Addition of Cyanide Ion to Nicotinamide Cations in Acetonitrile. Formation of Non-productive Charge-transfer Complexes

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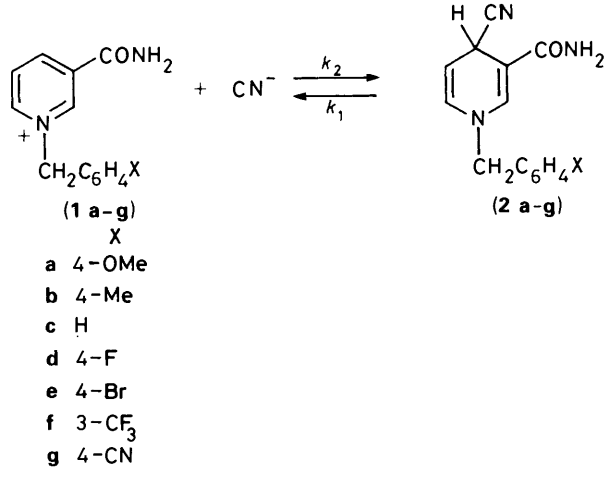
The mixing of equal volumes of 0.2 mmol dm^{-3} 1-benzylnicotinamide ion and 2 mmol dm^{-3} cyanide ion results in the immediate formation of a transient absorption band at 375 nm which can be ascribed to a charge–transfer complex. This complex disappears within *ca.* 0.2 s with the formation of the 1,6-addition product which, in turn, is rapidly converted into the thermodynamically more stable 1,4-adduct. Methyl substitution at the 6-position of the nicotinamide ring inhibits the formation of the 1,6-adduct, resulting in an increase in the lifetime of the charge–transfer complex. Subsequently a mixture of the 1,4-cyanide adduct and, most likely, the 1,2-adduct is formed. Rate effects with variation of substituents in the 1-benzyl group reveal that charge–transfer complex formation is counter-productive to the formation of addition products.

The reversible addition of cyanide ion to 1-substituted nicotinamide cations has been studied extensively in view of its resemblance to the $NAD^+/NADH$ transformation in biological redox reactions.[1–3]

There is ample evidence to suggest that in aqueous solution, the addition of cyanide ion to (**1**) forms the 1,4-adduct (**2**) as a product of both kinetic and thermodynamic control.[1] In 1 mol dm^{-3} aqueous KCN (pH 11.3) the 1,4-adduct (**2c**) is formed from (**1c**) with 75% completion,[1] but in solvents of lower polarity, *e.g.* acetonitrile, the equilibrium is almost completely shifted to the 1,4-adduct side.[3] However, the rate of dissociation in this solvent can be established by entrapment of the liberated cyanide ion with $ZnBr_2$, which strongly ligates the cyanide ion.[3] As expected for a process of charge separation, the dissociation of (**2**) proceeds considerably slower in acetonitrile than in water. For example, the first-order rate constant, k_1, for dissociation of (**2c**) is 2.15×10^{-2} s^{-1} in aqueous solution and 1.6×10^{-4} s^{-1} in acetonitrile. Moreover, the effects of substituent variation in the benzyl group are more manifest in acetonitrile than in water, as exemplified by their ρ values for dissociation of −0.63 and −0.41, respectively (Table 1). The reverse reaction, addition of cyanide ion to the nicotinamide cation, gives the normal second-order kinetic pattern to the 1,4-adduct when water is the solvent, but shows quite different behaviour in acetonitrile. The mixing of equal volumes of 0.2 mmol dm^{-3} of (**1c**) and 2 mmol dm^{-3} of KCN in acetonitrile with the aid of a rapid kinetics accessory and monitoring of the absorption spectra at intervals of 0.2 s with a diode-array spectrophotometer reveals the immediate appearance of a transient absorption band at 375 nm which disappears within *ca.* 0.2 s with the formation of a new absorption band at 350–440 nm and an absorption peak at 255 nm. This spectrum changes with a half-life of *ca.* 5 s to the final spectrum which has an absorption maximum at 333 nm (Figure 1). This final spectrum is identical with that of an authentic sample of the 1,4-adduct (**2c**) in acetonitrile. The rate of formation of (**2c**) in this process was measured by following either the decrease in absorption at 390 nm or the increase of the absorption at 333 nm and in both cases identical first-order rate constants were obtained which were independent of variation in the cyanide concentration in the range 1–10 equiv.

The effect of variation of the benzyl substituent X upon the rate of formation of (**2**) in acetonitrile is the *opposite* of that in aqueous solution (Table 2). In acetonitrile, formation of (**2**) is retarded by electron-withdrawing substituents (ρ = −0.45),



Scheme 1.

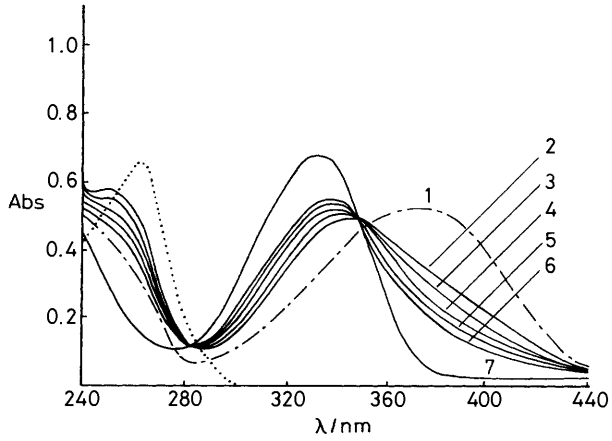


Figure 1. Change in the absorption spectrum after mixing (**1c**) (0.1 mmol dm^{-3}) with KCN (1.0 mmol dm^{-3}) in acetonitrile. Dashed line, 1, gives the spectrum immediately after mixing. Solid lines: 2, after 0.1 s; lines 2–6, Δt = 2 s; line 7, after 25 s. Dotted line: (**1c**) (0.1 mmol dm^{-3}).

whereas in aqueous solution electron-withdrawing substituents enhance the rate of addition (ρ = +0.55). This latter effect is expected for cyanide addition to the nicotinamide ring since in

Table 1. First-order rate constants for dissociation of (**2**) in water[a] and acetonitrile[b] at 25 °C.

	X	Water $k_1/10^{-2}$ s^{-1}	MeCN $k_1/10^{-5}$ s^{-1}
(**2a**)	4-OCH_3	2.61	23.1
(**2b**)	4-CH_3	2.35	20.5
(**2c**)	H	2.07	16.0
(**2d**)	4-F	1.94	14.0
(**2e**)	4-Br	1.60	11.7
(**2f**)	3-CF_3	1.32	8.05
(**2g**)	4-CN	1.06	7.07
Reaction constant (ρ)		−0.41	−0.63

[a] Phosphate buffer pH 7.41, μ = 0.1 mol dm^{-3}. [b] In the presence of 0.1 mol dm^{-3} $ZnBr_2$ 7.5 × 10^{-2} mol dm^{-3} KBr and 0.1 mol dm^{-3} 18-crown-6.

Table 2. Second-order rate constants, k_2, for formation of (**2**) in water[a] and observed rate constants, k_{obs}, for formation of (**2**) in acetonitrile[b] at 25 °C.

	X	Water $k_2/10^{-2}$ dm^3 mol^{-1} s^{-1}	MeCN $k_{obs}/10^{-2}$ s^{-1}
(**2a**)	4-OCH_3	4.09	15.4
(**2b**)	4-CH_3	4.35	14.8
(**2c**)	H	4.98	12.8
(**2d**)	4-F	5.81	10.3
(**2e**)	4-Br	7.16	8.93
(**2f**)	3-CF_3	9.50	6.90
(**2g**)	4-CN	12.5	6.59
Reaction constant (ρ)		+0.55	−0.45

[a] pH 10.92, second-order rate constants are calculated by the method of Behme and Cordes.[1,16b] Conditions: 0.1 mmol dm^{-3} (**1**) and 1 mmol dm^{-3} KCN dissolved with 1.33 mmol dm^{-3} 18-crown-6.

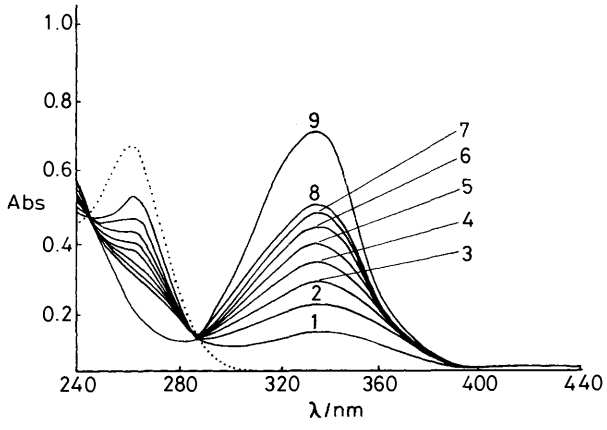


Figure 2. Change in the absorption spectrum after mixing (**1c**) (0.1 mmol dm^{-3}) with KCN (1.0 mmol dm^{-3}) in acetonitrile–water (90:10, v/v). Solid lines 1–8, Δ*t* = 3 s; line 9, after 10 min. Dotted line: (**1c**) (0.1 mmol dm^{-3}).

this process the positive charge becomes partially neutralized in the transition state. The negative value found for ρ in acetonitrile, however, indicates that formation of (**2**) is preceded by a rate-determining process in which there is an increase of positive charge in the nicotinamide ring. The negative ρ value clearly reflects the breakdown of a transient species preliminary to the formation of the 1,4-adduct. The appearance of this transient species is highly dependent on the solvent polarity. Addition of 3 vol% water reduces the transient absorption bands considerably and in solutions of 10 vol% water no transient absorption bands are observed and the absorption of (**1**) (λ_{max} = 265 nm) decreases concomitantly with the increase of the absorption of (**2**) (Figure 2).

There is evidence that in alcoholic solution the initial attack of cyanide ion to certain pyridinium ions occurs predominantly at the 6-position of the pyridinium ring and that the 1,6-adduct (**3**) is slowly converted into the thermodynamically more stable 1,4-adduct upon standing.[4] In order to obtain more insight into the possibility of the occurrence of the 1,6-adduct as the transient species in acetonitrile we also studied the cyanide addition to a series of 1-(X-benzyl)-3-carbamoyl-6-methyl pyridinium ions (**4**) and to the 1-benzyl-3-carbamoyl quinolinium ion (**6**). In these compounds addition to the 6-position of the pyridinium ring is sterically hindered and completely blocked, respectively. The changes in absorption spectra upon mixing 0.1 mmol dm^{-3} of (**4**) or (**6**) with 1 mmol dm^{-3} cyanide ion in acetonitrile are illustrated in Figures 3 and 4. The important difference as compared with (**1**) is that for (**4**) and (**6**) the initial absorption band at *ca.* 380 nm is slower to disappear and is directly converted into an absorbance spectrum with maxima near 308 and 327 nm. The maximum at 327 nm can be assigned to the 1,4-addition product, and the maximum at 308 nm most likely originates from the 1,2-addition product since an original sample of 1-benzyl-4-cyano-6-methyl-1,4-dihydronicotinamide, (**5**), gives an absorption maximum at 327 nm which equilibrates with a half-life of 3 min into the observed spectrum.

The absorption maxima for cyanide addition to the nicotinamide ring of (**4**) can be assigned as follows: the 2-position at 308 nm, the 4-position at 327 nm, and, for (**1**), the 6-position at 255 and 360 nm. This makes it reasonable to conclude that the absorption maximum at 380–390 nm, appearing immediately after mixing of cyanide and nicotinamide ion, is due to charge–transfer complexation. This conclusion is supported by the observation that this absorption band disappears when the polarity of the solvent is increased by addition of water to the acetonitrile solution.[5] Previous studies have shown that nicotinamide cations are able to form charge–transfer complexes with iodide ion,[6,7] cysteine–thiol groups[8] and aromatic π-donors such as phenol,[9] indole,[7,10] adenine,[11] and flavine.[12]

It has been suggested that charge–transfer complexation determines the position of attack of nucleophiles on the nicotinamide cation,[5] accounting for the observation that in aqueous solution polarizable ions like cyanide, iodide, sulphide, and dithionite yield preferentially the 1,4-addition products and less polarizable ions such as hydroxide and alkoxide form predominantly the 1,6-addition products. However, the observations made here suggest that charge-transfer complexation does not lead to a preferential formation of 1,4-addition products. The spectra in Figure 1 indicate that the charge-transfer complex is rapidly converted into the kinetically controlled 1,6-adduct and that this becomes, in turn, rapidly transformed into the more stable 1,4-adduct.

For (**4**), formation of the 1,6-adduct is sterically unfavourable, and this results in a longer life-time for the charge-transfer complex and the formation of a mixture of 1,2- and 1,4-addition products. Remarkably, electron-withdrawing substitution in the benzyl group retards the transformation of the charge-transfer complex into addition products (Table 3). This suggests that adduct formation is preceded by an increase in the charge density on the nicotinamide ring in the transition state, indicating that the charge-transfer complex has firstly to be broken down (at least partly) before addition of cyanide ion to the pyridinium ring can occur. A possible reaction scheme is given in Scheme 2. The important conclusion from these observations is that the rapid formation of a charge-transfer

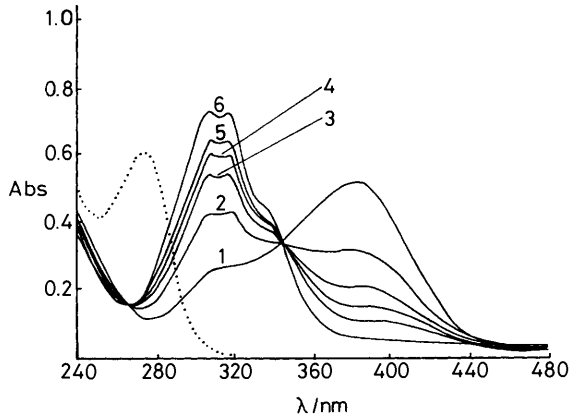


Figure 3. Change in the absorption spectrum after mixing (**4c**) (0.1 mmol dm^{-3}) with KCN (1.0 mmol dm^{-3}) in acetonitrile. Solid line, 1, gives the spectrum immediately after mixing; lines 1–5, Δt = 1 s; line 6, after 20 s. Dotted line: (**4c**) (0.1 mmol dm^{-3}).

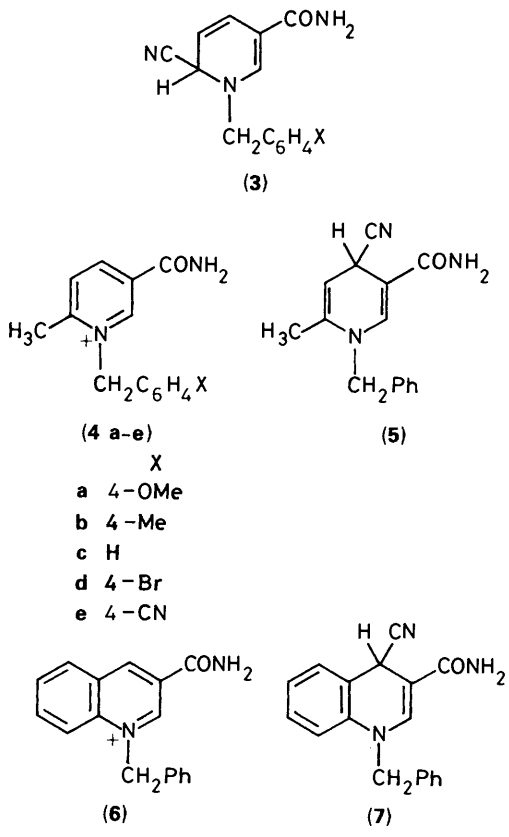


Table 3. Observed rate constants, k_{obs}, for disappearance of the charge-transfer complex of (**4**) and cyanide ion[a] at 25 °C.

	X	$k_{obs}/10^{-2}$ s^{-1}
(**4a**)	4-OCH_3	66.8
(**4b**)	4-CH_3	65.3
(**4c**)	H	56.2
(**4d**)	4-Br	42.2
(**4e**)	4-CN	31.3
Reaction constant (ρ)		−0.39

[a] Conditions: 0.1 mmol dm^{-3} (**4**) and 1 mmol dm^{-3} KCN dissolved with 1.33 mmol dm^{-3} 18-crown-6.

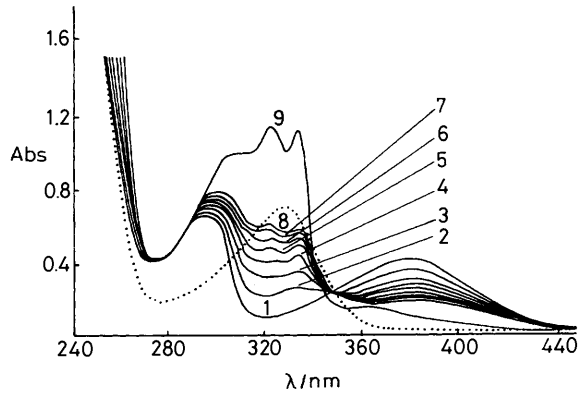
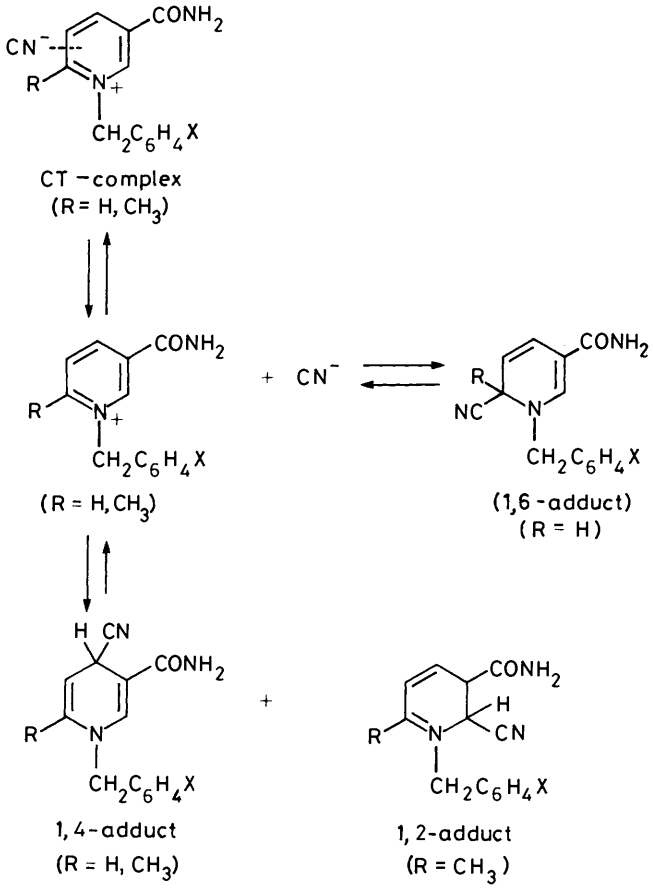


Figure 4. Change in the absorption spectrum after mixing (**6**) (0.1 mmol dm^{-3}) and KCN (1.0 mmol dm^{-3}) in acetonitrile. Solid lines 1–8, Δt = 2 min; line 9, after 100 min. Dotted line: (**6**) (0.1 mmol dm^{-3}).



Scheme 2.

complex is not a promotive step in the process of adduct formation, as one would intuitively expect, but rather contributes to the initial state stabilization of the nicotinamide cation and is, therefore, counter-productive to adduct formation.

Experimental

Materials.—The bromide or chloride salts of (**1a–g**) and (**4a–e**) were prepared in 60–95% yield by allowing the appropriately substituted benzyl bromide or chloride to reflux for 16–24 h with nicotinamide and 6-methylnicotinamide, respectively. The products were recrystallized twice from ethanol and characterized by ^1H NMR spectroscopy (90 MHz; solvent [$^2H_6$]DMSO,

Table 4. M.p. and ^{1}H NMR data for 1-(X-benzyl)-4-cyano-1,4-dihydronicotinamide derivatives (**2a–g**), (**5**), and (**7**).

Compound	M.p. (decomp.)/°C	δ_H(ppm)	Solvent
(**2a**)	130–132	3.74 (3 H, s), 4.32 (2 H, s), 4.58 (1 H, d), 4.73 (1 H, dd), 6.06 (1 H, d), 6.47 (2 H, br s), 6.86 (2 H, d), 7.17 (2 H, d), 7.31 (1 H, s)	$CDCl_3$ + [$^2H_6$]DMSO
(**2b**)	123–125	2.33 (3 H, s), 4.40 (2 H, s), 4.60 (1 H, d), 4.75 (1 H, dd), 6.13 (1 H, d), 6.69 (1 H, br s), 7.17 (4 H, s), 7.82 (2 H, br s)	$CDCl_3$ + [$^2H_6$]DMSO
(**2c**)	119–120	4.48 (2 H, s), 4.57 (1 H, d), 4.80 (1 H, dd), 6.32 (1 H, d), 6.94 (2 H, br s), 7.30 (6H, m)	[$^2H_6$]DMSO
(**2d**)	109–113	4.42 (2 H, s), 4.66 (1 H, d), 4.84 (1 H, dd), 6.09 (1 H, d), 6.39 (2 H, br s), 6.95–7.40 (5 H, m)	$CDCl_3$ + [$^2H_6$]DMSO
(**2e**)	139–143	4.39 (2 H, s), 4.58 (1 H, d), 4.76 (1 H, dd), 6.08 (1 H, d), 6.54 (2 H, br s), 7.13 (2 H, d), 7.40 (3 H, m)	$CDCl_3$ + [$^2H_6$]DMSO
(**2f**)	69–72	4.48 (2 H, s), 4.60 (1 H, d), 4.87 (1 H, dd), 5.62 (2 H, br s), 6.04 (1 H, d), 7.19 (1 H, s), 7.50 (4 H, m)	$CDCl_3$
(**2g**)	162–165	4.60 (2 H, s), 4.65 (1 H, d), 4.88 (1 H, dd), 6.20 (1 H, d), 6.73 (2 H, br s), 7.43 (1 H, s), 7.48 (2 H, d), 7.78 (2 H, d)	$CDCl_3$ + [$^2H_6$]DMSO
(**5**)	112–115	1.78 (3 H, s), 4.47 (1 H, d), 4.63 (3 H, m), 5.77 (2 H, br s), 7.29 (5 H, m)	CD_3CN
(**7**)	136–138	4.82 (2 H, s), 5.22 (1 H, s), 5.98 (2 H, br s), 6.70–7.50 (10 H, m)	$CDCl_3$

standard Me_4Si) and, for the new compounds, also by elemental analysis. All nicotinamide salts decompose upon melting. (**1a**), chloride salt, m.p. 245–246 °C (lit.,[13] 236–237 °C); (**1b**) bromide salt, m.p. 242–243 °C (lit.,[2f] 238–239 °C); (**1c**) bromide salt, m.p. 207–208 °C (lit.,[2f] 206–208 °C); (**1d**), bromide salt, m.p. 255 °C (lit.,[2f] 246–247 °C); (**1e**) bromide salt, m.p. 265–266 °C (lit.[2f] 263–264 °C); (**1f**), chloride salt, m.p. 240–241 °C; (Found: C, 53.0; H, 3.9; N, 8.8. $C_{14}H_{12}ClF_3N_2O$ requires C, 53.09; H, 3.82; N, 8.85%); δ_H 6.02 (2 H, s, NH_2), 7.50–8.10 (4 H, m, Ph), 7.95 and 8.80 (2 H, br s, N–CH_2), 8.30 (1 H, dd, *J* 7 and 8 Hz, 5-H), 9.06 (1 H, d, *J* 8 Hz, 6-H), 9.37 (1 H, d, *J* 7 Hz, 4-H), and 9.83 (1 H, s, 2-H). (**1g**), bromide salt, m.p. 284–286 °C (lit.,[2f] 275–276 °C); (**4a**) chloride salt, m.p. 191–193 °C; (Found: C, 61.3; H, 5.7; N, 9.4. $C_{15}H_{17}ClN_2O_2$ requires C, 61.53; H, 5.85; N, 9.56%); δ_H 2.82 (3 H, s, Me), 3.76 (3 H, s, MeO), 5.92 (2 H, s, CH_2–N), 6.98 and 7.40 (4 H, dd, J_{AB} 8 Hz, C_6H_4), 8.13 and 9.03 (2 H, br s, NH_2), 8.20 (1 H, d, *J* 9 Hz, 5-H), 9.03 (1 H, d, *J* 9 Hz, 4-H), and 9.89 (1 H, s, 2-H). (**4b**) bromide salt, m.p. 195–197 °C; (Found: C, 56.3; H, 5.3; N, 8.6. $C_{15}H_{17}BrN_2O$ requires C, 56.08; H, 5.33; N, 8.72%); δ_H 2.38 (3 H, s, *Me*C_6H_4), 2.89 (3 H, s, Me), 5.92 (2 H, s, CH_2–N), 7.22 (4 H, br s, Ph), 8.11 and 8.65 (2 H, br s, NH_2), 8.22 (1 H, d, *J* 8 Hz, 5-H), 8.93 (1 H, d, *J* 8 Hz, 4-H), and 9.64 (1 H, s, 2-H). (**4c**), bromide salt, m.p. 180–181 °C; (Found: C, 54.4; H, 4.8; N, 8.9. $C_{14}H_{15}BrN_2O$ requires C, 54.73; H, 4.92; N, 9.12%); δ_H 2.79 (3 H, s, Me), 5.85 (2 H, s, CH_2–N), 7.26–7.45 (5 H, m, Ph), 8.07 and 8.49 (2 H, br s, NH_2), 8.19 (1 H, d, *J* 8 Hz, 5-H), 8.87 (1 H, d, *J* 8 Hz, 4-H), and 9.47 (1 H, s, 2-H). (**4d**), bromide salt, m.p. 215–216 °C; (Found: C, 43.4; H, 3.7; N, 7.3. $C_{14}H_{14}Br_2N_2O$ requires C, 43.54; H, 3.65; N, 7.25%); δ_H 2.85 (3 H, s, Me), 6.02 (2 H, s, CH_2–N), 7.33 and 7.67 (4 H, dd, J_{AB} 8 Hz, C_6H_4), 8.18 and 8.60 (2 H, br s, NH_2), 8.25 (1 H, d, *J* 9 Hz), 8.93 (1 H, d, *J* 9 Hz, 4-H), and 9.68 (1 H, s, 2-H). (**4e**) bromide salt, m.p. 247–249 °C; (Found: C, 54.1; H, 4.2; N, 12.4. $C_{15}H_{14}BrN_3O$ requires C, 54.22; H, 4.24; N, 12.65%); δ_H 2.72 (3 H, s, Me), 6.09 (2 H, s, CH_2–N), 7.49 and 7.90 (4 H, dd, J_{AB} 8 Hz, C_6H_4), 8.04 and 8.58 (2 H, br s, NH_2), 8.23 (1 H, d, *J* 8 Hz, 5-H), 8.92 (1 H, d, *J* 8 Hz, 4-H) and 9.63 (1 H, s, 2-H). (**6**), bromide salt, m.p. 243–245 °C (lit.,[14] 224–225 °C). The 4-cyano addition products (**2a–g**), (**5**), and (**7**) were prepared by addition of excess of KCN to a solution of the pyridinium salts according to the method of Karrer and co-workers.[15] The precipitate was washed with a concentrated KCN solution and dried in the dark at room temperature *in vacuo*. The products were characterized by NMR spectroscopy (Table 4). Elemental analysis showed 1–5 mol% contamination with KCN. In the kinetic experiments the compounds were used with a view to the possibility of the 1,4-adducts rearranging on recrystallization from organic solvents (see the text). Spectroscopic grade acetonitrile, containing < 0.05% water, was used in all kinetic experiments. Potassium cyanide (p.a.) and 18-crown-6 were obtained from Merck.

Kinetic Studies.—The rates of dissociation of (**2a–g**), given in Table 1, were determined by following the decrease of the absorption maximum at 340 nm or by running repetitive scans in the 220–400 nm range with a Beckman DU-7 spectrophotometer equipped with a thermostatted cell compartment maintained at 25.0 ± 0.1 °C and supplied with a kinetic device. For the determination of the rates of dissociation in water, sample solutions were prepared by injecting a solution of (**2**) in acetonitrile (10 mm^3 of a 20 mmol dm^{-3} solution) into a phosphate buffer (2 cm^3), pH 7.41 and ionic strength 0.1 mol dm^{-3}. The rates of dissociation in acetonitrile were obtained by addition of (**2**) in acetonitrile (10 mm^3 of a 20 mmol dm^{-3} solution) to 2 cm^3 of an acetonitrile solution containing 0.1 mol dm^{-3} $ZnBr_2$, 7.5 × 10^{-2} mol dm^{-3} KBr and 0.1 mol dm^{-3} 18-crown-6. The [$ZnBr_2$·Br^-] complex in this solution serves to trap the dissociated cyanide ion.[3] The presence of KBr in the $ZnBr_2$ solution is necessary in order to prevent complexation of zinc ion to (**2**), which would result in zinc-promoted cyanide ion dissociation from (**2**).[3] The rates of dissociation follow strictly first-order kinetics with respect to (**2**) and first-order rate constants were obtained from plots of ln ($A_t - A_\infty$) *vs.* time. All rates were determined at least twice. Spectra after completion of the reaction were stable with respect to time and were both qualitatively and quantitatively identical with that of equivalent concentrations of the nicotinamide salts.

For the determination of the rates of formation of (**2**) from (**1**) and cyanide ion in water (Table 2), stock solutions were prepared of the following: 4 × 10^{-3} mol dm^{-3} of (**1**) in water; 0.5 mol dm^{-3} KCN in 0.05 mol dm^{-3} aqueous Na_2HPO_4, pH 10.92; and 0.5 mol dm^{-3} aqueous Na_2HPO_4, pH 10.92. Both buffer solutions were mixed to a total volume of 2 cm^3 in the sample cuvette, so that the KCN concentration varied from 0.1–0.5 mol dm^{-3} and the ionic strength was kept constant. After addition of 100 mm^3 of a stock solution of (**1**), the formation of (**2**) was followed by measuring the increase of the absorption at 340 nm. Second-order rate constants were calculated using the method described by Behme and Cordes.[1,16] Reactions of cyanide ion with (**2**), (**4**) and (**6**) in acetonitrile were monitored by the following procedure. Equal volumes (0.2 cm^3) of a solution of (**2**), (**4**) or (**6**) (0.2 mmol dm^{-3}) and KCN (2 mmol dm^{-3}, dissolved with 2.66 mmol dm^{-3} 18-crown-6) in

acetonitrile were mixed at 25 °C with the aid of a Hi-Tech SFA 11 rapid kinetic accessory and absorption spectra were recorded at 0.1–1 s time intervals with an HP 8452A diode array spectrophotometer. Table 2 gives the observed rates of conversion of the absorption band at 360 nm [1,6-adduct of (**2**), see text] to the absorption band at 333 nm [1,4-adduct of (**2**)]. Table 3 gives the rate constants for the decay of the absorption at 380 nm, ascribed to the charge–transfer complex. All reactions show good first-order kinetics and rate constants have been calculated from at least six measurements which were all reproducible to within 2%.

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