

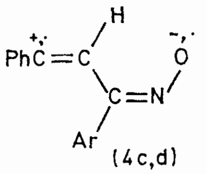
The occurrence of a two-step mechanism in 1,3-addition is required mainly by the absence of an isotope effect which makes carbon–carbon bond formation in concert with a hydrogen shift quite improbable. On the other hand hydrogen migration should occur rapidly *after* the rate-determining step since initial proton transfer from the acetylene to the nitrile oxide and a subsequent rate-determining reaction between charged species, the acetylenic carbanion and the protonated nitrile oxide, is less easily reconciled with the direction of the substituent effect ‡ and also requires that the rate is highly dependent on solvent polarity. Hence the intermediate is a species where the hydrogen is still bonded to the *sp* carbon atom and which is derived from electrophilic addition of the CNO group (for substituted benzonitrile *N*-oxides $\rho_{\text{ox}} = +1{\cdot}04$) to the *p* electrons of the triple bond of phenylacetylene (for substituted phenylacetylene [2b] $\rho = -1{\cdot}42$). This intermediate may be anything from the π-complex (4a) to a covalent species (4b), which can undergo internal collapse to give the product. The small size of the ρ values is more compatible with the bridged structures (4a) or (4b) than with the open zwitterion (4c).[2b,5b] In this case one would predict larger substituent effects on the rate, especially for substitution in phenylacetylene, as normally found [15] in electrophilic additions to arylacetylenes *via* vinyl cations where a large positive charge can develop on the carbon adjacent to the phenyl ring. The solvent effects (Table 2) are also in accord with this conclusion. The lack of a correlation between the observed rates and the solvent polarity suggests that the polarity of the transition state is not very different from those of the reactants. This is compatible with a transition state such as (4a) or (4b) where the charge separation is small and similar to that of ground state whereas one would expect the transition state leading to (4c) to be higly polar. Hence, even though it may be conceived that the contribution of a carbene-type resonance hybrid such as PhC̈–CH=C(Ar)NO could mitigate the polar character of the zwitterion (4c), its presence is unlikely. As discussed recently [5b] the diradical (4d) is also unlikely to be the intermediate of this reaction.



(4a)



(4b)



(4c,d)

In conclusion, two independent pathways for 1,3-addition and 1,3-cycloaddition appear quite probable. A point which may still be questionable is the similarity of the activation parameters (Table 3) although this could be due merely to a coincidence; this is not so improbable when it is considered that we are dealing with parallel reactions. Finally it may be noted that the formation of acetylenic oximes is not an isolated case of 1,3-addition to the CNO group by a nucleophile, other representative examples being the addition [11,16] of amines, thiols, and phenols. From their formal similarity it is possible that all these reactions occur by mechanisms having common features. Also in this respect it seems rather unwarranted to consider the formation of the acetylenic oximes in the reactions of nitrile oxides with acetylenes as evidence for a two-step mechanism [3] for the competitive cycloaddition leading to isoxazoles.

EXPERIMENTAL

Apparatus and Materials.—The apparatus, preparation, and purification of nitrile oxides (1), phenylacetylene, and solvents have been described.[2,14,17] Phenyl[^{2}H]acetylene was obtained with isotopic purity >99% (by n.m.r.) by literature methods.[18]

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* In addition to the arguments of Huisgen [5b] it may be also noted that for the observed differences of substituent effects, the partitioning of a postulated common intermediate should occur in two separated steps having considerable energies of activation, and hence through transition states advanced enough to show an appreciable isotope effect.

† The cycloaddition is regioselective [9–11] with a few exceptions [9,10] which, however, can be rationalized by the postulate of a concerted mechanism.[12]

‡ The substituent effect alone cannot rule out this mechanism because of the balance between the substituent effect on the proton transfer and that on forming the carbon–carbon bond.

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Reactions between Benzonitrile N-*Oxides* (1) *and Phenylacetylene.*—The nitrile oxide (0·05M) and a ten-fold molar excess of phenylacetylene in carbon tetrachloride were set aside overnight at 25°. The solvent was then removed under reduced pressure at room temperature and the residue was chromatographed on silica. Elution with benzene–light petroleum (6 : 1) gave unchanged phenylacetylene, traces of furazan *N*-oxide, and isoxazole (3); subsequent elution with diethyl ether afforded the oxime (2). The total yield calculated on the amounts of isoxazole and oxime was *ca.* 85—90%. The m.p.s and n.m.r. spectra of 3-aryl-5-phenylisoxazoles (3a—e) and (3g) were as previously described.[10] 3-(2,6-*Dichlorophenyl*)-5-*phenylisoxazole* (3f) had m.p. 75—76° (from ethanol) (Found: C, 61·9; H, 3·2; N, 5·0; Cl, 24·15. $C_{15}H_9Cl_2NO$ requires C, 62·0; H, 3·13; N, 4·8; Cl, 24·4%), τ ($CDCl_3$) 2·65—3·35 (m, ArH) and 3·90 (s, 4-H of isoxazole ring). The α-acetylenic oximes (2) (Table 5) showed typical spectral characteristics: $\nu_{max.}$ (CCl_4–CS_2) 3580, *ca.* 3300br (OH), and 2220 ($C\equiv C$) cm^{-1}; τ ($CDCl_3$) 0·6—1·0br (OH, shifted by dilution, disappeared on addition of D_2O). The oximes (2) isomerize to the corresponding isoxazoles (3); in CCl_4 at 25°, $t_{1/2}$ ranged between 20 and 60 days.

TABLE 5

Physical and analytical data of 1-aryl-3-phenylprop-2-ynone oximes (2) [a]

		Found (%)			Required (%)		
Compound	M.p. (°C)	C	H	N	C	H	N
(2a)	76—77	70·3	4·0	5·5	70·5	3·95	5·5
(2b)	106—107 [b]						
(2c)	103—104 [c]						
(2d)	97—98	81·7	5·55	6·0	81·7	5·55	5·95
(2e)	99—100	76·5	5·45	5·55	76·5	5·2	5·6
(2f)	95—96	62·1	3·2	4·75	62·0	3·15	4·8
(2g)	*d*	82·0	6·5	5·35	82·1	6·5	5·3

[a] All products were crystallized from benzene–light petroleum. [b] Ref. 2*a*. [c] Ref. 7. [d] The m.p. could not be determined since that observed (91—92°) corresponded to that of the isomeric isoxazole (3g). A mixed m.p. of (2g) and (3g) was 70—82°.

Rate Measurements.—For reactions in CCl_4 and $CHCl_3$, the apparatus and technique were those previously described.[2a] In the case of the low melting[11] (*ca.* 14°) benzonitrile *N*-oxide (1c), the initial concentration was established by volumetric analysis[14a] of stock solutions of the reactant; from the concentrations and the absorption at 2290 cm^{-1}, the apparent molar extinction coefficient was evaluated. Reactions were carried out under pseudo-first-order conditions with at least a ten-fold molar excess of phenylacetylene over nitrile oxide. In the majority of cases the reactions were followed spectrometrically by monitoring the nitrile oxide (2290 cm^{-1}), the oxime (3580 cm^{-1}), and the isoxazole (950 cm^{-1}). The k_{tot}, k_{Ox}, and k_{Is} values were calculated as described.[2a]

For reactions of (1b) in ethanol, dioxan, and DMF the k_{tot} values were obtained by volumetric analysis[14a] of the nitrile oxide, whereas the ratios $C_{Ox} : C_{Is}$ were measured at the end of each run as follows. After five or six half-lives (only traces of nitrile oxide could be detected by t.l.c.), two or three samples (10 ml) were removed from the reaction solution and the solvent was evaporated under reduced pressure (oil pump) at room temperature, the residue was treated with a few ml of CCl_4, and the above operation was repeated, and finally the residue was dissolved in CCl_4 (10 ml) and the concentrations of the oxime (C_{Ox}) and isoxazole (C_{Is}) were determined by i.r. The errors in the C_{Ox} and C_{Is} values measured on different samples were *ca.* ±1·5%. The same procedure repeated after ten half-lives gave identical values. The stability of the oxime (2b) for the same period as in the above experiments was checked on samples dissolved in dioxan and treated as described; the concentration of (2b) was constant within ±1·5%.

Product Distributions in the Reactions of p-*Chlorobenzonitrile* N-*Oxide* (1b) *and* p-*Toluonitrile* N-*Oxide* (1d) *with Phenylacetylene* (*PA*) *and Phenyl*[^{2}H]*acetylene* ([^{2}H]*PA*) *in Dioxan.*—A solution of the nitrile oxide (0·0010—0·0012 mol) and PA or [^{2}H]PA (0·018—0·023 mol) in dioxan (100 ml) was allowed to stand at the selected temperature (Table 4) for 3 h. For reactions with PA, the solution was successively treated with D_2O (2 ml) and 5% NaOD (2 ml) in D_2O and then stirred overnight. The solvent was removed *in vacuo* and the mixture of light and heavy isoxazoles was recrystallized from ethanol. The same procedure was employed for reactions with [^{2}H]PA, except that H_2O and a solution of NaOH in H_2O were used. The relative amounts of light and heavy isoxazoles corresponding to the original product composition derived from the two concurrent reactions,[19] were evaluated by i.r. (see above) or n.m.r. analysis. The latter ($CDCl_3$) was based on the ratios between the peaks areas at τ 3·40 (s, 4-H of isoxazole ring) and at 2·20—3·05 (m, ArH) for (1b) or at 7·66 (s, Me) for (1d).

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