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Intramolecular Catalytic Substitution Reaction of *N*-(ω-Bromoalkyl)pyridinium Bromide with Potassium Cyanide

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It was found by means of NMR spectrometric and potentiometric titration technique that the intramolecular catalytic substitution of *N*-(ω-bromoalkyl)pyridinium bromide with KCN proceeds in the range $n=2$—6 of methylene chain on the pyridinium salt and the intermolecular substitution in $n=7$ and 9, and the addition of cyanide anion to the pyridine ring takes place only for $n=1$.

Our recent interest has been focused on the reaction selectivity resulting from the conversion of a bimolecular into an intramolecular reaction in view of entropy point. In the enzymatic reaction involving a typical intramolecular catalytic process, the formation of an adsorptive complex of enzymes with an appropriate substrate results in high reaction selectivity through a favorable orientation of reaction site on the catalytic center. Thus a substrate severely constrained in the complex should be a good model of the activated key-intermediates for our study.

The counter-anion of quaternary ammonium and phosphonium salts has been shown to behave as a nucleophile in phase-transfer catalyzed reaction.[1] When a reaction site and a nucleophile are involved in a quaternary salt at the same time, an intramolecular substitution might take place smoothly at the reaction site with significant interactions to the quaternary center.[2] In this paper we wish to report the reaction of pyridinium salts having a general formula $\mathrm{Py^+(CH_2)_n\text{-}CH_2Br\cdot Br^-}$ ($n=1$—9) with potassium cyanide in aqueous solution.

The key-intermediary pyridinium salts (**1a**—**1h**) were prepared by the direct quaternization of pyridine with a series of the corresponding α,ω-dibromoalkanes. Successful induction of reactions of these salts with potassium cyanide, sodium acetate, and sodium azide was proved by IR and/or NMR spectroscopy. Since NMR spectroscopic studies have shown that methylene protons bearing a cyano group can be clearly recognized at higher field, potassium cyanide was used as a nucleophile for examining details of the substitution. The reaction of pyridinium salts (0.5 mol/l) with potassium cyanide (0.55 mol/l) in deuterium oxide at 64.5 °C was monitored by NMR spectroscopy with regard to the changing intensities at δ 3.2—3.4 ($\mathrm{CH_2Br}$) and 2.6—2.8 ($\mathrm{CH_2CN}$). Since the series of the substitution product, *N*-(ω-cyanoalkyl)pyridinium bromide, is too hygroscopic for isolation and characterization, one of them (**3b**) was immediately treated with sodium borohydride[3] to give *N*-(3-cyanopropyl)-1,2,3,6-tetrahydropyridine.

In order to let an intramolecular reaction take place, a very dilute solution is used. With respect to the amount of cyanide anion left during the course of reactions, potentiometric titration was employed for tracing in the 0.02 mol/l concentration scale since it has much sharper responses than in NMR spectrometry. As shown in Fig. 1, the rate of the substitution reaction decreases along with the sequence **1e**$\approx$**1f**$\geq$**1h**$\approx$**1g**$\geq$**1d**$\approx$**1c**$\approx$**1b** as in the NMR study. In the case of **1a** ($n=1$), however, addition of cyanide anion to the pyridine ring took place, since the unstable product[4] obtained in chloroform–water system only was no longer a quaternary salt as confirmed on the basis of the absorption band of cyano group and C–C double bond in the IR spectrum. Such a difference between **1a** and **1b**—**1h** can be explained as follows. It is very hard for a four-membered cyclic intermediate to form on **1a** for the intramolecular catalytic substitution; in addition quaternary pyridinium salts are liable to undergo nucleophilic additions.[4] Thus the intramolecular catalytic substitution proceeds primarily if the cyclic intermediate is available, whereas addition takes place if not. Thus the case of $n=5$ or 6 (**1e** or **1f**)

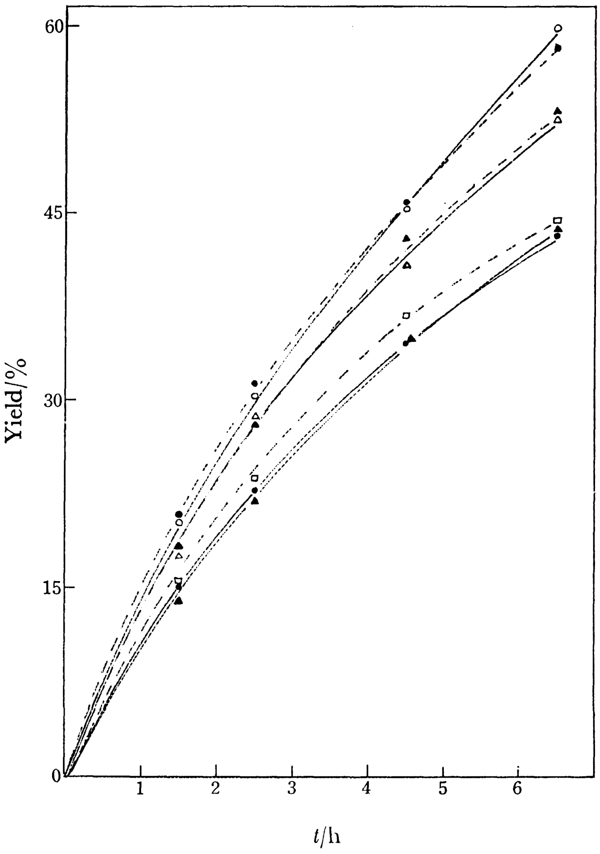


Fig. 1. Relationship between the yield and reaction time; **1** (0.020 mol/l) and potassium cyanide (0.021 mol/l) —●— **1b**; —▲— **1c**; ---□--- **1d**; —○— **1e**; ---●--- **1f**; —△— **1g**; ---▲--- **1h**.

showed the highest reaction rate through the maximum interaction between the catalytic center and the reaction site (Fig. 1). However, no first order reaction rate constant could be obtained from the results, since an ion-exchange equilibrium might take place between cyanide and bromide anions giving rise to the dependence of the reaction rate on the concentration of *N*-(ω-bromoalkyl)pyridinium cyanide (**2**). The reaction rate of **1b** and **1e**, in fact, were accelerated by addition of potassium cyanide and fairly retarded with potassium bromide as expected from the above assumption (Table 1).

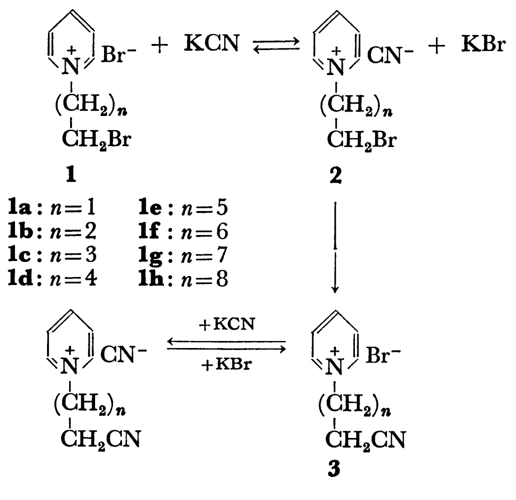
TABLE 1. EFFECT OF THE ADDED SALTS TO THE YIELD[a] OF *N*-(ω-CYANOALKYL)PYRIDINIUM SALTS

Concn. of salts mol/l	Starting material[b]	Reaction time (h)				
		0.5	1.5	2.5	3.5	4.5
KCN 0.021	**1b**	5.8	15.2	23.2	—	34.9
	1e	7.8	20.3	30.2	—	45.4
	1h	6.3	18.6	28.0	—	43.3
KCN 0.091	**1b**	17.0	43.0	60.7	69.4	78.6
	1e	29.1	55.1	70.1	78.2	86.6
	1h	20.7	48.6	67.1	74.2	79.1
KCN 0.181	**1b**	23.1	53.0	71.2	83.5	—
	1e	40.8	77.3	92.0	97.1	—
	1h	24.3	52.7	70.9	79.9	—
KCN 0.021 KBr 0.20	**1b**	4.1	11.0	—	—	—
	1e	4.8	15.0	—	—	—
	1h	6.0	18.7	—	—	—

a) Determined by the potentiometric titration. b) 0.020 mol/l was used in all cases.

Although there is no such effect of potassium bromide on **1h**, the reaction rate approached that of **1b** when potassium cyanide was added up to 0.19 mol/l. The reason for **1h** being more reactive than **1b** might be the term of the positive micellar effect[5] (cmc of **1h**: *ca.* 0.019 mol/l at 25 °C).[6]

The results show that the quaternary nitrogen atom plays a considerable catalytic role with favorable interactions to an appropriate reaction site even in aqueous solution. Such an idea might thus be applied to regio-specific substitutions in view of the intramolecular catalysts.



1a: *n*=1 **1e**: *n*=5
1b: *n*=2 **1f**: *n*=6
1c: *n*=3 **1g**: *n*=7
1d: *n*=4 **1h**: *n*=8

Experimental

Instruments. NMR and IR spectra were recorded with a Varian T-60 and Hitachi EPI-S2 spectrometers, respectively. The potentiometric titration was carried out with a Toa HM-5A potentiometer.

N-(ω-Bromoalkyl)pyridinium Bromide (1). After a mixture of pyridine (3.16 g, 0.05 mol) and α,ω-dibromoalkane (0.10 mol) had been refluxed in ethanol (50 ml) for 5 h, the solvent and excess α,ω-dibromoalkane were removed by means of evaporation, decantation, and extraction with ethyl acetate. The α,ω-bispyridinium salts was crystallized from 2-propanol (60 ml) (in the case of **1a**—**1e**) and from acetone (**1f**—**1h**) crystalline **1** deposited in an icebox after the solvent was concentrated to half. Recrystallization from ethanol (**1a**, **1b**, and **1c**) or 2-propanol (**1d** and **1e**) or acetone (**1f**, **1g**, and **1h**) gave pure salts. All these did not show clear melting points because of being too hygroscopic. Analytical data, **1a**; Found: C, 31.85; H, 3.58; N, 5.30%. Calcd for $C_7H_9NBr_2$: C,31.49; H, 3.40; N, 5.25%. **1b**; Found: C, 34.22; H, 3.58; N, 5.30%. Calcd for $C_8H_{11}NBr_2$: C, 34.19; H, 3.98; N, 4.99%. **1c**; Found: C, 36.96; H, 4.84; N, 5.01%. Calcd for $C_9H_{13}NBr_2$: C, 36.64; H, 4.44; N, 4.75%. **1d**; Found: C, 38.12; H, 4.93; N, 4.21%. Calcd for $C_{10}H_{15}NBr_2$: C, 38.86; H, 4.89; N, 4.53%. **1e**; Found: C, 41.14; H, 5.22; N, 4.23%. Calcd for $C_{11}H_{17}NBr_2$: C, 40.89; H, 5.30; N, 4.34%. **1f**; Found: C, 42.82; H, 5.13, N, 3.95%. Calcd for $C_{12}H_{19}NBr_2$: C, 42.75; H, 5.68; N, 4.16%. **1g**; Found: C, 44.76; H, 6.45; N, 4.10%. Calcd for $C_{13}H_{21}NBr_2$: C, 44.46; H, 6.03; N, 3.99%. **1h**; Found: C, 46.36; H, 6.41; N, 3.91%. Calcd for $C_{14}H_{23}NBr_2$: C, 46.05; H, 6.35; N, 3.84%.

Reduction of N-(3-Cyanopropyl)pyridinium Bromide (3c). A solution of *N*-(3-bromopropyl)pyridinium bromide (**1c**) (1.12 g, 4 mmol) and potassium cyanide (0.286 g, 4.4 mmol) in water (30 ml) was heated in a water bath for 6 h. After evaporation of water, the residue was dissolved in methanol (30 ml) and treated with sodium borohydride (1.52 g, 40 mmol) below 5 °C. After being stirred for 1 h, the reaction product obtained by evaporation was dissolved in water and then extracted with ether several times. The extracts were evaporated to give syrup which was chromatographed with silica gel (Wako C300) using a solvent system ethyl acetate–acetone 10: 1 (500 ml) and then 5: 1 (500 ml). The fractions eluted by the system 5: 1 were combined and distilled in a Ball Tube Oven at 150 °C/26 Torr. The compound was very unstable in the air. Found: C, 72.29; H, 9.34: N, 18.71%. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.39; N, 18.65%. IR(KBr) 2250 (CN) and 1610 cm^{-1} (C=C); NMR (CDCl$_3$) δ 5.67 (m, 2H, $J_{CH=CH}=1$ Hz, CH=CH) and 2.99 (s, 2H, NCH$_2$–CH=).

Reaction of 1 with Potassium Cyanide. *NMR Study*: A deuterium oxide solution of **1** (1.0 mol/l) and a potassium cyanide solution (1.1 mol/l) were prepared and then 0.2 ml of each was mixed in NMR tube at 5 °C. The mixture was kept at 64.5±2 °C in a Kugelrohr Oven and the intensities at δ 3.2—3.4 (CH$_2$Br) and 2.6—2.8 (CH$_2$CN) were measured at every 0.5 h.

Potentiometric Titration: An aqueous solution of **1** (0.2 mol/l) and that of potassium cyanide (0.21 mol/l) were prepared, and 10 ml of each was mixed and made up to 100 ml with water in a measuring flask. The solution was kept at 64.5 ±0.5 °C in a water bath. Two 5 ml portions of the solution were taken at regular time intervals, cooled immediately in ice–methanol bath and then titrated with silver electrode.

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