Substituent Effects in 1,3-Dipolar Cycloadditions. Variable Reaction Paths for the Cycloaddition of Benzonitrile *N*-Oxides to Styrenes

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ρ Constants for the cycloadditions of substituted benzonitrile *N*-oxides to styrene, *p*-methoxystyrene, and *p*-nitro-styrene are small and vary with the nature of the substituent in the phenyl ring of the dipolarophile. The observed variations of the ρ values are interpreted in terms of a one-step concerted mechanism with a different extent of bond formation which produces partial charges in the transition state. An explanation of the relative order of reactivity of the three sets of reactions is given in terms of the polarizability of the carbon–carbon double bond induced by the substituent in the dipolarophile.

A SET of experimental data including stereo- and regio-selectivity, the low dependence of the reaction rates on solvent and substituent changes, and large and negative activation entropies, together with theoretical approaches, such as orbital symmetry rules [1] and correlation diagrams,[2] point to the concerted

[1] R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Verlag Chemie, Weinheim, 1970, p. 87.

[2] A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey, and E. Spindler, *Chem. Ber.*, 1967, **100**, 2192.

one-step nature of the mechanism of 1,3-dipolar cyclo-additions.[3] The cycloadditions of nitrile oxides[4] to unsaturated substrates to give five-membered hetero-cycles are also viewed[3] as concerted reactions. How-ever, on the basis of a critical re-examination of the experimental and theoretical aspects of typical 1,3-di-polar cycloadditions, including those of nitrile oxides, a two-step mechanism involving a diradical intermediate has been advanced.[5] The 'diradical' mechanism has been less commonly accepted than the 'concerted' mechanism.

In this paper we report further results on the sub-stituent effect obtained from the cycloaddition of benzo-nitrile N-oxides to styrenes to yield 2-isoxazolines.[6] These results supplement those previously given[7] and allow comment on the mechanism of the reaction. Probably owing to experimental difficulties due to the instability[4c,8] of benzonitrile oxides, the effect of substitution in these compounds has scarcely been investigated. The same holds for other 1,3-dipolar reagents with, however, a few exceptions.[3b,9] The problem of the influence of substituents on rates of 1,3-dipolar cycloadditions is still poorly understood and experimental data are needed to substantiate some promising theoretical treatments[10] of this subject.

RESULTS AND DISCUSSION

The kinetics of the cycloadditions of benzonitrile N-oxides (1) to styrene (2a), p-methoxystyrene (2b),

$$X C_6H_4C \equiv N O \qquad Y C_6H_4C H = CH_2$$

$$(1) \qquad\qquad (2)$$

a; X = H   a; Y = H
b; X = p-OMe   b; Y = p-OMe
c; X = p-Me   c; Y = p-NO$_2$
d; X = p-Cl
e; X = m-Cl
f; X = m-NO$_2$

$$X C_6H_4C \underset{N}{\overset{\|}{-\!\!-\!\!-}} \underset{\underset{O}{\diagdown\diagup}}{C} H_2$$
$$\overset{}{\underset{}{\quad} CH C_6H_4Y}$$

(3)

and p-nitrostyrene (2c) were studied in carbon tetra-chloride. The reactions of (1) with (2) were regio-

selective cycloadditions and, irrespective of substituents X and Y, yielded the 3,5-diaryl-2-isoxazolines (3). Isomers of (3) which derive from a different orientation of the cycloaddition between nitrile oxides (1) and styrenes (2) were not observed by t.l.c. and by n.m.r. examination of the crude reaction mixture. On a preparative scale, the only by-product observed (<5%) was the diarylfuroxan derived from the dimerization of (1); this side reaction was, however, negligible in the kinetic experiments. The structure of 3,5-diaryl-2-isoxa-zolines (3) is supported by their [1]H n.m.r. spectra which showed three multiplets due to the heterocyclic ring protons at τ 3·90—4·35 (5-H) and at ca. 6·30 and 6·70 (4-H$_2$); the area of the methylene resonance to that of the methine resonance was in the ratio 2 : 1. The n.m.r. spectra of adducts (3) are in agreement with those reported[11] for other 2-isoxazolines substituted by alkyl or aryl groups at C-3 and C-5, for which the τ values of 4-H$_2$ were found to be in the range 5·70—6·95 and those of 5-H in the range 3·65—4·32. Upfield resonances (τ 5·38—5·72) have been reported[11a,b] for 5-H$_2$ of 3-aryl-2-isoxazolines. The structure of some compounds was also confirmed by comparison of their physical data with those from the literature.

TABLE 1

Rate constants (k/l mol^{-1} s^{-1}) for some reactions of nitrile oxides (1) (initial concn. C_N/M) with styrenes (2) (initial concn. C_S/M) in CCl$_4$ at 25°

p-Methylbenzonitrile N-oxide (1c) + p-methoxystyrene (2b)

$10^2 C_S$	2·78	2·79	3·31	3·80
$10^2 C_N$	1·03	0·97	1·05	1·06
$10^2 k$	1·02	0·983	0·965	0·935

p-Methylbenzonitrile N-oxide (1c) + styrene (2a)

$10^2 C_S$	3·48	3·91	4·64	5·21
$10^2 C_N$	1·02	1·25	1·03	1·03
$10^3 k$	8·33	8·42	8·70	8·73

p-Methoxybenzonitrile N-oxide (1b) + p-nitrostyrene (2c)

$10^2 C_S$	2·17	2·77	4·30
$10^2 C_N$	1·10	1·08	1·11
$10^2 k$	2·21	2·28	2·26

The reactions, followed to 80—85% completion, gave results which fitted the second-order rate equation,* first-order with respect to nitrile oxides (1) and to styrenes (2). Reproducible values of the rate co-efficients were obtained from experiments at different initial concentrations of the reactants (Table 1). Aver-

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* The agreement with the second-order rate laws was checked in more detail for the reaction of mesitonitrile N-oxide with styrene by varying the relative initial concentrations by a factor of one hundred (see ref. 7). This could not be done for the reactions reported here owing to their considerably higher rates.

[3] (a) R. Huisgen, Angew. Chem. Internat. Edn., 1963, 2, 565; (b) p. 633; (c) Bull. Soc. chim. France, 1965, 3431; (d) J. Org. Chem., 1968, 33, 2291.

[4] Recent reviews on nitrile oxides include (a) C. Grundmann, Synthesis, 1970, 344; (b) A. Quilico, Chimica e Industria, 1971, 53, 157; (c) C. Grundmann and P. Grünanger, 'The Nitrile Oxides,' Springer-Verlag, Heidelberg–New York, 1971.

[5] (a) R. A. Firestone, J. Org. Chem., 1968, 33, 2285; (b) 1972, 37, 2181.

[6] G. Stagno d'Alcontres and P. Grünanger, Gazzetta, 1950, 80, 831; P. Grünanger, ibid., 1954, 84, 359; P. Vita Finzi and P. Grünanger, Chimica e Industria, 1965, 47, 516.

[7] A. Battaglia and A. Dondoni, Ricerca Sci., 1968, 38, 201.

[8] G. Barbaro, A. Battaglia, and A. Dondoni, J. Chem. Soc. (B), 1970, 588.

[9] P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, J. Amer. Chem. Soc., 1965, 87, 306.

[10] R. Sustmann, Tetrahedron Letters, 1971, 2717, 2721; R. Sustmann and H. Trill, Angew. Chem. Internat. Edn., 1972, 11, 838; R. Sustmann and R. Schubert, ibid., p. 840.

[11] (a) M. C. Aversa, G. Cum, and M. Crisafulli, Gazzetta, 1966, 96, 1046; (b) R. Sustmann, R. Huisgen, and H. Huber, Chem. Ber., 1967, 100, 1802; (c) G. Lo Vecchio, G. Cum, and G. Stagno d'Alcontres, Gazzetta, 1965, 95, 206; (d) K. Kotera, Y. Takano, A. Matsuura, and K. Kitahonoki, Tetrahedron, 1970, 26, 539; (e) B. J. Wakefield and D. J. Wright, J. Chem. Soc. (C), 1970, 1165; (f) A. Dondoni, G. Barbaro, A. Battaglia, and P. Giorgianni, J. Org. Chem., 1972, 37, 3196; (g) A. Dondoni and F. Taddei, Boll. sci. Fac. Chim. ind. Bologna, 1967, 25, 145.

age rate constants, some of which have already been reported,[7] are collected in Table 2.

Rate constants [a] ($k/1$ mol^{-1} s^{-1}) for the cycloadditions of nitrile oxides (1) to styrenes (2) at 25° in carbon tetrachloride

| Nitrile oxide | Styrenes | | |
| | (2c) | (2a) | (2b) |
	10^2k	10^2k	10^2k
(1b)	2·25	0·731 [b]	0·856
(1c)	2·42	0·855 [b]	0·975
(1a)	2·45	1·10 [b]	1·23
(1d)	2·91	1·66 [b]	2·17
(1e)	3·67	2·20 [b]	2·94
(1f)	4·67	4·38	6·25
	$\rho_x = +0.33$	$\rho_x = +0.79$	$\rho_x = +0.90$

[a] Each value is the average of three or more independent runs with a standard deviation of 2—3%. [b] Taken from ref. 7.

As observed for the reaction with phenylacetylene,[12] the rates of cycloaddition of substituted benzonitrile N-oxides (1) to each styrene (2a)—(2c) are well correlated by Hammett plots. The reaction constants ρ_x decrease linearly with the increasing electron-withdrawing characteristics of the substituent Y in (2), as expressed by the Hammett σ value: $\rho_x = +0.90$ ($r = 0.99$) for p-methoxystyrene, $\rho_x = +0.79$ ($r = 0.99$) for styrene, and $\rho_x = +0.33$ ($r = 0.98$) for p-nitrostyrene. Even more widespread variations of ρ values have been reported [3b] for the 1,3-dipolar cycloadditions of phenyl azides to olefinic dipolarophiles of different electronic density, viz. $\rho = -1.2$ (maleic anhydride), $\rho = -0.7$ (N-phenylmaleimide), $\rho = +0.8$ (norbornene),[9] $\rho = +2.6$ (pyrrolidinocyclohexene). Results similar to ours have been obtained for the Diels–Alder reaction of phenylbutadienes with nitrosobenzenes.[13]

These observations can be easily accommodated by a one-step concerted mechanism in which a four-centre transition state (4) with a charge imbalance is involved. This mechanism fits other experimental data,[7] namely the slight and non-linear dependence of the reaction rate on meta- and para-substitution in Ar^2, the low sensitivity of the rate constants to solvent polarity (carbon tetrachloride, 1,2-dichloroethane, chloroform, ethanol, acetonitrile), the low energy of activation (ca. 13 kcal mol^{-1}), and the large negative entropy of activation (ca. -27 cal mol^{-1} K^{-1}). By contrast, a two-step mechanism involving a zwitterionic intermediate with a positive charge on the carbon atom α to Ar^2 and a negative charge on the oxygen of the nitrile oxide, is a remote possibility since much larger substituent and solvent effects would be expected in this case.

A charge imbalance in the transition state has been suggested to explain the substituent and solvent effects of other concerted 1,3-dipolar cycloadditions.[9,14] Moreover, a transition state as a linear combination of

(4)

unpolar and zwitterionic structures, as reported for the Diels–Alder reaction cited above,[13] may be viewed according to the same standpoint. The positive values of ρ_x indicate that the CNO group is acting as an electron acceptor and C=C as an electron donor and that the formation of partial charges in the transition state (4) is consistent with a larger extent of carbon–carbon than carbon–oxygen bond formation. However, the relative extent of the new σ bonds varies with the polar nature of substituent Y as indicated by the variable ρ_x values. The decrease in ρ_x when Y becomes less electron-releasing points to a lowering of the polarity of the transition state (4), and this may be the consequence of increased bond formation between oxygen and carbon and decreased bond formation between carbon and carbon.

The polar effect of the substituents X and Y seems, however, not to be the only factor determining the rate of the reaction which is increased by every substituent Y other than hydrogen, regardless of the direction of its electronic effect. This is evident from the inspection of the rate data of Table 2 and from the V shaped Hammett correlation, where the lowest point corresponds to Y = H.[7] As has been already pointed out [3] for 1,3-dipolar cycloadditions in general and has been specifically observed for the reaction of a nitrile oxide with phenylacetylenes,[15] in the present case also the enhanced polarizability of the π system of the dipolarophile by substitution in the phenyl ring is an additional factor which has to be taken into account to explain the observed reactivity trend.* Hence the substituent Y affects the π electron densities and polarizability of the ethylenic carbon atoms so that the observed rate constants are due to the balance of these effects. The lowest rates are observed for Y = H since the rate-enhancing polarizability effect is absent in this case. The contribution of the polarizability effect of substituent X in the nitrile oxide cannot be excluded, but the observed linear Hammett plots indicate that in this case the polar effect dominates.

In conclusion, from the foregoing discussion it appears

* The accelerating effect by electron-releasing and -withdrawing groups in the dipolarophile can be also explained by a recent theoretical treatment [10] of the substituent effect of concerted cycloadditions based on a frontier orbital perturbational model. This approach which seems able to give an extensive explanation of the experimental facts, is not in contradiction with the conclusions reached by the conventional polarizability model.

[12] A. Dondoni, Tetrahedron Letters, 1967, 2397; A. Dondoni and G. Barbaro, to be published.

[13] G. Kresze and W. Kosbahn, Tetrahedron, 1971, 27, 1931; G. Kresze, H. Saitner, J. Firl, and W. Kosbahn, ibid., p. 1941.
[14] R. Huisgen and P. Otto, J. Amer. Chem. Soc., 1968, 90, 5342; P. Beltrame and C. Vintani, J. Chem. Soc. (B), 1970, 873; P. K. Kadaba, Tetrahedron, 1966, 22, 2453; P. K. Kadaba and T. F. Colturi, J. Heterocyclic Chem., 1969, 6, 829; P. K. Kadaba, Tetrahedron, 1969, 25, 3053; A. Battaglia, A. Dondoni, G. Maccagnani, and G. Mazzanti, J. Chem. Soc. (B), 1971, 2096.
[15] P. Beltrame, C. Veglio, and M. Simonetta, J. Chem. Soc. (B), 1967, 867.

that a one-step concerted mechanism with 'non-synchronous' * bond formation in the transition state fits the experimental data. However it seems that a general, detailed description of the transition state cannot be given, since, specifically from the inspection of the substituent effect, it appears that the relative extent of formation of the new bonds varies with the characteristics of the groups in the 1,3-dipole and in the dipolarophile. Hence it is not possible to exclude the intervention of a two-step mechanism involving a zwitterionic intermediate when the polar characteristics

recorded in deuteriochloroform with a JNM-PS-100 instrument at 25 °C, tetramethylsilane being used as internal standard.

Materials.—Preparations of the majority of nitrile oxides (1) have been reported.[8] *m*-Nitrobenzonitrile *N*-oxide (1f) was obtained as described [19] and recrystallized from benzene–light petroleum, m.p. *ca.* 84° in a preheated bath. Pure grade commercial samples of styrene (2a) and *p*-methoxystyrene (2b) were purified by distillation at reduced pressure. *p*-Nitrostyrene (2c), m.p. 29°, was prepared according to the literature method.[20] Reagent grade carbon tetrachloride was purified as reported.[8]

TABLE 3

N.m.r. spectra [a], physical and analytical data [b] of 3-(XC₆H₄)-5-(YC₆H₄)-2-isoxazolines (3)

Compound	Substituents		Chemical shifts (τ)			M.p. (°C)	Found (%)			Required (%)		
	X	Y	5-H	4-H	4-H		C	H	N	C	H	N
(3a)	*m*-NO₂	H	4·15	6·17	6·63	B.p. 195° at 0·4 mmHg	67·2	4·7	10·2	67·2	4·5	10·4
(3b)	*p*-OMe	*p*-OMe	4·33	6·33	6·95	139—140	72·1	6·1	4·95	72·3	6·05	4·95
(3c)	*p*-Me	*p*-OMe	4·45	6·41	6·81	128—129	77·0	6·65	5·2	76·4	6·4	5·25
(3d)	H	*p*-OMe	4·27	6·27	6·67	104—105 [c]	75·8	6·05	5·6	75·9	5·95	5·55
(3e)	*p*-Cl	*p*-OMe	4·33	6·32	6·72	156—157	66·5	4·95	4·85	66·8	4·9	4·85
(3f)	*m*-Cl	*p*-OMe	4·36	6·34	6·76	105—106	66·9	5·0	4·95	66·8	4·9	4·85
(3g)	*m*-NO₂	*p*-OMe	4·21	6·24	6·53	80—82	64·3	4·95	9·4	64·4	4·75	9·4
(3h)	*p*-OMe	*p*-NO₂	4·21	6·18	6·75	108—109	64·4	4·85	9·3	64·4	4·75	9·4
(3i)	*p*-Me	*p*-NO₂	4·21	6·15	6·72	166—167	68·1	5·05	9·95	68·1	5·0	9·9
(3j)	H	*p*-NO₂	4·12	6·06	6·63	133—134 [d]	67·0	4·65	10·4	67·2	4·5	10·4
(3k)	*p*-Cl	*p*-NO₂	4·24	6·17	6·69	116—117	59·4	3·85	9·15	59·5	3·65	9·25
(3l)	*m*-Cl	*p*-NO₂	4·09	6·10	6·70	100—101	59·6	3·85	9·25	59·5	3·65	9·25
(3m)	*m*-NO₂	*p*-NO₂	3·91	5·96	6·55	156—157	57·7	3·55	13·3	57·5	3·55	13·4

[a] In CDCl₃. Only the chemical shifts of the isoxazoline ring protons are given; error in chemical shift is ±0·4 Hz. [b] All solid products were crystallized from benzene–light petroleum. [c] Lit. m.p. 106—107° (P. Grünanger, *Gazzetta*, 1954, **84**, 359); 103—104° (K. V. Auwers and H. Brink, *Annalen*, 1932, 493). [d] Lit. m.p. 132—133° (F. Monforte and G. Lo Vecchio, *Gazzetta*, 1953, **83**, 416).

TABLE 4

Typical run for cycloaddition of *p*-ClC₆H₄CNO (1d) (0·00986M) to *p*-MeOC₆H₄CH=CH₂ (2b) (0·0229M) at 25° in carbon tetrachloride

Time (s)	0	23	240	480	780	1080	1385	1680	1980	2340	2760	3180	3720
O.D.[a] × 10³	566	559	504	448	395	353	312	274	248	217	185	164	136
Reaction (%)	0	1·2	10·9	20·9	30·2	37·6	44·8	51·6	56·2	61·7	67·3	71·0	76·0
$10^2 k/l$ mol⁻¹s⁻¹		2·17	2·17	2·25	2·18	2·11	2·12	2·18	2·14	2·15	2·17	2·12	2·14

[a] Apparent optical density at 2285 cm⁻¹ (1 mm sodium chloride cell); the apparent molar extinction coefficient ε was 57·4.

of the reagents are such that the two bonds may be formed in distinct steps. Whenever this conclusion is generalized to other 1,3-dipolar cycloadditions, one might expect a mechanistic spectrum instead of *one* unique path.† In the same way, the extensive acceptance for these reactions of a two-step mechanism involving a diradical intermediate [5] seems not to be justified. For instance, results on the secondary deuterium isotope effect [17] appear inconsistent with this mechanism, and theoretical treatments [18] of some aspects of these cycloadditions, such as their regioselectivity, account for the experimental facts without considering the intervention of diradical intermediates.

EXPERIMENTAL

I.r. measurements were determined with a Perkin-Elmer 257 grating spectrophotometer, n.m.r. spectra were

* For a precise distinction between the terms 'concerted' and 'synchronous' in cycloaddition reactions, see ref. 3d.
† Cautionary notes on the extensive acceptance of a single mechanism for multicentre reactions, such as Diels–Alder and 1,3-dipolar cycloadditions, have appeared.[16]

3,5-Diaryl-2-isoxazolines (3).—Standard conditions similar to those of the kinetic experiments were employed for the preparations of cycloadducts (3). Nitrile oxide (1) (0·0035 mol) and arylethylene (2) (0·0082 mol) were left overnight at 25 °C in carbon tetrachloride (150 ml). The solvent was distilled off under reduced pressure and the residue was treated with light petroleum (15 ml) to dissolve the excess of (2) and induce the crystallization of (3). The isoxazoline (3; X = *m*-NO₂, Y = H) was an oil which could be distilled under high vacuum. In the other cases the filtration of the solid material gave the isoxazoline (*ca.* 90%) which on t.l.c. [silica; benzene–light petroleum (1 : 1)] showed only traces of diarylfuroxan as an impurity. The light petroleum filtrate, after distillation of the solvent

[16] R. W. Alder, R. Baker, and J. M. Brown, 'Mechanism in Organic Chemistry,' Wiley-Interscience, New York, 1971, ch. 4.
[17] W. R. Dolbier, jun. and S. H. Dai, *Tetrahedron Letters*, 1970, 4645; W. F. Bayne and E. I. Snyder, *ibid.*, p. 2263; K. N. Houk and C. R. Watts, *ibid.*, p. 4025.
[18] J. Bastide, N. El Ghandour, and O. Henri-Rousseau, *Tetrahedron Letters*, 1972, 4225; K. N. Houk, *J. Amer. Chem. Soc.*, 1972, **94**, 8953.
[19] G. Bianchi and G. Frati, *Gazzetta*, 1966, **96**, 562.
[20] R. H. Wiley and N. R. Smith, *Org. Synth.*, 1963, **4**, 731.

and chromatography of the residue [silica; benzene–light petroleum (1 : 1)] gave a further quantity (*ca.* 5%) of (3) and furoxan (2—3%). The n.m.r. spectra of the crude 2-isoxazolines (3) showed, besides the aromatic (and occasionally methyl) resonances, a quartet at τ *ca.* 4·2 and two multiplets at 6·30 and 6·70. Resonances which could be attributed to the presence of the regio-isomer of (3) were not observed. Crystallization of the crude material from suitable solvents gave products of analytical purity and whose n.m.r. spectra were practically unchanged with respect to the uncrystallized products. The i.r. spectra of some cycloadducts (3) have been previously reported.[21] Table 3 summarizes some of the characteristics of 2-isoxazolines (3) not previously described.[7,11g]

Kinetics.—Rates of reaction were measured as described [8,12] by following the disappearance of the nitrile oxide band at *ca.* 2290 cm^{-1}. The measured absorbances were transformed to molar concentration values by calibration curves which were linear in the range of concentrations employed [0·008—0·012M for (1) and 0·02—0·06 for (2)]. The rate constants were calculated graphically in the majority of runs from the linear plots by a least-squares fit of the experimental data according to the second-order rate equation. The results of a typical run, also including the rate constants calculated at intervals, are shown in Table **4**. The competitive dimerization of nitrile oxides to furoxans was considered to be negligible within the limits of the method of analysis employed. This is supported by the reproducibility of the rate constants calculated at intervals as shown in Table 4 and by the considerably lower rates of dimerization.[8,12]

[21] Sadtler Standard Spectra Catalog, 1969, spectra no. 36516–36525.