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Direct Substitution Reaction of Phenylethyl Bromides

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Abstract

Halongen exchange reactions of phenylethyl bromides have been studied in acetone at 25° and 35°. Results show that the reaction proceeds by a typical S_N2 path, and steric crowding effect in 1-phenylethyl bromide gives large variation in the activation parameters for chloride exchange.

요 약

25° 및 35°C의 아세톤 용액에서 부롬화 훼네틸들의 할로겐 교환반응을 연구하였다. 결과로 이 반응은 전형적인 SN2형 반응이고 염소 교환의 경우 1-부롬화 훼네틸의 입체 반해작용으로 활성화 파라메터에 큰 변화를 가져옴을 알았다.

1. Introduction

Displacement of halogen or halogen exchange reaction is a typical example of the direct substitution of a leaving group, X, by a nucleophile, Y^-, *i.e.*, SN2 reaction[1].

$$RX+Y \rightarrow RY+X^- \qquad (A)$$

The halogen exchange reaction has been studied widely for the saturated carbon center[2]. The factors influencing rate of exchange reaction are (1) internal effect due to the structural changes in substrates and (2) external effects like basicity and polarizability of nucleophile and solvent changes[3].

In this work we have studied the halogen exchanges of 1-phenylethyl and 2-phenylethyl bromide with halide ions Cl^-, Br^- and I^-, and discussed the mechanism involved in the light of effects due to various internal and external factors. In the actual determination of reaction rate, exchanged halides of radioactive isotopes(^{36}Cl, ^{82}Br, ^{131}I) were extracted and counted using scintillation counters.

Since the isotope exchange method is one of the most important and widely used method of the labeled compound synthesis today, the elucidation of mechanism of exchange has the practical as well as academic importance.

2. Experimental

(1) Material

1-phenylethyl bromide and 2-phenylethyl bromide were G.R. grade which were used without further purification. LiCl was obtained by reacting LiOH with NH_4Cl, and used after recrystalization and vacuum drying. LiBr was similarly prepared and purified. Lil was Merck G.R. reagent, which was used without further purification.

Radioactive chlorine, ^{36}Cl was purchased from the Radiochemical Center, Amersham, England, in HCl form Radioactive bromine, ^{82}Br, and iodine ^{131}I were obtained from AERI.

Acetone was first fractionally distilled using a Todd Column(reflux ratio 10: 1) after passing through a calcium chloride column. b. p. 56-56.5°C. This was then passed through an activated alumina cotumn(diameter 3cm, length 20cm). This treatment gives water content of less than 0.8%. (E. Muller, "Methoden der Organische Chemie" 4th ed., Georg Thieme Verlag, Stuttgart, 1958, p 163).

(2) Stock Solution

Substrates were dissolved in acetone to $1\text{-}3\times10^{-2}$ M and salts were dissolved in acetone $1\text{-}3\times10^{-4}$M.

(3) Determination of Rate Constant

The following general procedure was adopted for measurements of rate constants. To 20ml of substrate solution, 15ml of salt solution was added after the two solutions were kept in a thermostatic bath at a set temperature to ±0.03°C. At timed intervals, 5ml aliquot of the reaction mixture was pippetted from the flask to benzene-water mixture and shaked vigorously. One ml portion of the organic layer was used in detecting radioactivity.

Chlorine-36 activity was counted using Aloka-1600 liquid scintillation counter. The scintillator solution used was combination of toluene, solvent, PPO(2,5-diphenyl oxazole), primary solute. and POPOP(2,2-phenylene-bis(5-phenyl oxazole)), secondary solute. The actual counting solution was made up by adding 1ml of organic layer(extract) to 19ml of scintillator solution. Bromine-82 and iodine-131 activities were measured using well-type scintillation counter.

The increase in activity of the organic layer with time represented the progress of reaction, and rate constants were calculated by the equation (B)[4] for bromide exchange reaction and by the equation (C)[4] for chloride and iodide exchanges.

$$k=-\frac{1}{a+b}\cdot\frac{1}{\alpha t}\ln(1\text{-}F) \qquad (B)$$

$$k=-\left(\frac{c-b}{a-b}\right)\cdot\frac{1}{Dt}\ln(1\text{-}F) \qquad (C)$$

where a and b are initial concentrations of substrates and salt, respectively, and $C=\frac{1}{2}(D+K+4b)$, and $D=(K^2+4Kb)^{\frac{1}{2}}$. F represents the fraction reacted at time t and K is ion-pair dissociation constant of salt in acetone[5]. α in equation (B) is degree of dissociation of a salt at the concentration used[5]. According to the equations (B) and (C), straight line plots of log(1-F) against t will give the rate constant, k. A typical plot is given in Fig. 1. The rate constant determined in this way was reproducible to ±3%.

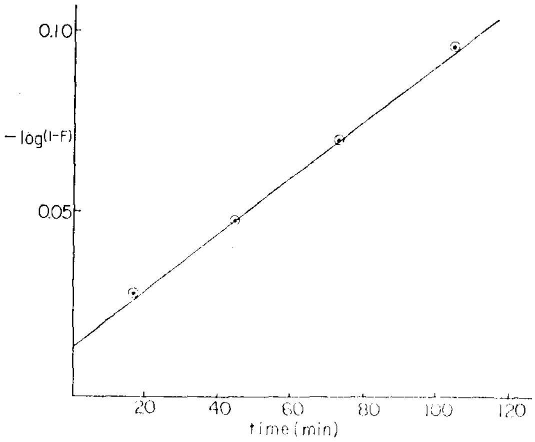


Fig. 1. Determination of k.
For $1\text{-}PEB+Cl\rightarrow1\text{-}PEC+Br^-$ at 25°C.
$a=3.044\times10^{-2}M$
$b=1.025\times10^{-3}M$.

(4) Determination of Activation Parameters

From the rate constants determined at 25° and 35°, enthalpy of activation, $\Delta H^{\neq}$ and entropy of activation, $\Delta S^{\neq}$, were calculated using Eyring's absolute rate equation[6].

3. Results and Discussion

The second order rate constants, k, at 25° and 35°C are summarized in Table 1. Since it is generally accepted that the leaving ability of bromide is greater than that of chloride[1,3], phenylethyl bromide is expected to have greater k values than phenylethyl chloride under the same condition. Indeed the leaving ability of bromide is greater for phenylethyl halides, since 1-phenylethyl chloride had k value of 9.00×10^{-4} M^{-1} sec^{-1} at 55°C[7] as compared with the k value of 9.83×10^{-3} M^{-1} sec^{-1} for 1-phenylethyl bromide at 25°C for chlorine exchanges. The fact that bromide has a greater leaving ability means that at the transition state bond-breaking of C-Br is progressed to a greater extent compared to that of C-Cl.

Table 1. Summary of rate constants, $k_2\times10^3$ (M^{-1} sec^{-1}), for halide exchanges of 1-and 2-phenylethyl bromides, (1-PEB and 2-PEB)

Substrate	Temp. °C	Cl^-	Br^-	I^-
1-PEB	25	9.83	3.61	2.58
	35	11.70	8.91	4.34
2-PEB	25	6.60	2.75	4.57
	35	11.43	4.96	8.73

Table 1 shows that the order of nucleophilicity of halide ions for 1-phenylethyle bromide increases as,

$I^- < Br^- < Cl^-$

This is the order normally observed for halide ions in an aprotic solvent like acetone, and it is the reverse order observed in a protic solvent like water. The nucleophilicity of halides in water increases in the order[8],

$Cl^- < Br^- < I^-$

The main causes of this reversal of nucleophilicity order are believed to be solvation or desolvation of halide ions in the solvents and polarizabilities of the ions. In water Cl^- is better solvated than I^-, while in acetone I^- is more extensively solvated than Cl^-. Greater degree of solvation requires large desolvation energy in the formation process of the transition state and thus the transition state formation becomes more difficult and the rate of reaction decreases. The order of nucleophilicity of halide ions for 2-phenylethy bromide is,

$Br^- < I^- < Cl^-$

and shows the scrambling of the relative order. Thus for the exchange reaction of this substrate, the nucleophilicity of I^- is greater than Br^-. Since the carbon atom at reaction center in this compound is more polarizable compared with that in 1-phenylethyl bromide, the more polarizable nucleophile will react faster.

The transition state formation is easier for the more polarizable nucleophile, *i,e.*, I^-, as compared with the less polarizable, *i, e.*, Br^-. This tendency will increase as the polarizability of reaction center becomes greater. Thus the scrambling of nucleophilicity order observed for 2-phenylethyl bromide can be attributed to the polarizability contribution combined with the strong desolvation effect. Similar phenomena has been reported for exchange reactions of benzyl chloride[2].

Enthalpy of activation, ΔH^{+}, and entropy of activation, ΔS^{+}, calculated are summarized in Table 2. In general ΔH^{+} value is relatively small and ΔS^{+} has large negative value. This is the general tendency observed in an SN2 type reaction and fact this tendency is believed to be a charateristic of an SN2 reaction[8]. Therefore activation parameters suggest that halogen exchange reaction of phenylethyl bromide proceeds by the SN2 path. In the case of 2-phenylethyl bromide, ΔH^{+} and ΔS^{+} values for each halide ions are not significantly different. This implies that the exchange mechanism for this compound is uniform SN2

Table 2. Summary of activation parameters

a) Enthalpy of activation, ΔH^{+}, (KCal/mole)

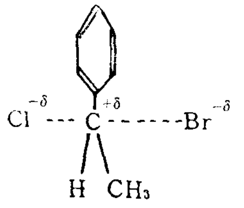
Substrate	Cl^-	Br^-	I^-
1-PEB	2.6	15.9	8.9
2-PEB	9.4	10.2	11.2

b) Entropy of activation, ΔS^{+}, (e.u.)

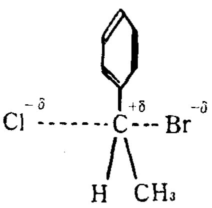
Substrate	Cl^-	Br^-	I^-
1-PEB	59.1	16.4	40.6
2-PEB	36.9	36.2	31.8

type for each halides. On the other hand in the case of 1-phenylethyl bromide, chloride, exchange has the largest ΔH^{+} and $-\Delta S^{+}$ values compared to other halide exchanges.

Considering the degree of bond-formation and bondbreaking in the transition state for SN2 reaction, the following two cases may be envisaged⁹⁾. In (I), the bond-formation has progressed more than in (II), and would require less energy in breaking C-Br bond



(I)



(II)

due to the partially formed C-Cl bond, whereas in (II) larger energy is needed to break C-Br bond since C-Cl bond-formation has not progressed to a significant degree. 1-phenylethyl bromide has a CH_3-group at the reaction center which causes steric crowding for the carbon center. Therefore steric inhibition is expected for the approaching nucleophile of bulky halides like Br^- and I^-, and the transition state may well be of the type (II). However for the less bulky halide Cl-, realtively less steric inhibition is expected and nearer approach at the transition state is possible forming type (I) transition state. This may be the explanation for a large variation in ΔH^{+} and ΔS^{+} values for 1-phenylethyl bromide exchanges shown in Table 2.

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