A Kinetic Study of the 1,3-Cycloaddition of Benzonitrile Oxides to *para*-Substituted β-Aminocinnamonitriles

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Stable arylnitrile oxides undergo 1,3-cycloaddition to β-aminocinnamonitriles at the C≡N or the C=C bond, which gives rise to 3,5-disubstituted 1,2,4-oxadiazoles or 3,5-diaryl-4-cyanoisoxazoles, respectively, by parallel reactions in different solvents. Overall kinetics were measured at temperatures in the range 50–90 °C; product selectivities were determined by HPLC rate coefficients for the parallel reactions were, thus, obtained. Rates were enhanced by increasing the solvent polarity. Hammett plots for substitution on the nitrile oxide benzene ring were V-shaped; those for substitution on the enaminonitrile benzene ring had negative ρ-values.

In the 1,3-cycloadditions of benzonitrile oxides to unsaturated molecules the C=C and C≡N bonds, when considered separately, are dipolarophiles of quite different reactivity, the former being stronger than the latter. For instance, for the reactions of mesitonitrile oxide with styrene and with benzonitrile in CCl_4 at 50 °C, rate coefficients of 1.94×10^{-3} and 4.60×10^{-5} dm^3 mol^{-1} s^{-1}, respectively, were reported,[1] *i.e.* the rate of attack at C=C is greater by a factor of 42. Moreover, in the case of aliphatic nitriles, 1,3-cycloaddition involving nitrile oxides can only be effected under certain conditions.[2] We have now chosen β-enaminonitriles as dipolarophiles since both unsaturated centres are carried on the same molecule. Reports on the chemistry of systems of this type have been published,[3] with evidence of parallel–consecutive reactions which seemed to deserve a kinetic study.

The stable nitrile oxides (**1a–e**) and enaminonitriles (**2f–j**) have been employed and found to yield adducts of general formulae (**3**) and (**4**) (Scheme). Measurements show the influence of substituents X and Y, of solvent and of temperature on the rates of the parallel reactions onto C≡N and C=C bonds.

In the Scheme, β-aminocinnamonitriles (**2**) are written in the more usual *Z*-configuration.[4] As a consequence adducts (**3**) are written in the corresponding configuration. The dimethyl-substituted benzene ring should be viewed as rotated out of the plane of systems (**3**) and (**4**).

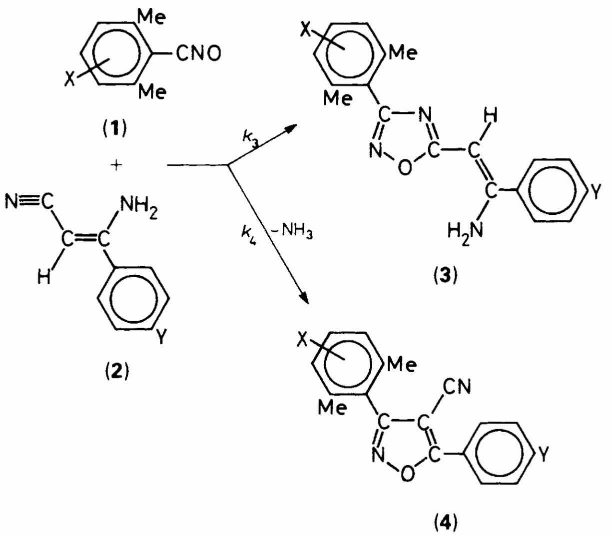
Experimental

M.p.s are uncorrected. IR spectra were recorded with a Perkin-Elmer 1310 spectrometer, ^{1}H NMR spectra with a Varian FT 80 instrument ($SiMe_4$ internal standard, $CDCl_3$ as the solvent).

Reagent grade reagents and solvents were used. The following solvents were employed: 1,1,2,2-tetrachloroethane (TCE), chloroform, and mixtures of *N*,*N*-dimethylformamide (DMF) with TCE or $CHCl_3$, or CCl_4, containing different amounts of DMF (8 and 16% by volume in mixtures indicated as (*A*) and (*B*), respectively).

Materials.—Nitrile oxides (**1a–e**) were obtained as described.[5] β-Amino-cinnamonitriles (**2f–j**) were prepared by reported procedures.[3]

General Procedure for the Reaction of Compounds (**1a–e**) *with β-Enaminonitriles* (**2f–j**).—A solution of (**1**) (0.01 mol) and (**2**) (0.02 mol) in chloroform or in $CHCl_3$/DMF(*B*) was kept at 50–60 °C for 48 h.



a; X = 4-OMe	**f**; Y = OMe
b; X = 4-Me	**g**; Y = Me
c; X = H	**h**; Y = H
d; X = 4-Br	i; Y = Cl
e; X = 3,5-Cl_2, 4-Me	**j**; Y = CF_3

Scheme.

The solvent was evaporated under reduced pressure and the residue was fractionated by flash chromatography on silica gel (Merck) (230–400 mesh) column of 25 cm length and 3.2 cm internal diameter, eluting with a mixture of light petroleum (40–70 °C): acetonitrile 97:3 (v:v). The flow rate of eluant was 5 cm min^{-1}. Separated products were recrystallized: (**3**) from a light petroleum–benzene mixture and (**4**) from light petroleum. The compound (**4c** + **h**) was further purified by HPLC chromatography. Compounds (**3**) and (**4**) (all of them so far not described) were characterized by elemental analysis and ^{1}H NMR spectroscopy (Tables 1 and 2). The IR analysis showed typical bands at 3 500–3 490 and 3 310–3 300 cm^{-1} (NH_2) for (**3**) and a band at 2 240–2 220 cm^{-1} (CN) for (**4**).

Reaction Selectivities.—Besides the excess β-enaminonitrile, the analysis revealed the occurrence of compounds (**3**) and (**4**), exclusively. These products were determined in the reaction

Table 1. Analytical data for cycloadducts (**3**).

Adduct (**3**)	M.p./ °C	Formula	Elemental analysis (%)[a]			δ_H(ppm)					
			C	H	N	H_{ar}(range)	$-NH_2$ (s)	CH=C (s)	Y (s)	X (s)	CH_3 (*ortho*) (s)
(**a** + **f**)	192	$C_{20}H_{21}N_3O_3$	68.5 (68.3)	6.2 (6.0)	11.9 (12.0)	7.75–6.75	6.60	5.58	3.95	3.88	2.25
(**a** + **h**)	164	$C_{19}H_{19}N_3O_2$	70.6 (71.0)	6.1 (6.0)	12.8 (13.1)	7.80–6.78	6.60	5.62		3.88	2.25
(**b** + **f**)	196	$C_{20}H_{21}N_3O_2$	71.8 (71.6)	6.2 (6.3)	12.4 (12.5)	7.63–6.90	6.56	5.53	3.85	2.32	2.24
(**b** + **h**)	172	$C_{19}H_{19}N_3O$	74.5 (74.7)	6.4 (6.3)	13.7 (13.8)	7.78–7.01	6.62	5.60		2.34	2.22
(**b** + **i**)	203	$C_{19}H_{18}ClN_3O$	67.0 (67.1)	5.4 (5.3)	12.4 (12.4)	7.58–6.95	6.55	5.54		2.33	2.23
(**c** + **f**)	173	$C_{19}H_{19}N_3O_2$	70.9 (71.0)	5.9 (6.0)	13.1 (13.1)	7.63–6.95	6.60	5.58	3.90		2.25
(**c** + **h**)	150	$C_{18}H_{17}N_3O$	73.8 (74.2)	6.0 (5.9)	14.3 (14.4)	7.82–7.08	6.62	5.60			2.28
(**c** + **i**)	182	$C_{18}H_{16}ClN_3O$	66.6 (66.3)	4.9 (5.0)	13.0 (12.9)	7.63–7.05	6.51	5.55			2.26
(**d** + **f**)	199	$C_{19}H_{18}BrN_3O_2$	56.9 (57.0)	4.6 (4.5)	10.4 (10.5)	7.70–6.92	6.60	5.60	3.88		2.28
(**d** + **h**)	200	$C_{18}H_{16}BrN_3O$	58.2 (58.4)	4.5 (4.4)	11.2 (11.4)	7.80–7.30	6.65	5.60			2.25
(**d** + **i**)	200	$C_{18}H_{15}BrN_3ClO$	53.5 (53.4)	3.7 (3.7)	10.4 (10.4)	7.58–7.30	6.55	5.55			2.24
(**e** + **f**)	240	$C_{20}H_{19}Cl_2N_3O_2$	59.2 (59.4)	4.8 (4.7)	10.2 (10.4)	7.63–6.90	6.56	5.54	3.86	2.57	2.24
(**e** + **g**)	254	$C_{20}H_{19}Cl_2N_3O$	61.7 (61.9)	5.1 (5.2)	10.7 (10.8)	7.55–7.17	6.52	5.57	2.41	2.57	2.24
(**e** + **h**)	230	$C_{19}H_{17}Cl_2N_3O$	61.2 (61.0)	4.6 (4.6)	11.5 (11.2)	7.70–7.30	6.60	5.59		2.58	2.25
(**e** + **i**)	240	$C_{19}H_{16}Cl_3N_3O$	55.7 (55.8)	4.1 (4.0)	10.1 (10.3)	7.66–7.40	6.55	5.56		2.58	2.24
(**e** + **j**)	268.5	$C_{20}H_{16}Cl_2F_3N_3O$	54.1 (54.3)	3.8 (3.7)	9.3 (9.5)	7.85–7.75	6.65	5.62		2.58	2.25

[a] Calculated values in parentheses.

mixtures, after reaction for *ca.* 10 half-lives (solvent, temperature, and reactant concentrations as in the kinetic runs), followed by dilution with chloroform, using reversed-phase HPLC analysis.

Column RSil C_{18} Alltech (length 25 cm, internal diameter 4.6 mm), or Microbondapak C_{18} Waters (length 30 cm, internal diameter 3.9 mm) were employed. The eluant (1 cm^3 min^{-1}) was usually a mixture methanol–water (water content in the range 2–15% v:v), while, in the case of the reaction of (**1b**) with (**2h**), it was a mixture of methanol–water–acetonitrile (70:18:12 by volume). A UV detector was employed in the range 285–320 nm.

All determinations were carried out on the basis of calibration plots on the pure compounds. Stilbene was used as a reference; its solutions in chloroform were used shortly after preparation and kept in the dark. Duplicate analyses were carried out, and results averaged.

Selectivity values s_3 and s_4 were obtained from the molar concentrations c_3 and c_4 since $s_3 = c_3/(c_3 + c_4)$; $s_4 = c_4/(c_3 + c_4)$.

Direct evidence for parallel reactions (as indicated in the Scheme) was obtained for the case of (**1e**) + (**2f**) in solvent TCE/DMF(*B*) at 80 °C: aliquots taken at different times, corresponding to 12, 30, 45, 62, and 75% fractional conversion, showed a constant s_3 (0.48 ± 0.02) in agreement with the 'infinity' value (s_3 = 0.49). Product (**3e** + **f**) was shown to be stable in the reaction solvent, at 80 °C, in the presence of excess (**2f**).

Kinetics.—The reactions were carried out in a thermostatted 1 mm sodium chloride cell (Beckmann FH-01 variable temperature cell) positioned in an IR spectrometer. The temperature was kept constant to within ± 0.2 °C. Quantitative analyses were made of the band at 2 280–2 300 cm^{-1}, typical of nitrile oxides (**1**). The concentration of the latter was *ca.* 0.02 mol dm^{-3}, while for enaminonitriles (**2**) it was in the range 0.2–0.5 mol dm^{-3}.

Absorbance values were obtained from the peak heights and the concentration read from calibration plots. Kinetic runs were carried out for up to one to two half-lives, and results interpreted by the equation for second-order reactions [equation (1)].

$$\ln(c_2/c_1) = (c_2{}^0 - c_1{}^0)kt + \text{constant} \qquad (1)$$

The overall kinetic coefficients (k) were then split into k_3 and k_4 parameters on the basis of the selectivity values s_3 and s_4, since for parallel reactions: $k_3 = ks_3$; $k_5 = ks_4$. Duplicate kinetic runs were always carried out with good reproducibility.

Results and Discussion

Most runs were carried out either in TCE or in TCE/DMF (*B*). Other solvents or solvent mixtures were employed in a few cases, mainly concerning reaction (**1e**) + (**2f**).

Two kinds of runs were carried out, one aimed at determining the reaction products, the other at measuring the overall rate of disappearance of reactant (**1**). A combination of these experimental results gave the rate coefficients k_3 and k_4 for the formation of (**3**) and (**4**), respectively.

No products other than (**3**) and (**4**) were detected; therefore, the picture, with our sterically hindered benzonitrile oxides, is simpler than in the case of the unsubstituted or *p*-substituted benzonitrile oxides previously considered.[3] Formation of (**3**) is a

Table 2. Analytical data for cycloadducts (**4**).

			Elemental analysis (%)[a]			δ_H(ppm)			
Adduct (**4**)	M.p./ °C	Formula	C	H	N	H_{ar}(range)	Y (s)	X (s)	CH_3 (*ortho*) (s)
(**a** + **f**)	120	$C_{20}H_{18}N_2O_3$	71.6	5.7	8.3	8.22–6.74	3.95	3.86	2.25
			(71.8)	(5.4)	(8.4)				
(**a** + **h**)	124	$C_{19}H_{16}N_2O_2$	74.8	5.4	9.4	8.32–6.72		3.88	2.18
			(75.0)	(5.3)	(9.2)				
(**b** + **f**)	112	$C_{20}H_{18}N_2O_2$	75.7	6.0	9.0	8.19–6.95	3.92	2.32	2.22
			(75.4)	(5.7)	(8.8)				
(**b** + **h**)	110	$C_{19}H_{16}N_2O$	78.9	5.6	9.8	8.35–7.05		2.38	2.22
			(79.1)	(5.6)	(9.7)				
(**b** + **i**)	132	$C_{19}H_{15}ClN_2O$	70.4	4.7	8.7	8.25–7.05		2.38	2.22
			(70.7)	(4.7)	(8.7)				
(**c** + **f**)	102	$C_{19}H_{16}N_2O_2$	74.7	5.5	9.2	8.32–7.08	3.96		2.30
			(75.0)	(5.3)	(9.2)				
(**c** + **h**)	74.5	$C_{18}H_{14}N_2O$	78.7	5.4	10.0	8.30–7.28			2.25
			(78.8)	(5.2)	(10.2)				
(**c** + **i**)	153	$C_{18}H_{13}ClN_2O$	70.2	4.7	9.1	8.30–7.00			2.18
			(70.0)	(4.3)	(9.1)				
(**d** + **f**)	114	$C_{19}H_{15}BrN_2O_2$	59.1	4.2	7.5	8.30–7.05	3.92		2.25
			(59.5)	(4.0)	(7.3)				
(**d** + **h**)	109	$C_{18}H_{13}BrN_2O$	60.9	3.8	8.0	8.28–7.22			2.18
			(61.2)	(3.7)	(7.9)				
(**d** + **i**)	167	$C_{18}H_{12}BrClN_2O$	55.4	3.2	7.2	8.22–7.30			2.25
			(55.8)	(3.1)	(7.2)				
(**e** + **f**)	160	$C_{20}H_{16}Cl_2N_2O_2$	61.9	4.3	7.4	8.16–7.00	3.90	2.57	2.24
			(62.0)	(4.2)	(7.2)				
(**e** + **g**)	173	$C_{20}H_{16}Cl_2N_2O$	64.4	4.3	7.5	8.21–7.35	2.47	2.59	2.25
			(64.7)	(4.4)	(7.6)				
(**e** + **h**)	196	$C_{19}H_{14}Cl_2N_2O$	63.6	3.9	7.7	8.34–7.56		2.62	2.25
			(63.9)	(4.0)	(7.8)				
(**e** + **i**)	174	$C_{19}H_{13}Cl_3N_2O$	57.9	3.3	7.0	7.63–6.90		2.60	2.24
			(58.2)	(3.4)	(7.2)				
(**e** + **j**)	163	$C_{20}H_{13}Cl_2F_3N_2O$	56.4	3.1	6.5	8.45–7.85		2.62	2.25
			(56.5)	(3.1)	(6.6)				

[a] Calculated values in parentheses.

straightforward cycloaddition to the C≡N bond; the concurrent cycloaddition onto the C=C bond is accompanied by loss of ammonia, giving rise to adducts (**4**). The results concerning the selectivities s_3 and s_4 are collected in Table 3.

By examining Table 3 it can be appreciated that only a mild effect is observed when changing X on the nitrile oxide; for instance, in the set of reactions (**1a–e**) + (**2f**) at 70 °C, s_4 varies only in the range 0.22–0.35 with TCE as solvent, and from 0.42 to 0.57 when the solvent is TCE/DMF(*B*). So, the most noticeable effect is the dependence on the solvent composition, rather than on the nature of the substituent X. Selectivity s_4 is almost doubled by the presence of DMF (16%) in the solvent.

A change of substituent Y on the enaminonitrile has a stronger effect on selectivity: for the set of reactions (**1e**) + (**2f–j**) at 70 °C, results in Table 3 show that s_4 varies in the range 0.35–0.08 in solvent TCE, and from 0.57 to 0.22 in TCE/DMF(*B*); s_4 is again markedly increased by the addition of DMF to the solvent. As to the sign of the substituent effects, an increase in the electronegativity of X has a substantially positive effect on s_4, while a similar increase for Y has a negative effect.

The positive effect on s_4 of the addition of DMF to the solvent, noticed for the TCE/DMF system, is present also when the $CHCl_3$/DMF or the CCl_4/DMF systems are considered [Table 3; reaction (**1e**) + (**2f**) at 50 °C].

Kinetic runs were carried out in the range 50–90 °C, choosing 70 °C as the temperature for systematic comparisons. Results are presented in Tables 4 and 5.

Substituent effects on the rates of the parallel reactions can be obtained by examination of Table 4. Two Hammett plots (for k_3 and k_4, respectively) can be drawn for each of the following sets of reactants: (**1a–e**) + (**2f**), both in solvent TCE and in TCE/DMF (*B*), (**1a–e**) + (**2h**) in solvent TCE; (**1e**) + (**2f–j**) in both solvents. Of these ten plots, six refer to the kinetic effects of substituent X, four to substituent Y. The six plots of the former type all have a 'V-shape', with a minimum rate coefficient, generally for X=H; the right-hand branches show slopes of the order of +1, both for k_3 and for k_4 coefficients; the left-hand branches present slopes in the range from −0.3 to −1.0 for k_3 values, and from *ca.* 0 to −0.6 for k_4 values. An example of V-shaped plot is given in the Figure. The change of solvent, from TCE to TCE/DMF(*B*), affects k_3 very little, and has a substantial (accelerating) effect only on k_4, *i.e.* on the addition to the C=C bond (Table 4).

The Hammett plots for reactions (**1e**) + (**2f–j**), that is those referring to the effect of substituents Y, are not perfectly linear plots but consistently present negative slopes. Approximate ρ-values from k_3 coefficients are very low (−0.2, −0.1), while those from k_4 coefficients are of the order of −1. In most cases, the solvent effect is modest on k_3 coefficients, while the DMF addition substantially increases k_4, as already noted.

Further kinetic measurements are reported in Table 5. Among these, some refer to the reaction (**1e**) + (**2f**) at 50 °C in different solvents. Three series were considered, *i.e.*, (*i*) TCE, TCE/DMF(*A*), TCE/DMF(*B*); (*ii*) $CHCl_3$, $CHCl_3$/DMF(*A*), $CHCl_3$/DMF(*B*); (*iii*) CCl_4/DMF(*A*), CCl_4/DMF(*B*). In all cases, an increase in relative permittivity along the series is involved. The relative permittivities of the mixed solvents, calculated on the ideal assumption of a linear combination of

Table 3. Reaction products of type (3) and (4), as determined by HPLC after complete reaction.

				Molar fraction of products	
T/°C	Solvent[a]	Nitrile oxide[b]	Dipolar-ophile[b]	(3)	(4)
70	TCE	**(1a)**	**(2f)**	0.78	0.22
	TCE/DMF(*B*)			0.58	0.42
	TCE		**(2h)**	0.87	0.13
	TCE/DMF(*B*)			0.78	0.22
	TCE	**(1b)**	**(2f)**	0.76	0.24
	TCE/DMF(*B*)			0.58	0.42
	TCE		**(2h)**	0.89	0.11
	TCE	**(1c)**	**(2f)**	0.70	0.30
	TCE/DMF(*B*)			0.49	0.51
	TCE		**(2h)**	0.89	0.11
	TCE	**(1d)**	**(2f)**	0.70	0.30
	TCE/DMF(*B*)			0.51	0.49
	TCE		**(2h)**	0.83	0.17
50	TCE	**(1e)**	**(2f)**	0.60	0.40
60				0.63	0.37
70				0.65	0.35
80				0.70	0.30
50	TCE/DMF(*A*)			0.48	0.52
50	TCE/DMF(*B*)			0.38	0.62
60				0.42	0.58
70				0.43	0.57
80				0.49	0.51
50	$CHCl_3$			0.64	0.36
	$CHCl_3$/DMF(*A*)			0.51	0.49
	$CHCl_3$/DMF(*B*)			0.43	0.57
	CCl_4/DMF(*A*)			0.53	0.47
	CCl_4/DMF(*B*)			0.38	0.62
50	TCE	**(1e)**	**(2g)**	0.76	0.24
70				0.80	0.20
80				0.84	0.16
70	TCE/DMF(*B*)			0.54	0.46
50	TCE	**(1e)**	**(2h)**	0.83	0.17
70				0.85	0.15
80				0.86	0.14
70	TCE/DMF(*B*)			0.66	0.34
60	TCE	**(1e)**	**(2i)**	0.86	0.14
70				0.88	0.12
80				0.89	0.11
90				0.90	0.10
70	TCE/DMF(*B*)			0.70	0.30
60	TCE	**(1e)**	**(2j)**	0.92	0.08
70				0.92	0.08
80				0.93	0.07
90				0.93	0.07
70	TCE/DMF(*B*)			0.78	0.22

[a] TCE = 1,1,2,2-tetrachloroethane; DMF = *N*,*N*-dimethylformamide; (*A*) and (*B*) indicate solvent mixtures with 8% and 16% by volume of DMF, respectively, that is having C_{DMF} = 1.033 and 2.066 mol dm^{-3}, respectively; [b] initial concentrations: **(1)**, *ca.* 0.02; **(2)**, 0.2–0.5 mol dm^{-3}.

the constants of pure solvents, based on their volume fraction in the mixture, increase along the series as follows: (*i*) 8.08, 10.4, 12.7; (*ii*) 4.80, 7.4, 9.9; (*iii*) 5.0, 7.8. In the last case a comparison is possible with measured constants of the mixtures, which were reported[6] as 4.5 for CCl_4/DMF(*A*) and 6.9 for CCl_4/DMF(*B*), in fair agreement with the estimated values. Values of k_3 in Table 5 are only weakly, if at all, increasing when the solvent polarity increases; on the other hand, coefficient k_4 increases rather steeply, along the following sequences: (*i*) 0.19:0.39:0.60; (*ii*) 0.16:0.35:0.49; (*iii*) 0.60:1.15. This is in agreement with the previous observations about data in Table 4.

Table 5 also contains results about the temperature dependence of the reactions in the system **(1e)** + **(2f–j)**, mostly in solvent TCE. Activation parameters were evaluated (Table 6). Values of $\Delta E_{a,3}$ are larger than those of $\Delta E_{a,4}$, *i.e.* higher temperatures favour the production of adducts **(3)** (see values of s_3 in Table 3). Activation entropies are all large and negative (in most cases $\Delta S^‡ < -100$ J $mol^{-1}K^{-1}$), a common finding for concerted cycloadditions.

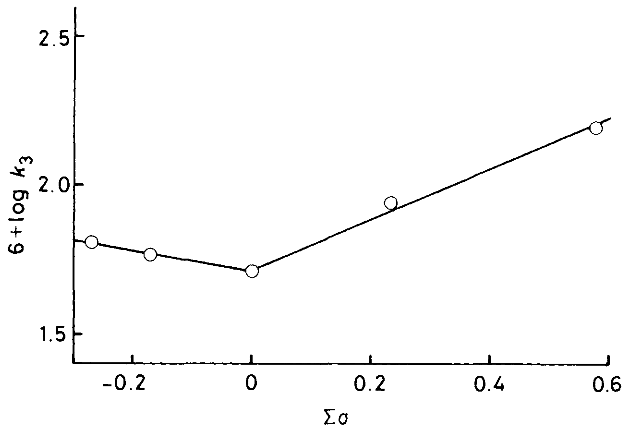


Figure. Hammett plot for rate coefficients k_3 of reactions **(1a–e)** + **(2h)** in TCE at 70 °C. Left-hand and right-hand branches have slopes ρ −0.34 and +0.85, respectively.

Discussing first the solvent effects, it seems worth considering that DMF, when added to the chlorinated hydrocarbons, besides increasing the solvent polarity, makes the solvent a better hydrogen-bond acceptor. This can have noticeable consequences, since there is evidence[7] that the transition states of the 1,3-cycloaddition of benzonitrile oxide to *o*-acylaminobenzonitriles and of 4-chlorobenzonitrile oxide to β-aminocinnamonitriles are stabilized by a hydrogen bond between the NHR group of the dipolarophile and CNO oxygen of the 1,3-dipole, provided the solvent is not a strong hydrogen-bond acceptor; the stabilization is substantially reduced when a solvent like DMF is used instead. If a similar interaction is present in the transition state of our reaction on the path to adducts **(3)**, the interacting moieties being the NH_2 group of **(2)** and the CNO oxygen of **(1)**, the addition of DMF to a chlorinated solvent would disturb the internal hydrogen bond and would tend to determine a decrease of the coefficient k_3.

The adduct **(3)** itself, in a conformation similar to the one drawn in the Scheme, is likely to present a hydrogen bond between NH_2 and O, as can be checked using molecular models.

Summing up, the solvent effect found experimentally can be interpreted as being due to the polar nature of both transition states [on the paths to adducts **(3)** and **(4)**], so that an increasing solvent polarity tends to enhance the rates of both reactions. However, when the increase of polarity is obtained by adding DMF, which has the negative effect on k_3 mentioned above, the net result is that coefficients k_3 are little affected, while coefficients k_4 are markedly enhanced.

Thus, fairly polar transition states (that is, more polar than the initial system (**1** + **2**) corresponding to each of them) are consistent with the measured solvent effects. Such a polar nature should derive from the asynchronous character of the concerted cycloadditions, leading to one bond formation being ahead of the other. This can also justify the substituent effects. So, for addition of **(1a–e)** to **(2h)**, electron-releasing X substituents can stabilize transition states with a partial positive charge on the nitrile oxide moiety, deriving from a O . . . C bond formation in advance with respect to the C . . . C or C . . . N bond formation;

Table 4. Kinetic runs at 70.0 °C.

Nitrile oxide	Dipolar-ophile	Kinetic coefficients/10^{-4}dm^3 mol^{-1}s^{-1} [a] k	k_3	k_4
		Solvent: TCE		
(1a)	**(2f)**	1.060 ± 0.032	0.83	0.23
	(2h)	0.743 ± 0.003	0.64	0.10
(1b)	**(2f)**	0.910 ± 0.018	0.70	0.21
	(2h)	0.658 ± 0.008	0.59	0.07
(1c)	**(2f)**	0.773 ± 0.020	0.54	0.23
	(2h)	0.586 ± 0.006	0.52	0.07
(1d)	**(2f)**	1.37 ± 0.05	0.96	0.41
	(2h)	1.052 ± 0.072	0.87	0.18
(1e)	**(2f)**	2.39 ± 0.07	1.55	0.84
	(2g)	1.83 ± 0.01	1.47	0.36
	(2h)	1.80 ± 0.03	1.52	0.28
	(2i)	1.60 ± 0.03	1.41	0.19
	(2j)	1.13 ± 0.03	1.04	0.09
		Solvent: TCE/DMF(*B*)[b]		
(1a)	**(2f)**	1.44 ± 0.07	0.84	0.60
(1b)		1.21 ± 0.01	0.70	0.51
(1c)		0.950 ± 0.027	0.46	0.49
(1d)		2.10 ± 0.01	1.07	1.03
(1e)	**(2f)**	4.15 ± 0.06	1.79	2.36
	(2g)	2.90 ± 0.07	1.57	1.33
	(2h)	2.45 ± 0.10	1.61	0.84
	(2i)	2.08 ± 0.01	1.45	0.63
	(2j)	1.99 ± 0.04	1.56	0.43

[a] k_3 and k_4 were obtained by the equation: $k_i = k$ (fraction of product *i*); [b] 16% by volume of DMF.

electron-withdrawing X substituents can stabilize transition states with a partial negative charge on the nitrile oxide, as derives from the opposite timing of bonds formation. Similar considerations also apply to the case of the system (**1a**–**e**) + (**2f**).

When the case of (**1e**) + (**2f**–**j**) is considered, the CNO group in (**1e**) has to be taken as being partially positive, due to the electronegative character of the substituents on the aryl group ($\Sigma\sigma = 0.576$); therefore, the C ... C or C ... N bond is likely to be formed ahead of the O ... C bond. A partial positive charge would be present on the enaminonitrile moiety of the transition state, and negative ρ-values are well justified. It is understandable that stronger effects are found on coefficients k_4, since for addition to the C=C bond the substituted aryl group is just at the reaction site, while for addition to C≡N bond it is farther away.

The charge imbalance that determines these effects has to be, in any case, rather mild, since moderate effects were observed. It can be mentioned, as to the effect of substituents X, that similar V-shaped Hammett plots had already been obtained for the 1,3-cycloaddition of the same nitrile oxides to aliphatic nitriles.[2]

A different way of considering 1,3-cycloadditions is based on the concept of frontier molecular orbitals (FMO).[8] This approach can be applied to the case of the reaction onto the C=C bond of (**2**), of rate coefficient k_4.

Consideration of the reaction series (**1a**–**e**) + (**2h**): With HCNO as a model for the nitrile oxides, and considering (**2h**) as an ethylene molecule carrying substituents CN, NH_2, and Ph, the FMO approach, qualitatively applied according to Houk *et al.*,[8] leads to the prediction of a LUMO (dipole)-controlled reaction, that is, a reaction in which the nitrile oxide acts as an electrophile, while the β-enaminonitrile acts as a nucleophile. So, with a series of substituents on (**1**), one would expect a positive ρ-value for k_4. Experimental results agree with this prediction only partially, since the Hammett plot for k_4 is V-shaped, with a left-hand branch with $\rho = -0.6$ and a right-hand branch with $\rho = +1.2$. Probably, when substituents X are electron releasing, HCNO is no longer a good model of the nitrile oxides (**1**); a HOMO (dipole)-controlled reaction could be envisaged, justifying the negative ρ-value.

Table 5. Kinetic runs at temperatures other than 70.0 °C.

Nitrile oxide	Dipolar-ophile	T/°C	Kinetic coefficients/10^{-4}dm^3 mol^{-1}s^{-1} k	k_3	k_4
			Solvent: TCE		
(1e)	**(2f)**	50	0.482 ± 0.003	0.29	0.19
		60	1.069 ± 0.005	0.67	0.40
		80	5.44 ± 0.17	3.80	1.64
	(2g)	50	0.379 ± 0.017	0.29	0.09
		60	0.844 ± 0.032		
		80	3.53 ± 0.21	2.96	0.57
	(2h)	50	0.427 ± 0.012	0.36	0.07
		60	0.893 ± 0.025		
		80	3.30 ± 0.04	2.83	0.47
	(2i)	60	0.718 ± 0.044	0.62	0.10
		80	3.14 ± 0.04	2.80	0.34
		90	6.23 ± 0.18	5.62	0.61
	(2j)	60	0.497 ± 0.005	0.46	0.04
		80	2.59 ± 0.06	2.40	0.19
		90	5.26 ± 0.15	4.90	0.36
			Solvent: TCE/DMF(*A*)[a]		
(1e)	**(2f)**	50	0.752 ± 0.024	0.36	0.39
			Solvent: TCE/DMF(*B*)[a]		
(1e)	**(2f)**	50	0.959 ± 0.007	0.36	0.60
		60	1.93 ± 0.03	0.81	1.12
		80	8.30 ± 0.06	4.05	4.25
			Solvent: $CHCl_3$		
(1e)	**(2f)**	50	0.438 ± 0.009	0.28	0.16
	(2h)	50	0.454 ± 0.002		
			Solvent: $CHCl_3$/DMF(*A*)[a]		
(1e)	**(2f)**	50	0.713 ± 0.008	0.36	0.35
			Solvent: $CHCl_3$/DMF(*B*)[a]		
(1e)	**(2f)**	50	0.859 ± 0.018	0.37	0.49
			Solvent: CCl_4/DMF(*A*)[a]		
(1e)	**(2f)**	50	1.28 ± 0.02	0.68	0.60
			Solvent: CCl_4/DMF(*B*)[a]		
(1e)	**(2f)**	50	1.85 ± 0.07	0.70	1.15

[a] (*A*) and (*B*) correspond to 8% and 16% by volume of DMF, respectively.

When the reaction series (**1e**) + (**2f**–**j**) is considered, the electrophilic character of the nitrile oxide is certain, due to its substitution pattern; therefore, a LUMO (dipole)-controlled reaction is foreseen, and with a series of substituents on the nucleophile (**2**) a negative ρ-value for k_4, as experimentally found, is justified.

It should also be mentioned that, by the FMO approach, it can be predicted that cycloaddition to the C=C bond of dipolarophiles (**2**) gives, regioselectively, products having the CN group in the 4-position and the aryl group in the 5-position, as found in adducts (**4**).

A more intriguing point is the site selectivity of the reactions of 1,3-dipoles with conjugated cyanoalkenes. Different results were obtained from reactions of this class: for instance, using a

Table 6. Values of activation energy (ΔE_a) and activation entropy ($\Delta S^‡$) from rate coefficients k_3 and k_4 for reactions of nitrile oxide (**1e**).

Reaction	Solvent	$\Delta E_{a,3}$/kJ mol^{-1}	$\Delta E_{a,4}$/kJ mol^{-1}	$\Delta S_3^‡$/J mol^{-1}K^{-1}	$\Delta S_4^‡$/J mol^{-1}K^{-1}
(**1e** + **2f**)	TCE	81.4 ± 2.3	67.7 ± 0.8	−90 ± 10	−135 ± 4
	TCE/DMF(*B*)[a]	76.2 ± 1.6	63.0 ± 2.0	−104 ± 7	−140 ± 9
(**1e** + **2g**)	TCE	74.1 ± 1.1	58.4 ± 4.2	−112 ± 5	−170 ± 19
(**1e** + **2h**)	TCE	65.9 ± 1.1	60.2 ± 1.8	−136 ± 5	−165 ± 8
(**1e** + **2i**)	TCE	73.8 ± 1.3	59.6 ± 1.0	−114 ± 6	−171 ± 5
(**1e** + **2j**)	TCE	80.2 ± 0.9	72.2 ± 1.3	−97 ± 4	−141 ± 6

[a] 16% by volume on DMF.

nitrone as the 1,3-dipole and 1,1-dicyanostyrene as the dipolarophile, Ottenheijm and co-workers[9] reported exclusive attack onto the C≡N bond, while Hassaneen *et al.*,[10] from nitrilimines and substituted acrylonitriles (including 1,1-dicyanostyrene) reported only attack onto the C=C bond.

The present case, in which benzonitrile oxides react with β-aminocinnamonitriles, is an interesting case of rather balanced cycloadditions on both C=C and C≡N positions.

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