

**SUBSTITUENT EFFECT IN ADDITION OF CYANIDE ION
TO *p*-SUBSTITUTED 1-BENZYL-3-CARBAMOYLPIRIDINIUM
CHLORIDES***

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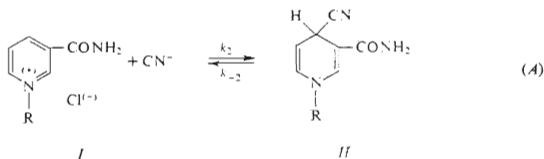
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The rate constants k_2 and equilibrium constants $K = k_2/k_{-2}$ of the title process (*A*) have been measured in aqueous solutions of eight quaternary salts of nicotinamide *I* ($R = p\text{-XC}_6\text{H}_4\text{CH}_2$) at 298 K. The substituent effects of $X = \text{CH}_3\text{O}$, CH_3 , H , F , Cl , COOCH_3 , CN , and NO_2 exhibiting the Hammett dependence have been correlated with half-wave potentials of reduction of the depolarizers *I*, and the correlation results have been discussed with respect to mechanism of the reaction (*A*).

Quaternary salts of nicotinamide *I* (as models of NAD^{1-6}) as well as the coenzyme NAD itself^{2,4,6} undergo easy equilibrium addition of cyanide ion (*A*). In this addition the substrate *I* is attacked at 4 position of its heteroaromatic ring (to give the corresponding 1,4-dihydropyridines *II*), *i.e.*, at the same position at which a hydrogen equivalent is transferred in biochemical oxidations. This fact was interpreted theoretically either by the presumption⁷ that cyanide ion is a soft nucleophile or by the possibility that the 1,4-dihydro derivatives *II* are preferred thermodynamically to their 1,2- and 1,6-isomers⁸. Lindquist and Cordes⁴, studying the substituent effects in the reaction (*A*) for the series $R = \text{CH}_3$, $n\text{-C}_3\text{H}_7$, $\text{CH}_2\text{C}_6\text{H}_5$, $2,6\text{-Cl}_2\text{C}_6\text{H}_3\cdot\text{CH}_2$, $4\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2$, and $2\text{-Cl-4-NO}_2\text{C}_6\text{H}_3\text{CH}_2$, found that the 1,4-dihydro adducts are transformed, after a certain time, into secondary products which were considered⁴ to be the corresponding 1,2- or 1,6-isomers. From this finding it was concluded⁴ that formation of the 1,4-dihydro derivatives *II* in aqueous medium is controlled kinetically and not thermodynamically. The corresponding Taft correlations resulted in the values of the reaction parameters $\rho^* = 2.2$ and 3.7 for the k_2 and $K = k_2/k_{-2}$, constants, respectively. Bunting and Sindhuatmadja⁹ also found close Hammett correlations for the equilibrium constants of the reaction (*A*) in the series $R = \text{XC}_6\text{H}_4\text{CH}_2$ where $X = 4\text{-CH}_3$, 4-H , 4-F , 4-Br , 4-CN , 3-F , and 3-CN with the parameters $\rho = 0.88$ and 0.95 in aqueous and aqueous-acetonitrile media, respectively.

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R = *p*-XC₆H₄CH₂, where X = CH₃O, CH₃ H, F, Cl, COOCH₃, CN, NO₂

In the present work we have investigated the substituent effects in an analogous but topologically more homogeneous series R = 4-XC₆H₄CH₂ with a somewhat broader selection of the substituents X = OCH₃, CH₃, H, F, Cl, COOCH₂, CN, and NO₂ with respect to the σ_p parameter scale. We have focused attention on the both constants k_2 and K and on investigation of their relations to the reduction half-wave potentials $E_{1/2}$ measured polarographically¹⁰ for the same depolarizers with the aim to obtain information on possible electronic mechanism of the processes studied.

EXPERIMENTAL

Preparation of the compounds I was described in a previous work¹⁰. The UV spectra of the studied compounds I (R = *p*-CH₂C₆H₄X) exhibited (in accordance with the literature data²) in aqueous solutions absorption curves having maxima at $\lambda = 263$ nm ($\log \epsilon = 3.63$) practically insensitive

TABLE I

Rate and equilibrium constants of addition of CN⁻ to the compounds I in aqueous solutions. Composition of the solution measured: $2 \cdot 10^{-4}$ mol l⁻¹ compound I, pH 10.8, ionic strength $\bar{\mu} = 0.5$; temperature 298.15 ± 0.1 K

Substituent X	c_{CN^-} mol l ⁻¹	K mol ⁻¹	k_2 10 ² mol ⁻¹ s ⁻¹	k_{-2} 10 ² s ⁻¹
OCH ₃ ^a	0.01 — 0.1	0.78	2.197	2.82
CH ₃ ^a	0.01 — 0.1	1.47	3.825	2.60
H	0.05 — 0.5	2.47	5.227	2.12
F	0.025 — 0.5	2.78	5.785	2.08
Cl	0.025 — 0.5	4.08	7.293	1.79
COOCH ₃	0.01 — 0.25	7.41	12.276	1.66
CN	0.01 — 0.1	12.5	14.825	1.19
NO ₂	0.01 — 0.1	18.18	24.113	1.33

^a Due to great rate of the reverse reaction, the measurements were carried out at the substrate concentration $8 \cdot 10^{-4}$ mol l⁻¹.

to substituent effects, which is analogous to UV spectra of the corresponding 4-cyano adducts *II* with maxima at 260 and 340 nm (ref.⁴). No attempts have been made to isolate the 4-cyano adducts *II*.

The kinetic measurements were carried out spectrophotometrically with a Specord UV-VIS (Zeiss, Jena) apparatus in a tempered cell at 298 ± 0.1 K. The reactions of compounds *I* with cyanide were carried out in aqueous solutions at pH 10.8 at the ionic strength $\bar{\mu} = 0.5$ adjusted by addition of KCl. Solution of compound *I* (0.2 ml) was added to 1.8 ml cyanide solution, and time dependence of absorbance *A* of the mixture was followed at 340 nm. The ranges of the concentrations measured: $2 \cdot 10^{-4}$ to $8 \cdot 10^{-4}$ mol l⁻¹ compound *I* and $1 \cdot 10^{-2}$ to $5 \cdot 10^{-1}$ mol. l⁻¹ KCN. In all the cases the excess of cyanide ion was sufficient to ensure the reaction to have pseudomonomolecular character⁴. The rate constant k_{obs} of the pseudomonomolecular reaction was evaluated from the slope of the dependence $\ln(A_{\infty} - A_t)$ vs $(t_{\infty} - t_t)$, where *A* is absorbance of the reaction mixture. The rate constant of the second order reaction was calculated from the relation $k_2 = k_{\text{obs}}/[\text{CN}^-] + K^{-1}$. The equilibrium constant *K* of the reaction was evaluated, according to Behm and Cordes¹¹ from the slope of the relation $(A_0 - A_{\infty})/[\text{CN}^-]$ vs A_{∞} , where A_0 and A_{∞} mean the absorbance of the substrate and that of the equilibrium reaction mixture, respectively. Table I summarizes the measured rate and equilibrium constants k_2 , k_{-2} and *K* of the process (*A*).

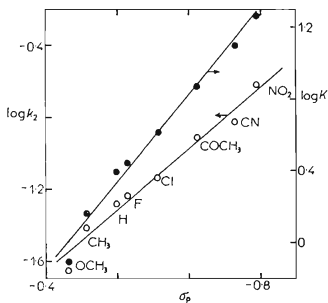


FIG. 1

Correlation of k_2 and *K* constants of the addition of CN^- ion to compound *I* with the σ_p parameters of the substituents. The linear regression gave the values $\rho_{\text{kin}} = 0.894$ ($r = 0.985$) and $\rho_{\text{eq}} = 1.222$ ($r = 0.993$)

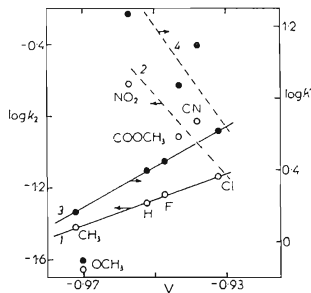
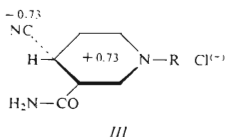


FIG. 2

Dependence of k_2 and *K* constants of the addition of CN^- ion to compound *I* on half-wave potentials $E_{1/2}$ of polarographic reduction of compound *I* measured in aqueous media¹⁰. The linear regression gave the following values of slopes: the straight line 1 7.03 ($r = 0.999$); 2 -22.2 ($r = 0.91$); 3 11.1 ($r = 0.999$); 4 -32.3 ($r = 0.82$)

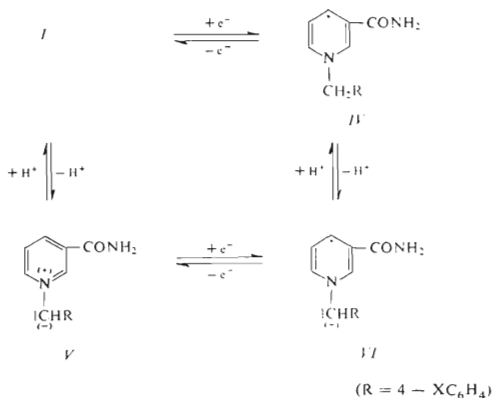
RESULTS AND DISCUSSION

Substituent effects. From Table I it follows that the *p*-X substituents affect significantly the equilibrium (*A*) and the rate of its establishing. On going from the most electropositive substituent $X = \text{OCH}_3$ to the most electronegative $X = \text{NO}_2$ the equilibrium constant $K = k_2/k_{-2}$ and the second order rate constant k_2 are increased by the factors 23 and 11, respectively. The both constants (k_2 and K) exhibit very good Hammett correlations (Fig. 1) except for the data of $X = \text{OCH}_3$ which are, however, loaded with a larger experimental error under the given conditions. The corresponding reaction parameters are $\rho_{\text{kin}} = 0.894$ and $\rho_{\text{eq}} = 1.222$, the latter being somewhat higher than analogous date for the former series⁹ of aqueous solutions of *meta* and *para*-substituted *I* derivatives ($R = \text{XC}_6\text{H}_4\text{CH}_2$). This fact is obviously connected with lower ionic strength of medium (0.5) in our experiments as compared with that (1.0) chosen by the authors⁹. Sometimes it is presumed^{4,9} that the ratio $\rho_{\text{kin}}/\rho_{\text{eq}}$ can express the partial charge localized at the transition state of the reaction. In our case, its rather high value 0.73 could indicate a relatively low charge transfer from the reagent to the substrate which takes place (according to the theoretical presumption¹²) in the saddle region of the potential energy valley near the 4 position of the heterocyclic ion *I*, *i.e.*, in accordance with the situation represented by formula *III*. Also other authors⁹ arrived at a conclusion (based on experimental data) that the mentioned transition state resembles more the left-hand side of Eq. (*A*).



Correlation with reduction half-wave potentials. Fig. 2 gives correlations between the half-wave potential values $E_{1/2}$ of polarographic reduction¹⁰ of aqueous solutions of quaternary salts *I* ($R = 4\text{-XC}_6\text{H}_4\text{CH}_2$) and the k_2 and K constants. Obviously, the correlation is divided into two parts, *viz.* that for π -donor substituents ($X = \text{CH}_3\text{O}, \text{CH}_3, \text{H}, \text{F}, \text{Cl}$) and that for π -acceptor ones ($X = \text{NO}_2, \text{CN}, \text{COOCH}_3$). This situation resembles that of correlation¹⁰ of the $E_{1/2}$ values with the σ_p parameters, except, however, for a striking deviation of the substituent $X = \text{OCH}_3$. These findings indicate that the mentioned splitting of the Hammett correlation reflects exclusively the processes taking place on the electrode or in the electrode double layer, because it is not observed with the process (*A*) in homogeneous media. The presumption¹⁰, that in the case of the electron-acceptor substituents ($X = \text{NO}_2, \text{CN}, \text{COOCH}_3$), a C-deprotonation pre-equilibrium is involved, is obviously caused

by different orientation of the ion I near the electrode and by influence of the electrode field, since both the cyanide ion addition and the polarographic reduction proceeded at similar pH values (11 and 9.5–10, respectively). Thus it can be stated that in aqueous media the reduction of the ions I with π -donor substituents ($X = \text{CH}_3, \text{H}, \text{F}, \text{Cl}$ and perhaps also OCH_3) goes by a simple E mechanism¹³ $I \xrightarrow{E} IV$, whereas in the case of the π -acceptor substituents ($X = \text{NO}_2, \text{CN}, \text{COOCH}_3$) the radicals IV are formed by a three-step CEC mechanism $I \xrightarrow{C} V \xrightarrow{E} VI \xrightarrow{C} IV$ (Scheme 1).



SCHEME 1

Most probably the operation of CEC mechanism is enabled by increasing electronegativity of the X substituent as well as by the presence of water molecules in the electrode double layer. This conclusion is supported by the following facts: From Fig. 3 it can be seen that the correlation of $\log k_2$ or $\log K$ with the $E_{1/2}$ values measured in aqueous-ethanolic medium¹⁰ only shows a distinct deviation for the most π -acceptor substituent ($X = \text{NO}_2$), which can be interpreted by the CEC mechanism of the electrode process (for less electronegative substituents, $X = \text{CN}$ and COOCH_3) being suppressed by the presence of less-solvating ethanol molecules in the mentioned double layer. Besides that, the correlation of $\log k_2$ and $\log K$ with the $E_{1/2}$ potentials measured in acetonitrile¹⁰, *i.e.*, with *a priori* exclusion of the CEC mechanism represented in Scheme 1, does not show any deviation for the 4-nitro derivative Ih (Fig. 4), whereby also the possibility is excluded that the polarographic reduction involves the depolarizer with electrochemically changed X substituent.

Striking is the systematic deviation for the substituent $X = \text{OCH}_3$ in all the correlations in Figs 2 to 4. The most likely explanation is seen in the possibility that the polarographic reduction – also in this case – goes by the simple E mechanism without participation of protons, the orientation of the ion I to the electrode surface being different. In this context it is worth mentioning that different behaviour of methoxy derivatives in polarographic reduction was found in other cases, too¹⁴.

Electronic mechanism of cyanide ion addition. The correlation of $\log k_2$ with the $E_{1/2}$ reduction potentials was also used for interpretation of the probable electronic mechanism of the process (A) from the point of view of its similarity to the purely one-electron E mechanism of Scheme 1. For this purpose we used the following simplifying presumptions: 1) In the both cases the processes are reversible and are characterized by the changes of Gibbs energies $\Delta G^0(\text{A}) = -RT \ln k_2$ and $\Delta G^0(\text{E}) = -nFE_{1/2}$, respectively, where n means the number of the electrons exchanged. 2) If the mechanisms of the two processes (A) and (E) were fully identical, it could be expected that $\Delta G^0(\text{A}) = \Delta G^0(\text{E}) + \text{const.}$, hence the theoretical value of slope in the correlation $\log k_2 = a \cdot E_{1/2} + b$ should be $a = nF/2 \cdot 303RT$. In our case ($T =$

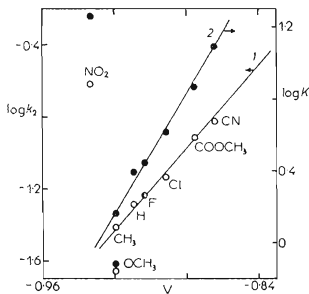


FIG. 3

Dependence of k_2 and K constants of addition of CN^- ion to compound I on the half-wave potentials $E_{1/2}$ of polarographic reduction of compounds I measured in aqueous-ethanolic medium¹⁰. The linear regression gave the following values of slopes: the straight line 1 10.87 ($r = 0.996$); 2 16.13 ($r = 0.996$)

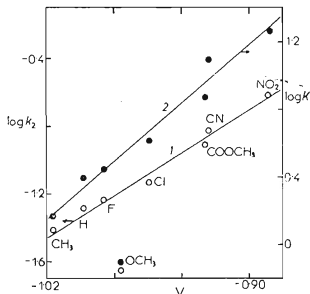


FIG. 4

Dependence of k_2 and K constants of the addition of CN^- ion to compound I on the half-wave potentials $E_{1/2}$ of polarographic reduction of compounds I measured in acetonitrile¹⁰. The linear regression gave the following values of slopes: the straight line 1 6.25 ($r = 0.992$); 2 8.77 ($r = 0.984$)

= 298.15 K) it is $a = 16.8$ for $n = 1$ and $a = 33.8$ for $n = 2$, whereas the experimental slope read from the correlation in Fig. 3 has the value $a = 10.9$, which rather indicates a radical character of the nucleophilic attack by the CN^- ion in the sense of *e.g.* S_{RN} mechanism taking place *via* CT-complex, *i.e.*, $I + \text{CN}^- \rightarrow$ activated complex $III \rightarrow$ CT-complex $I' \text{Cl}^- \text{CN}^- \rightarrow$ the second activated complex $\rightarrow II + \text{Cl}^-$. This mechanism agrees with the idea of cyanide ion being a soft nucleophile⁷ in the attack on the substrate type *I*.

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