The Rearrangement of N-Deuterated Aromatic Amine Hydrochloride into its Ring-deuterated Analogue in the Solid Phase: The Rearrangements of o- and m-Toluidine Hydrochlorides and the Effect of Anions on the Rate of Rearrangement of Anilinium Salts

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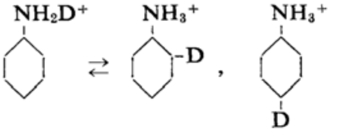
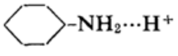
When aniline hydrochloride-*N-d* is heated at about 150°C or above, it rearranges into its ring-deuterated analogues[1]



The reaction may as well be regarded as the deuterium exchange reaction between the NH_3^+ group and the benzene nucleus in aniline hydrochloride. The rearrangement occurs well below the melting point of the hydrochloride. The deuterated positions of the benzene nucleus have been determined by the reverse rearrangement of *o*, *p*-trideuterio-aniline hydrochloride to be the ortho and the para positions[1b]. It has been suggested that the mechanism of this rearrangement is an electrophilic substitution as in the case of the liquid phase deuteration of aromatic nucleus by acidic deuterating agents[2], and that anilinium ion acts as proton acceptor at least in the state of partial dissociation in the solid phase,



Further study of this rearrangement with *p*-toluidine hydrochloride[3] has shown that the number of nuclear hydrogen atoms which take part in the rearrangement is 2, probably ortho positions, when the rearrangement takes place in the solid phase, and 4, probably ortho and meta positions, when the rearrangement takes place in the molten phase. This qualitative difference in exchange equilibria suggests that different mechnisms are responsible for the exchange reaction in the solid and for that in the molten phase, and serves to exclude the possibility that the exchange reaction in the solid phase might be caused by local melting due to the presence of a small amount of moisture or other contaminations.

The purpose of the present work is to supplement the earlier results with the study of the exchange reaction of *o*- and *m*- toluidine hydrochloride and with the comparative study of the rate of rearrangement of aniline hydrochloride and hydrobromide, in the hope of approaching the elucidation of the mechanism of this rearrangement.

Experimental

Materials.—Commercial *o*-toluidine (extra pure reagent) was first treated with oxalic acid in order to exclude the possible contamination with para isomer. After repeated distillations, it was neutralized with hydrochloric acid (special grade reagent), and recrystallized twice from water.

m-Toluidine was synthesized partly from *p*-toluidine and partly from benzaldehyde by the usual methods. It was acetylated, and the aceto-toluidide obtained was purified by repeated recrystallization from water. Then the amine was again set free, distilled repeatedly and neutralized with hydrochloric acid. The hydrochloride was recrystallized from water twice (m. p. 215.5∼216.0°C, corrected).

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[1] a) M. Harada and T. Titani, This Bulletin, **11**, 554 (1936). b) N. Okazaki, *J. Chem. Soc. Japan*, **62**, 52 (1941); N. Okazaki and M. Koizumi, This Bulletin, **16**, 371 (1941).

[2] C. K. Ingold, C. G. Raisin and C. L. Wilson, *J. Chem. Soc.*, **1936**, 1637.

[3] N. Okazaki and J. Kuroda, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kwagaku Kwaisi*), **62**, 57 (1941); This Bulletin, **11**, 417 (1941).

Commercial aniline (special grade) was neutralized with hydrochloric acid, and the salt solution was treated with steam to remove the possible contamination with nonbasic compounds. Then the amine was again set free, distilled repeatedly, and neutralized with hydrochloric acid (special grade) or redistilled hydrobromic acid (first grade). The salts were recrystallized three times from alcohol.

Procedure. — The experimental procedures are almost the same as those described in the earlier paper[1b]. A known amount of *N*-deuterated anilinium or toluidinium salt which was prepared by the exchange reaction with heavy water (ca. 1%) and dried in a vacuum desiccator over phosphorus pentoxide, was sealed in vacuo in a glass tube, and heated for a definite time in a vapor bath of organic liquid.

The relation between the initial and equilibrium deuterium contents, D_i and D_e, of the NH_3^+ group of the salt is given by

$$nk = 3(D_i - D_e)/D_e$$

where k is the deuterium partition coefficient between the NH_3^+ group and the benzene nucleus, n is the number of the nuclear hydrogen atoms which take part in the exchange reaction.

As the value of k may be taken to be nearly unity, the number n of exchangeable hydrogen atoms of the benzene nucleus may be judged readily from the value of nk.

The value of α defined by an analogous relation,

$$\alpha = 3(D_i - D_t)/D_t$$

may be used to follow the exchange reaction, where D_t is the deuterium content of NH_3^+ group at time t. At equilibrium α is equal to nk.

The deuterium content of the NH_3^+ group was determined by equilibrating the salt with water of known amount and known deuterium content at low temperature (ca. 60°C or below). The deuterium content of the equilibrated water was measured by the floatation method, the proportionality of the deuterium atom fraction of heavy water to its excess density being assumed.

Kinetic Formula.—If it is assumed that the rate of the deuteration of ortho and para positions of anilinium salt may be described by one and the same rate constant, the reaction may be treated as a first order reversible reaction with respect to the deuterium content. The appropriate rate equation is

$$k_1 = (kD_e/tD_i)\ \ln\left((D_i - D_e)/(D_t - D_e)\right)$$

where, k_1 is the first order rate constant of the deuterium exchange reaction between NH_3^+ and aromatic nucleus, or the rate of the corresponding hydrogen exchange in undeuterated salts.

In terms of α, defined above, the rate equation becomes,

$$k_1 = (2.303/t)(k/k+1)\ \log\left((\alpha+3)/(3-(\alpha/k))\right)$$

Results and Discussion

I. The Rearrangements of *o*- and *m*-Toluidine Hydrochlorides.—Fig. 1 shows the rates of the exchange reactions, expressed by the value of α after one hour from the start of the exchange reaction, of *o*- and *m*-toluidine hydrochlorides at various temperatures. For comparison, the rate-temperature curves of aniline and *p*-toluidine hydrochlorides are also shown. In the latter salt, the rate is expressed by the value of α, after 3.5 hr. from the start of the reaction.

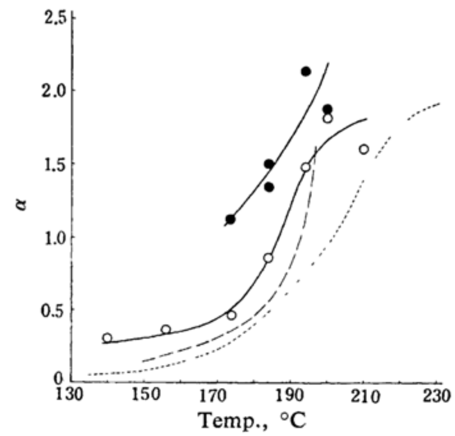

Fig. 1. Rearrangement of aniline and toluidine hydrochlorides at various temperatures. ●, *m*-Toluidine hydrochloride; ○, *o*-Toluidine hydrochloride; – – –, Aniline hydrochloride; ------, *p*-Toluidine hydrochloride

The exchange reaction of *o*-toluidine hydrochloride is measurable even at 140°C (ca. 75°C below its melting point). Apart from the exchange reaction of *m*-toluidine hydrochloride in which the methyl group cooperates with the amino group to facilitate the deuteration of the ortho and the para positions to the amino group, the ease of the exchange reactions of the hydrochlorides is in the order,

o-toluidine hydrochloride
>aniline hydrochloride
>*p*-toluidine hydrochloride

This corresponds to the reverse of the order of the basic dissociation constants of the amines at ordinary temperature (the values of K_B are 3×10^{-10}, 5×10^{-10} and 2×10^{-9} at 25°C, respectively[4]), or to the order of the acid strengths of their conjugate acids, *o*-toluidinium, anilinium and *p*-toluidinium ions. This order of the acid strengths of the conjugate acids would probably hold even at the temperatures of the rearrangement. Thus, the ease of the exchange reaction increases with the increasing proton releasing power of the NH_3^+ group for the aromatic nuclei of comparative reactivities.

This fact serves to confirm the earlier view that the mechanism of this exchange reaction is an electrophilic substitution, and that anili-

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[4] Landolt, "Physikalisch-chemische Tabellen", Bd. II, 5te Auflage, P. 1160.

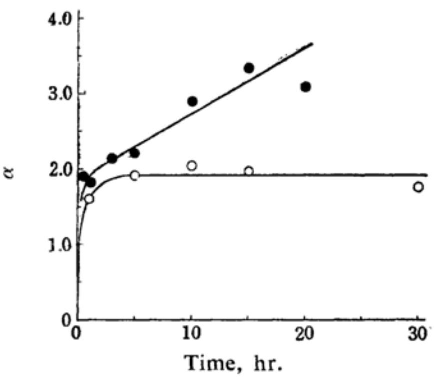

Fig. 2. Difference of equilibria between the exchange reactions of *o*-toluidine hydrochloride in the solid phase and in the liquid phase. ○, 210°C (solid phase), ●, 224°C (liquid phase)

nium or toluidinium ion acts as a proton acceptor at least in the state of partial dissociation. This is also a necessary condition for the NH_3^+ group to act as a proton donator.

Figure 2 shows the variation of the value of α with time for *o*-toluidine hydrochloride. At 210°C (below the melting point of the hydrochloride), the value of α reaches the equilibrium value of about 2 in less than five hours, but does not exceed 2 even after thirty hours. On the other hand, at 224°C (above the melting point of the hydrochloride) the value of α definitely exceeds 2 after three hours, and increases steadily towards the equilibrium value of probably 4.

The equilibrium values of α for the exchange reaction of *m*-toluidine hydrochloride at 200 and 218°C are shown in Table I, the melting point of the hydrochloride being 216°C.

TABLE I. THE EQUILIBRIUM VALUES OF α FOR THE EXCHANGE REACTION OF *m*-TOLUIDINE HYDROCHLORIDE AT 200 AND 218°C

Temp. °C	Time hr.	*nk*	Temp. °C	Time hr.	*nk*
200	5	2.54	218	10	4.20
200	7	2.82	218	15	4.32
200	10	2.59	218	20	4.07

Table I shows that three hydrogen atoms are exchangeable in the solid phase exchange reaction, and four hydrogen atoms take part in the liquid phase exchange.

If it were assumed that these differences in the *nk* values are due to the effect of temperature on the rate of exchange of the third or the fourth nuclear hydrogen atoms, then it should follow that, for the rearrangement of *o*-toluidine hydrochloride, the rate of this exchange at 224°C is at least ten times as fast as the rate at 210°C, and the exchange reaction is associated with an improbably large activation energy of 80 kcal. or more. The difference can not of course be attributed to the ordinary effect of temperature on the exchange equilibria. Therefore, these differences in the values of *nk* should be due to the difference of the mechanism between the solid phase and the liquid phase exchanges.

The values of *nk* found with hydrochlorides of aniline and toluidines are as follows;

	Below the m.p.	Above the m.p.
Aniline hydrochloride	3(ortho, para)	—
o-Toluidine 〃	2	—
m-Toluidine 〃	3	4
p-Toluidine 〃	2	4

The results are reasonably interpreted in terms of the assumption that only the ortho and the para positions of the benzene nucleus are reactive in the solid phase exchange reaction, and in the liquid phase meta positions are deuterated slowly. This lends support to the view that the mechanism of this reaction is an electrophilic substitution. The deuteration of meta positions in the liquid phase exchange may be due to toluidinium ions acting as proton acceptors. The fact that in the solid phase deuteration occurs exclusively at ortho and para positions, requires that the proton acceptor in this exchange reaction should be the molecules of toluidine or the toluidinium ions at least in the state of partial dissociation.

The crystals of toluidine hydrochlorides are probably composed of toluidinium ions and chlorine ions, by analogy with the crystals of aniline hydrochloride⁵⁾ and hydrobromide⁶⁾. In view of this fact, it is rather surprising that meta positions are not deuterated in the solid phase exchange. Two mechanisms are possible for the exchange reaction; intermolecular and intramolecular mechanisms.

If the exchange reaction in the solid state occurs intermolecularly, probably through the intervention of lattice imperfections, for example, between two toluidinium ions, the absence of meta deuteration requires that, whenever two toluidinium ions react, the proton-accepting toluidinium ion as well as the donating one should be at least in the state of partial dissociation. This is equivalent to the requirement that almost all of the toluidinium ions in the crystal should be at least in the state of partial dissociation at the temperatures of the rearrangement, which seems improbable. The presence of an appreciable amount of toluidinium ions would make

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5) J. C. Brown, *Acta Cryst.*, 2, 228 (1949).

6) I. Nitta, T. Watanabe and I. Taguchi, *X-rays* (*Japan*), 5, 31 (1948).

the meta deuteration observable. Moreover, if the toluidinium ions in the crystal were in the state of partial dissociation to any extent which makes the meta deuteration unobservable, they would at least remain so in the liquid phase, and the meta deuteration should be unobservable even in the liquid phase.

An alternative mechanism is an intramolecular shift of proton from the NH_3^+ group along the π-electron cloud of the benzene nucleus (formation of π-complex or the like) to the positions of the attack. In this case, the toluidinium ions react necessarily in the dissociated state, and the exclusive deuteration of ortho and para positions may be readily explained.

In the liquid phase, increased degrees of freedom of molecular motion would allow the toluidinium ions to collide with the proton donating species, and deuteration of meta positions takes place.

II. The Rates of Rearrangement of Aniline Hydrochloride and Hydrobromide. — The intramolecular character of the rearrangement of aromatic amine hydrochlorides being accepted, it is interesting to see whether the rate of rearrangement differs with the nature of the anion. As the rearrangement in the solid phase occurs in the nearly ordered arrangement of ions on which information is available from X-ray crystal analyzes[5,6], it would be suited for the study of the role of anions.

Figure 3 shows the variations of α with time for various temperatures for the rearrangement of aniline hydrochloride. Figure 4 is the corresponding figure for aniline hydrobromide. It will be seen that the rearrangement of the hydrochloride is considerably faster than that of the hydrobromide.

The equilibrium values of α are 2.72 and 2.37 for the hydrochloride and the hydrobromide respectively, the effect of temperature on the exchange equilibria being neglected. From this value, the number of the nuclear hydrogen atoms of the hydrobromide which take part in the exchange reaction may be determined as 3. The positions of these hydrogen atoms are probably ortho and para by analogy with the result obtained with the hydrochloride[1b]. The values of the partition coefficients k are 0.90_1 and 0.79_0 for the hydrochloride and the hydrobromide. It cannot be decided whether the difference is real or due to some experimental errors.

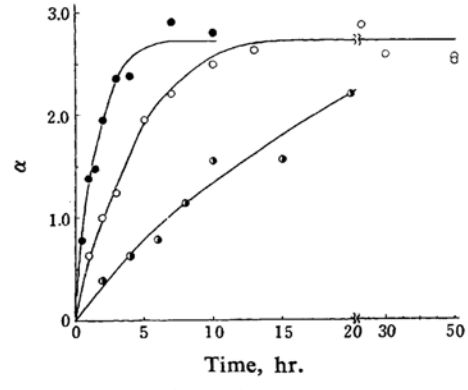

Fig. 3. Variation of α with time for the rearrangement of *N*-deuterio-aniline hydrochloride. ●, 194°C ○, 184°C ◑, 173°C

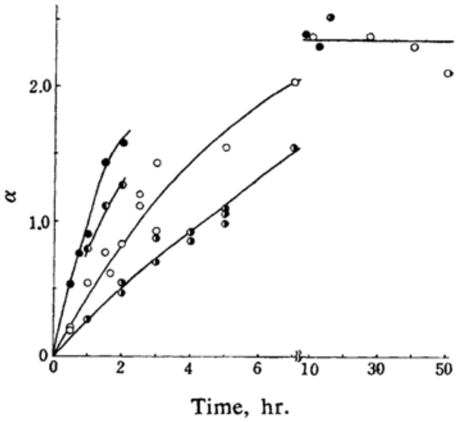

Fig. 4. Variation of α with time for the rearrangement of *N*-deuterio-aniline hydrobromide. ●, 225°C ◐, 222°C ○, 218°C ◑, 211°C

The first order plots of the rearrangement of the hydrochloride and the hydrobromide are shown in Figs. 5 and 6.

The linearity of the plots is not quite satisfactory. This is at least partly due to the

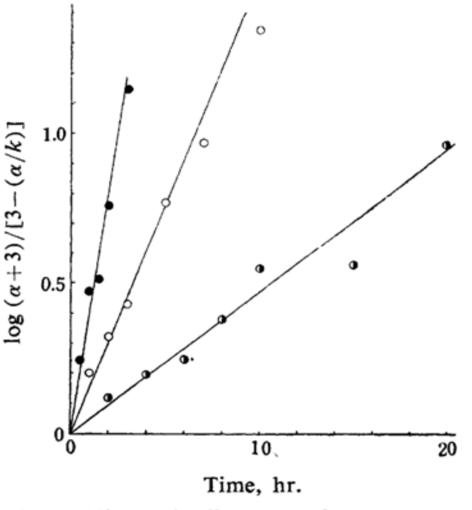

Fig. 5. First order linear plot for the rearrangement of *N*-deuterio-aniline hydrochloride. ●, 194°C ○, 184°C ◑, 173°C

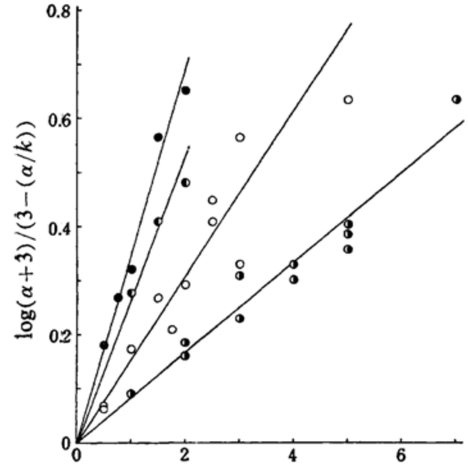

Fig. 6. Fist order linear plot for the rearrangement of *N*-deuterio-aniline hydrobromide.
●, 225°C ◐, 222°C ○, 218°C ◑, 211°C

indirect nature of the deuterium analysis (equilibration with water), and to the complicated sequence of operations. It is possible that the departure of the plots from linearity is partly caused by the failure of the assumption that the deuteration of the ortho and the para positions is characterized by the same rate constant.

Figures 7 and 8 are the Arrhenius plots. The Arrhenius parameters were determined by the method of least squares. The results are;

$$k_1^{\mathrm{Cl}}(\mathrm{sec}^{-1})=10^{16.7}\exp((44000\pm1200)\,\mathrm{cal.}/\boldsymbol{RT})$$

and

$$k_1^{\mathrm{Br}}(\mathrm{sec}^{-1})=10^{16.3}\exp((46000\pm2000)\,\mathrm{cal.}/\boldsymbol{RT})$$

for aniline hydrochloride and hydrobromide, respectively.

The entropies of activation were calculated by the equation, $A=e\cdot(kT/h)\cdot\exp(\varDelta S/R)$, to be 15 and 13 cal./deg. for the hydrochloride and the hydrobromide.

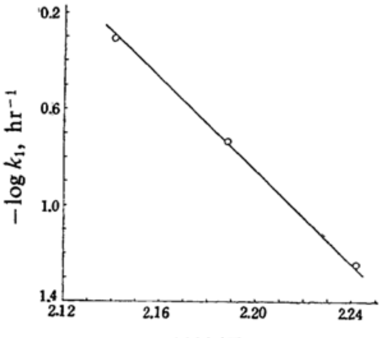

Fig. 7. Arrhenius plot for the rearrangement of *N*-deuterio-aniline hydrochloride.

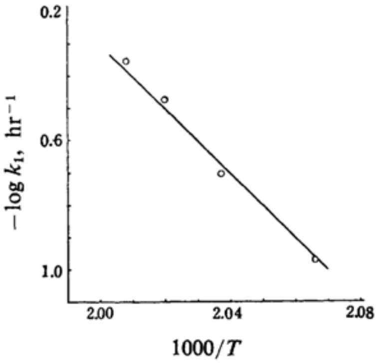

Fig. 8. Arrhenius plot for the rearrangement of *N*-deuterio-aniline hydrobromide.

Owing to the errors in the determinations of the rate constants, the accuracy of the absolute magnitudes of the energies and the entropies might not be claimed, but the order of magnitude of these values is probably correct, and they would be sufficient for the purpose of comparison.

These is no other example of the deuterium exchange reaction in the solid state to be compared with the present results. In pure liquid phase, the deuterium exchange reactions of phenol(7) and of *o*-cresol(8) have been studied. The reactions proceed through bimolecular mechanism. The values of activation energies are 34.8 kcal. for the exchange reaction of phenol and 23 kcal. for that of cresol. The value of the frequency factor for the exchange reaction of phenol is $10^{9.49}$. Comparison of these results with the present ones suggests that there is a difference in the mechanisms of nuclear deuteration between the two cases. As suggested above, the rearrangement probably proceeds through the intramolecular shift of protons from NH_3^+ groups to aromatic nuclei, where they attack the carbon atoms with higher electron densities. The protons leaving the NH_3^+ groups will move along the π-electron clouds to the nuclei, or they will combine with the halide ions to form transient molecules of hydrogen halide. The latter process is the necessary preliminary to the sublimation of the amine hydrochloride, which becomes marked side by side with the rearrangement with increasing temperature. Thus, the protons of the anilinium ions would be in a relatively free to-and-fro movement between NH_3^+ groups, Cl^- ions, and aromatic nuclei, at high temperatures. In the course of these movements, they will come across the ortho and the para

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7) A. I. Brodskii and I. I. Kukhtenko, *Zhur. Fiz. Khim.*, **25**, 920 (1951); *Chem. Abstr.*, **47**, 3814f.

8) I. I. Kukhtenko, *Doklady Akad. Nauk, S. S. S. R.*, **93**, 487 (1953); *Chem. Abstr.*, **49**, 3054.

positions and happen to attack the nuclear carbon atoms. The reaction may be formulated as,

$$C_6H_5NH_2D^+ \overset{K}{\rightleftarrows} C_6H_5NH_2 + D^+(\cdots X)$$

$$C_6H_5NH_2 + D^+(\cdots X) \xrightarrow{k_0} C_6H_4D\cdot NH_2 + H^+(\cdots X)$$

where, $H^+(\cdots X)$ may be the proton attached to the aromatic nucleus (formation of π-complex), or it may be the transient molecule of hydrogen halide, or some form of proton which is in a relatively free state.

According to the above scheme, the first order rate constant k_1 of the deuterium exchange, or the rate of hydrogen exchange between NH_3^+ and aromatic nucleus of undeuterated salt, may be expressed as,

$$k_1 = k_0(H^+)(C_6H_5NH_2) = k_0K(C_6H_5NH_3^+)$$

Therefore, the Arrhenius parameters obtained from the temperature dependence of k_1 contain, besides those of the rate-controlling step, the contributions from the energy and the entropy of the dissociation of the preequilibrium step, which by the nature of the reaction should have rather large positive values. Thus the large activation energies and large positive entropies of the rearrangement of anilinium halide may be interpreted qualitatively in terms of the above scheme.

The similarity of the Arrhenius parameters between the rearrangement of the two salts suggests that the role of anion in this reaction should be only subsidiary and the mechanism of the rearrangement involves primarily the anilinium ion alone, which is consistent with the intramolecular mechanism.

The difference of the rate of rearrangement between the two salts seems to be chiefly due to the difference in the activation energies, and it should be attributed to the effect of anions.

The results of X-ray crystal analysis[5,6] show that the NH_3^+ group is coordinated by four bromine ions, two at a distance of 3.48 Å and the other two at 3.65 Å, in the crystal lattice of the hydrobromide, and by three chlorine ions at a distance of 3.16 Å in that of the hydrochloride. The difference in the N–X distances is greater than that of the ionic radii of the halide ions, and it is expected that the chlorine ion exerts a more powerful polarizing effect upon the N–H bond. Thus, the protons of the NH_3^+ groups would be more loosened in the hydrochloride than in the hydrobromide in the initial state of the reaction, and this difference would contribute to the lowering of the energy of activation.

The distances between the halide ions and the ortho and the para carbon atoms may be calculated from the data of the X-ray crystal analyzes. The shortest distances are 3.87 Å for ortho and 3.98 Å for para carbon atoms in the crystal lattice of the hydrobromide, and 3.53 and 3.85 Å for ortho and para carbon atoms in that of the hydrochloride, the sum of van der Waals radii being 3.80 and 3.65 Å for hydrobromide and hydrochloride, respectively. It might be expected that the presence of the negatively charged anions in the neighborhood of the reaction centre would stabilize the positively charged activated complex. And, if it is the case, the extent of stabilization would also be in favor of the chlorine ions.

Summary

The rearrangement of *N*-deuterated aromatic amine hydrochloride into its ring-deuterated analogues has been studied in the solid and the liquid phases with *o*- and *m*-toluidines, and studied kinetically with anilinium chloride and bromide at 173∼194°C and at 210∼225°C, respectively.

The ease of the rearrangement of the hydrochlorides in the solid phase is in the order,

o-toluidine hydrochloride
>aniline hydrochloride
>*p*-toluidine hydrochloride

which is the reverse of the order of the basic dissociation constants of the amines at 25°C. *m*-Toluidine hydrochloride is more reactive than *o*-toluidine hydrochloride.

The numbers of nuclear hydrogen atoms which take part in the rearrangement are, 2 in the solid phase and >3 in the liquid phase rearrangement of *o*-toluidine hydrochloride, and for *m*-toluidine hydrochloride 3 and 4 in the solid and the liquid phases respectively. This result, taken in conjunction with the earlier ones with aniline and *p*-toluidine hydrochlorides, confirms the view that in the solid phase rearrangement the ortho and the para positions are exclusively deuterated, and in the liquid phase deuteration of the meta positions takes place.

The rearrangement of the anilinium salts is characterized by high activation energy (ca. 45 kcal.) and large positive entropy of activation (ca. 15 cal./deg.).

These results are reasonably interpreted by the intramolecular electrophilic mechanism.

A small difference of the activation energies between the rearrangement of the two anilinium salts (ca. 2 kcal.) may be explained in terms of the different polarizing effects of the halide ions on the initial state and possibly also on the activated complex.

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