3차아민의 4차화반응에 관한 연구 (제1보).
Phenethyltosylate와 치환 피리딘류의
반응에 관한 반응속도론적 연구

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(1978. 11. 25 접수)

Studies on the Quaternization of Tertiary Amines (I).
Kinetics and Mechanism for the Reaction of Phenethyltosylate with Substituted Pyridines

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(Received Nov. 25, 1979)

요 약. Phenethyltosylate와 치환 피리딘의 반응속도를 전기전도법으로 아세토니트릴 용매에서 50, 60, 및 70°C에서 측정하였다. 이 반응에서의 피리딘의 치환기 효과를 검토한 결과 피리딘의 전자주는 능력이 강할 수록 반응은 빨랐다. E_a와 ΔS^* 사이에는 동속관계가 성립되었고 동속온도는 240 °K였다.

Brønsted 도시는 4-아미노피리딘을 제외하고는 $\log k = 0.22 pKa - 3.71$ ($r = 0.986$)의 직선이 얻어졌다. Hammett 식에서도 역시 4-아미노피리딘을 제외하고 $\log k = -1.33\sigma + 0.08$ ($r = -0.987$)의 직선이었다. 이와 같이 4-아미노피리딘의 편차는 용매효과와 공명효과 및 σ 값 그 자체에 기인된다고 생각된다.

이상의 결과로서 본 반응은 전이상태에서 C···N 결합형성에 의하여 반응이 결정되는 S_N2 반응메카니즘으로 진행된다는 것을 알았다.

ABSTRACT. Kinetics of the reaction of phenethyltosylate with substituted pyridines at 50, 60 and 70°C in acetonitrile were investigated by an electric conductivity method. The effects of substituents on the reaction of phenethyltosylate with pyridines were discussed.

The rates of reaction were increased with electron donating power of substituents of pyridines. The isokinetic relationship was shown E_a and ΔS^*, it's temperature was 240°K.

Brønsted plots were excellent linear except for 4-amino pyridine given by the following equation, $\log k = 0.22 pKa - 3.71$ ($r = 0.986$). According to a plot of $\log k$ against Hammett substituent constants, the linearity was good except for 4-amino pyridine too, $\log k = -1.33\sigma + 0.08$ ($r = -0.987$). In both cases, deviation of 4-amino pyridine from linearity was considered to solvent effect, resonance effect and σ value itself. From all the above results, this reaction was found typical S_N2 reaction which the rates of reaction was determined by C···N bond formation at transition state.

INTRODUCTION

Quaternization for the reaction of tertiary amine with alkyl halide was many reported[1~2] previously, but few studies were reported for the reaction of compounds which have one hetero atom in the ring. Previously, kinetics for the reaction of benzyl arenesulfonate with substituted pyridines were studied in more detail[3].

In this study, the reaction of phenethyltosylate with pyridines in acetonitrile was measured by conductivity method. From Brønsted, Hammett equation and isokinetic relationship, the mechanism of this reaction was discussed and compared the rate constant of this reaction with that of benzyl arenesulfonate.

EXPERIMENTAL

Materials and Instruments. All materials used throughout were commercial products (Wako, Japan). Pyridine was a commercial product purified by several distillations over potassium hydroxide before use. Other liquid pyridines were used without further purification, but solid ones were recrystallized before use. All purified pyridines were stored in brown ampoule or bottle filled with nitrogen gas.

Acetonitrile was purified by distillation after standing with anhydrous potassium carbonate for 3 days at room temperature. IR spectra were recorded on a Hitachi EPI-2G Infrared Grating spectrometer, NMR spectra were recorded on vavian 60MHz spectrometer. Conductance measurements were used with a Conductivity-Meter LBR (Germany).

Phenethyltosylate. While stirring the temperature was kept 0 °C in a ice-water bath, 11. 2 g (0. 092 M)of 2-phenethylalcohol was dissolved in 100 ml of pure pyridine and subsequently 30 g (0. 138 M) of p-tosylchloride was gradually added at above temperature. After

stirring for 3 hours at 0 °C, the mixture was poured into ice-water and then collected colorless crystals. Recrystallization from n-hexane: m. p 38~39 °C　(*lit.* 36~37 °C), yields 69%.

Phenethyl Pyridiniumtosylate. 2 g (0. 072 M) of phenethyltosylate and 0. 57 g (0. 72 M) of pyridine were added in 80 ml of acetonitrile. The mixture was kept refluxing for 4 days. After keeping the mixture overnight at room temperature, the products obtained were separated from solvent and washed with anhydrous ether.

Recrystallization from isopropyl alcohol gave colorless crystal m. p 133~4 °C, yields 56 %. The products obtained were identified by their elementary analysis, IR and NMR spectra.

Anal. Calcd. for $C_{20}H_{21}NO_3S$: C, 67. 58; H, 5. 59; N, 3. 94; S, 9. 02, Found: C, 67. 48; H, 5. 86; N, 3. 94; S, 9. 02. IR spectrum(*Fig.* 1, in nujol), 1600 (C–C aromatic), 1355 ($\nu_{as\ SO_2}$), 1200(ν_{SO_2}), 1050($\nu_{S=0}$), 835 cm^{-1} (p-substituted), NMR spectrum (*Fig.* 2, DMSO), 8. 7 (2H, d, α-H), 8. 60 (1H, t, γ-H), 8. 2 (2H, t, β-H of pyridine), 7. 5 (10H, m. phenyl), 4. 8 (2H, t,

$$-CH_2 \overset{+}{\underset{|}{-N}} -),\ 3.\ 2\ (2H, t,\ C_6H_5CH_2),\ 2.\ 1\ ppm$$

(3H, s, CH$_3$).

As above mentioned, the reaction rotue is illustrated as follows:
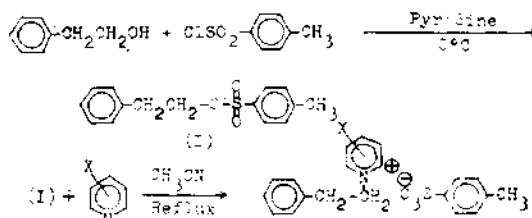
Kinetics. A typical kinetic run is described as follows.[4,5] 0. 1244 g of phenethyltosylate was added to a 15 ml volumetric flask which was filled with nitrogen and filled to the mark with acetonitrile about 1 cm below. The flask was

placed in a constant temperature water bath at 50±0.01°C.

After the solution was maintained at constant temperature, it was made up to mark a small additional quantity of acetonitrile. The final concentration of phenethyltosylate prepared was made just 0.015 mole/l.

That of pyridine was made just 0.300 mole/l with above same method and placed in a constant temperature water bath. A kinetic run was initiated by placing 15 ml of pyridine solution in the conductivity cell and adding 15 ml of the phenethyltosylate solution to give a reaction mixture that was 0.150 mole/l in pyridine and 0.0075 mole/l in phenethyltosylate. Reactions were generally run to $ca.$ 3~4 half-lives.

Pseudo 1st-order rate constants were calculated from the slopes obtained from conventional plots of $\log(K_\infty - K_t)$ against time using the least-squares method. Second-order rate constants were calculated from the slopes of plots
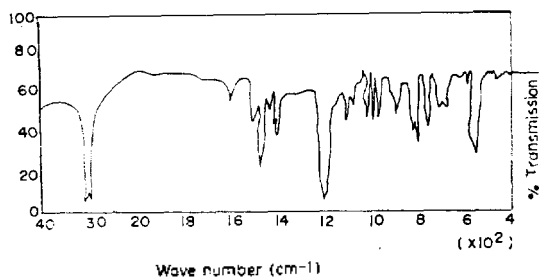

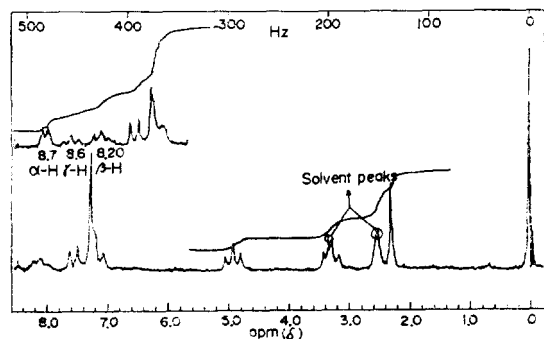Fig. 1. IR spectrum of phenethylpyridiniumtosylate.

Fig. 2. NMR spectrum of phenethyl pyridiniumtosylate.

of the observed first-order rate constants against pyridine concentration. Rate constants are estimated to be accurate to ±3%. The activation energies were calculated from Arrhenius plot.

RESULTS AND DISCUSSION

The kinetic data and activation parameter for the reaction of phenethyltosylate with substituted pyidrines are given in *Table* 1.

Rates contants are increased by electron donating substituents in pyridines, while electron with-drawing groups are retarded.

Activation parameters E_a and ΔS^* were about the same value of the other type of S_N2 Menschutkin reaction[6].

1. Brønsted Linear Relationship. It was generally accepted that Brønsted linear relationship was shown between reaction rates and basicities of nucleophiles in which attacking atom is the same in S_N2 reaction.

Good linearity of this Brønsted relationship has been reported[7] on quaternization of substituted dimethylanilines. In this study, a good linear relationship was shown (in *Fig.* 3.) between $\log k$ $vs.$ pKa of pyridines,

$$\log k = 0.218\,pKa - 3.71 \text{ at } 60\,°C \text{ (correlation}$$
coefficient $r = 0.986$).

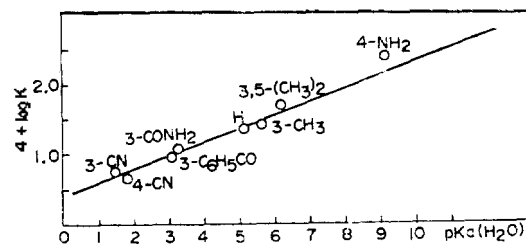In *Fig.* 3, 4-NH$_2$ group was deviated from the linearity and was so much faster than any

Fig. 3. Correlation between $\log k$ and pKa of pyridines for the reaction of phenethyltosylate with pyridines at 60°C.

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Table 1. Kinetic data for the reaction of phenethyltosylate with pyridines in acetonitrile.

Subst.	$K_2 \times 10^4$ l/mole·min			E_a (kcal/mol)	$-\Delta S^*$ (e. u)60°C
	50°C	60°C	70°C		
4-NH₂	90.8±20.	241.9±5.1	444.6±5.3	17.4±0.1	15.75±0.41
3,5-(CH₃)₂	16.5±0.5	47.7±0.6	106.1±1.6	18.1±0.1	17.03±0.33
3-CH₃	15.2±0.3	24.3±0.5	51.1±0.5	16.9±0.2	21.97±0.56
H		22.±0.5	48.9±1.0	18.1±0.1	18.80±0.10
3-CONH₂		12.1±0.2	24.7±0.4	16.2±0.1	25.46±0.29
3-C₆H₅CO		8.3±0.3	20.4±0.1	20.6±0.7	13.43±1.79
3-Br		6.2±0.2	12.7±0.1	16.3±0.4	26.82±1.04
3-CN		5.7±0.1	11.5±0.2	15.9±0.1	27.86±0.34
4-CN		4.3±0.1	9.1±0.2	17.1±0.1	24.88±0.2

other substituents.

Perhaps this fact was resulted from solvent effect. pKa values of pyridines were determined in water, but these reaction were carried out in acetonitrile. Amino group has hydrogen bond in water, but these bonds disappear entirely in acetonitrile, so amino group indicated stronger electron donating power. These results caused an accerleration of the rate of reaction. These properties of solvent agreed with Tsuruta's work.[2]

2. **Hammett Relationship.** In the case of a heterocyclic compound[8], it was reported that Hammett plot was not well correlated with σ value. The reason was that hetero atoms caused larger electronegativity than carbon in alicyclic compounds, but nucleophilic reaction with pyridines in S_N2 reaction was reported[9] to good linearity in some cases.

These rates are also correlated by the σ constants[10] giving a Hammett plot with $\rho = -1.33$ and the following equation was obtained from the Fig. 4,

$$\log k = -1.33\sigma + 0.076 \quad (r = -0.987).$$

In Fig. 5, 4-amino group in pyridine was larger than any other substittents. These discrepancies were resulted from resonance
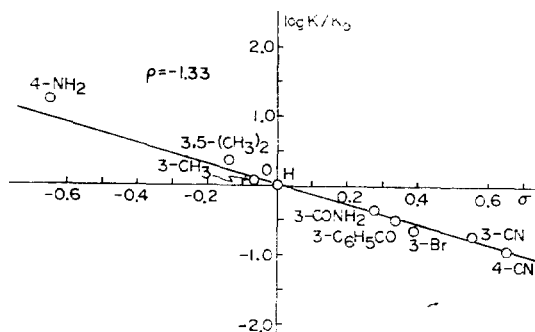

Fig. 4. Hammett plot for the reaction of phenethyltosylate with pyridines in acetonitrile at 60 °C.
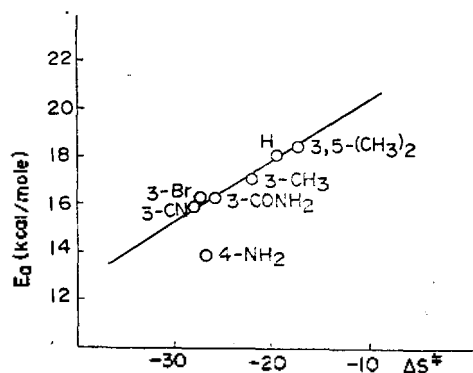

Fig. 5. The isokinetic relationship for the reaction of phenethyltosylate with pyridines in acetonitrile at 60°C

effects of 4-amino and solvent effect already discussed. So that 4-amino group made stronger electron donating power, these results caused an accerleration of the reaction rate.

3. Isokinetic Relationship. E_a vs. $\Delta S^{\neq}$ obtained in this reaction are shown in *Fig.* 5. The isokinetic relationship was well correlated except for 4-amino and it's temperature was 240 °K.

From these results, this reaction was found a typical S_N2 reation. If the rate of reaction is determined by C···N bond formation, the rates are influenced by substituents of pyridines, this fact was confirmed by negative slope of Hammett plots. On the contrary, if it's plots showed positive, the rate is determined by C···Br cleavage.

According to this investigation, the Hammett plots of this work showed negative slopes in acetonitrice ($\rho = -1.33$). The ρ value was about the same for benzyl arenesulfonate with pyridines in acetone ($\rho = -1.67$). Rate constants of benzyl benzenesulfonate with pyridine are larger than that of phenethyl tosylate.

This fact indicates that it's transition state, "benzyl pyridinum benzenesulfonate", is more stable than that of phenethyl pyridiniumtosylate, because the benzyl cation is more conjugated with it's phenyl ring. Both slopes are negative.

This suggests that rate of reaction of phenethyltosylate with pyridine is determined by C···N bond formation at transition state.

From all the above results, this reaction was found a typical S_N2 reaction in which the rates of reaction were determined by C···N bond formation at transition state.

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