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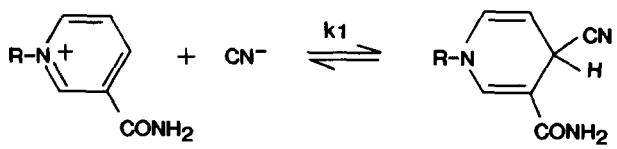
NOTE

Charge Distribution in the Transition State in Addition Reactions of Cyanide Anions to N_1-Substituted Nicotinamide Halides

The first systematic investigation of addition reactions of cyanide anions to N_1-substituted nicotinamide cations was undertaken by Wallenfels (*1, 2*). Ultraviolet, proton magnetic resonance, and mass spectra all suggest that the initial site of addition of cyanide to N_1-substituted nicotinamide ions in water occurs at position 4 (*3*).



[1]

Reaction [1] is fully reversible; the adduct is kinetically stable, but thermodynamically unstable, and undergoes a slow rearrangement in water (*3, 4*).

An attempt to estimate the structure and properties of the transition state of Reaction [1] was made by Lindquist and Cordes (*3*) and by Bunting and Sindhuatmadja (*5*); both authors have investigated the change in reactivity with changes in structures of N_1-substituents on the pyridinium ring. Lindquist and Cordes estimated the kinetic reaction constant ($\rho_{kin} \cdot \sigma = \ln(k_1/k_1^\circ)$) from the changes of reaction rates (k_1) and the equilibrium reaction constant ($\rho_{eq} \cdot \sigma = \ln(K_d/K_d^\circ)$) from the changes of equilibrium constants (K_d), in a series of six N_1-substituted nicotinamides. Bunting and Sindhuatmadja estimated the equilibrium reaction constant (ρ_{eq}) for a series of six additional N_1-substituted nicotinamides. The estimation of reaction constants was based on Hammet parameters which were not always known with precision (*3, 5–7*), and on a rather small series of compounds. Therefore, it occurred to us that the estimation of the charge distribution in the transition state might be achieved with much greater confidence.

For this purpose, we have extended the series of eleven compounds reported by Lindquist and Cordes by six additional compounds (Table 1).

Table 1 summarizes the experimentally measured values of bimolecular rate constants (k_1), overall equilibrium constants (K_d), and standard redox potentials (E_0'), for a series of 17 nicotinamide compounds. Table 1 presents the compilation of our experimental data (Compounds **3, 6, 7, 9a, 12–14, 17a**), and the experimental data of Lindquist and Cordes (compounds **1, 2, 4, 5, 8, 9, 10, 11, 15–17**), estimated under identical conditions. In order to correct for a small systematic difference

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TABLE 1

Rate and Equilibrium Constants for Addition Reactions of Cyanide Anions to N_1-Substituted 3-Carbamoylpyridinium Cations

Compound	K_d (M)	k_1 (M^{-1} min^{-1})	$-E'_0$ vs NHE (mV)[b]
1. *N*-Propyl-3-carbamoylpyridinium iodide[a]	5.40	0.84	394.1
2. *N*-Methyl-3-carbamoylpyridinium iodide[a]	4.20	0.97	390.9
3. *N*-(1-Phthalimidopropyl)-3-carbamoylpyridinium bromide	0.656	3.95	377.3
4. *N*-(β-Indolylethyl)-3-carbamoylpyridinium chloride[a]	1.20	2.50	374.8
5. *N*-(β-4′-Imidazolylethyl)-3-carbamoylpyridinium chloride[a]	0.93	2.60	371.5
6. 1,1′-Dimethylketonebis-(3-carbamoylpyridinium bromide)	0.38	5.51	370.3
7. *N*-(α-Methylbenzyl)-3-carbamoylpyridinium chloride	0.198	7.93	362.0
8. *N*-Benzyl-3-carbamoylpyridinium chloride[a]	0.33	3.90	358.3
9. *N*-(2,6-Dichlorobenzyl)-3-carbamoylpyridinium bromide[a]	0.16	5.80	349.0
9a. *N*-(2,6-Dichlorobenzyl)-3-carbamoylpyridinium bromide	0.072	13.41	349.0
10. *N*-(4-Nitrobenzyl)-3-carbamoylpyridinium bromide[a]	0.03	14.0	327.6
11. *N*-(2-Chloro-4-nitrobenzyl)-3-carbamoylpyridinium bromide[a]	0.02	20.0	322.4
12. *N*-Carboxamide-3-carbamoylpyridinium iodide	0.0166	18.24	330.2
13. *N*-(1-Hydroxy-4-nitrobenzyl)-3-carbamoylpyridinium bromide	0.618	1.06	376.6
14. *N*-Carboxymethyl-3-carbamoylpyridinium hydrate	0.293	3.81	367.0
15. β-Nicotinamide mononucleotide[a]	0.015	5.4	318.7
16. α-Nicotinamide adenine dinucleotide[a]	0.06	4.5	336.4
17. β-Nicotinamide adenine dinucleotide[a]	0.0061	11.0	323.8
17a. β-Nicotinamide adenine dinucleotide	0.004	20.0	323.8

[a] The experimental data have been taken from Lindquist and Cordes (*3*).

[b] E'_0 values have been calculated from K_d (*2*), assuming that E'_0 for compounds **9** and **9a** was −349 mV (*8*).

between both sets of data, each set was standardized independently; the first set of data (k_1, K_d) was standardized with respect to compound **9a** (k_1°, K_d°), while the second set of data was standardized with respect to compound **9,** in order to fit them all into a single linear free energy relationship (Eq. [2]).

$$\ln (k_1/k_1^\circ) = \alpha \cdot \ln (K_d/K_d^\circ) \qquad [2]$$

The data presented in Table 1 fitted the following Brønsted relationships (Eq. [2]):

$$\text{compounds } \mathbf{1–11}: \quad \ln (k_1/k_1^\circ) = -0.54 \ln (K_d/K_d^\circ) \qquad r = 0.997,$$

$$\text{compounds } \mathbf{1–12}: \quad \ln (k_1/k_1^\circ) = -0.51 \ln (K_d/K_d^\circ) \qquad r = 0.985,$$

$$\text{compounds } \mathbf{1–17}: \quad \ln (k_1/k_1^\circ) = -0.44 \ln (K_d/K_d^\circ) \qquad r = 0.880.$$

An excellent fit for compounds **1–11** indicates that Reaction [1] proceeded by a single mechanism for all these compounds. A poor fit for compounds **13–17** may be rationalized in the following way; in all these compounds, the negatively charged substituent on the ring nitrogen was able to interact with the positively charged pyridinium ring, while, most likely, the secondary valence forces interfered with the cyanide-addition reactions. Compound **12** did not fall in the above category, and we have no explanation for the poor fit of this compound.

Our estimation of a Brønsted parameter (α) offered more confidence than the previous estimation of reaction constants (*3, 5*), since it did not depend on the

TABLE 2

Molar Extinction Coefficients of Pyridinium Compounds and Their Cyanide Adducts

Compound	ε 266 nm (M^{-1} cm^{-1})[a]	ε 340 nm (M^{-1} cm^{-1})[b]
3	4443	6,163
6	9637	12,509
7	3972	6,923
9a	5015	6,958
12	4721	6,222
13	6332	3,728
14	4707	7,267

[a] Pyridinium compounds, in water, pH 6.0.

[b] Extinction coefficients of cyanide adducts at pH 11.3, estimated according to Lindquist and Cordes (*3*).

knowledge of Hammet constants, and was based on a larger series of compounds. The sign and magnitude of the Brønsted parameter indicated that −0.54 unit of negative charge developed in the pyridine ring in the transition state, suggesting that the transition state was approximately symmetrical (Fig. 1).

However, it should be borne in mind that the Brønsted parameter is the measure of the charge formed in the TS, rather than of the extent of bond formation (*9*).

EXPERIMENTAL

The determination of k_1 and K_d constants in Table 1 was performed under the experimental conditions identical to those of Lindquist and Cordes (*3*); the estimation was sufficiently rapid to eliminate the influence of the rearrangement of the Pyr–CN adduct.

Compound **3** was synthesized according to Meijer (*10*), compound **6** according to the general method of Craig *et al.* (*11*), compound **7** according to the general method for Zincke synthesis (*12*) as described by Meijer (*10*), and compound **9a**

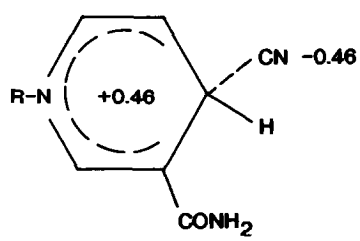

FIG. 1. Charge distribution in the TS of Reaction [1].

according to Kröhnke and Ellegast (*13*). Compounds **12, 13,** and **14** have been synthesized by alkylation of nicotinamide in dry methanol, at room temperature, by iodoacetamide, 2-hydroxy-4-nitrobenzyl bromide, or iodoacetic acid, respectively. Compounds **3, 6, 7, 9a,** and **12–14** displayed single spots on TLC (Silicagel GF, 0.25 mm; 95% methanol, 4% water, 1% acetic acid). Preparative procedures and elemental analyses are reported only for compounds synthesized via novel preparative routes.

Compound ***6***. One milliliter of 1,3-dibromoacetone (9.26 mmol) and 2.2 g of nicotinamide (18 mmol) were dissolved in 20 ml of dry methanol and refluxed for 24 h. A brown precipitate formed and was separated by decantation and washed with ether; the residue was dissolved in water and decolorized by charcoal. The product was recrystallized several times from water–ethanol and dried *in vacuo;* final yield, 31%, of pale brown-reddish powder.

MW 460.13. Found % (calcd) for $C_{15}H_{16}N_4O_3Br_2$: C 39.33 (39.16); H 3.61 (3.51); N 12.46 (12.18).

Compound ***7***. To the refluxing solution of 1.25 ml of (*S*)-(−)-1-phenylethylamine (9.45 mmol) in 16 ml of dry methanol, a solution of 3 g of 3-carbamoyl-1-(2,4-dinitrophenyl)pyridinium chloride (8.41 mmol) in 21 ml of dry methanol was added at such a rate that the red color almost disappeared when the next aliquot was introduced; after the addition was complete, refluxing was continued for 2 h. The solution was concentrated to 10 ml and a 10-fold volume of ether was added: the pyridinium salt precipitated, whereas the 2,5-dinitroaniline remained in solution and was removed by decantation. The precipitate was taken up in methanol and the process repeated three times. Further purification was carried out by refluxing the product in the presence of charcoal (50 ml MeOH, 100 min). Finally, the product was recrystallized from water. Yield 35%, of yellow crystals.

MW 280.78. Found % (calcd) for $C_{14}H_{15}N_2OCl.H_2O$: C 59.21 (59.89); H 6.27 (6.12); N 10.15 (9.98).

Compound ***13***. 1-Hydroxy-4-nitrobenzyl bromide (750 mg; 3.23 mmol) and 400 mg of nicotinamide (3.28 mmol) were dissolved in 10 ml of dry methanol. The yellow product separated rapidly at room temperature; the reaction was continued by refluxing for 3 h and the product was separated by decantation. The product was washed with hot dry ethanol and recrystallized from water; final yield, 80%, of yellow crystals.

MW 354.18. Found % (calcd) for $C_{13}H_{12}N_3O_4Br$: C 45.00 (44.09); H 3.46 (3.41); N 11.65 (11.86).

Compound ***14***. Iodoacetic acid (502 mg; 2.41 mmol) and 261 mg of nicotinamide (2.14 mmol) were dissolved in 5 ml of dry methanol and left in the dark at room temperature. The white product separated gradually; after 1 week, the product was separated by centrifugation, washed with dry methanol, and recrystallized from water. Final yield, 31%, of white crystals.

MW 198.20 · Found % (calcd) for $C_8H_8N_2O_3 \cdot H_2O$: C 48.50 (48.49); H 5.19 (5.10); N 14.27 (14.14).

Compound ***12***. Iodoacetamide (509 mg; 2.75 mmol) and 266 mg of nicotinamide (2.18 mmol) were dissolved in 5 ml of dry methanol and left in the dark at room temperature. The white product separated gradually; after 1 week, the product

was separated by centrifugation, washed with dry methanol, and recrystallized from water. Final yield, 50%, of white crystals.

MW 307.11. Found % (calcd) for $C_8H_{10}N_3O_2I$: C 31.00 (31.29); H 3.45 (3.29); N 14.11 (13.69).

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