Notes

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Studies on the Proton Magnetic Resonance Spectra in Aromatic Systems. XIX.[1] Hydrogen-Deuterium Exchange Reaction Mechanism of Deutero-aniline

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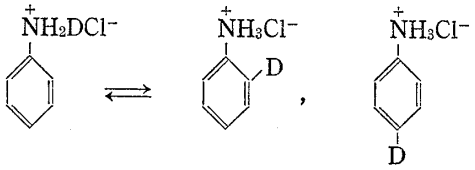
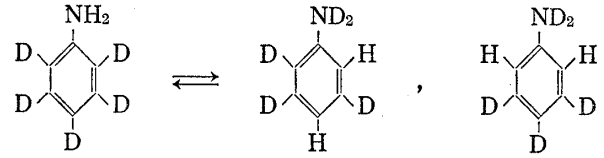
Introduction

Several papers have been published on the H-D-exchange reaction between amino deuterium and aromatic ring hydrogens of aromatic amines. For instance, Okazaki, *et al.*[3-6] reported on the intramolecular H-D-exchange reaction of anilinium salts in the following scheme:



Geller, *et al.*[7] described a similar exchange reaction of α-naphthylamine, and Tupitsyn, *et al.*[8] studied the H-D-exchange of aniline in the presence of small amounts of basic organic compounds (*e.g.* ArNDK or PhNDK).

Recently, we examined[9] the exchange reaction between ring deuterium and active hydrogen of the amino group of deutero-aniline, and found that this reaction was initiated by addition of an aliphatic halide as catalyst.



In this work, we studied the reaction mechanism for the H-D-exchange of deutero-aniline with aliphatic halides in detail, correlating our results with those of others.

Experimental

All the proton resonance spectra in this work were measured in $CDCl_3$ or in the neat liquid state using a Varian A-60D type spectrometer. The radio-frequency powers were always low enough to prevent error

1) Part XVIII: Y. Sasaki, M. Yoritaka, A. Takahata, H. Kawaki, and Y. Okazaki; *Chem. Pharm. Bull.* (Tokyo), **22**, 50 (1974).
2) Location: *a*) *Toneyama 6-1-1, Toyonaka, Osaka*; *b*) *Motoyamakitamachi 4-19-1, Higashinada, Kobe.*
3) M. Harada and T. Titani, *Bull. Chem. Soc. Japan*, **11**, 554 (1936).
4) N. Okazaki, *J. Chem. Soc. Japan*, **62**, 52 (1941).
5) N. Okazaki and J. Kuroda, *J. Chem. Soc. Japan*, **62**, 57 (1941).
6) N. Okazaki and A. Okumura, *Bull. Chem. Soc. Japan*, **32**, 989 (1961).
7) B.A. Geller and S. Samosvat, *Zh. Obshch. Khim.*, **33**, 4024 (1963) [*Chem. Abstr.*, **60**, 9114c (1964)].
8) I.F. Tupitsyn and V.I. Kiomarov, *Tr. Gos. Inst. Prikl. Khim*, **52**, 160 (1964) [*Chem. Abstr.*, **63**, 13005b (1965)].
9) Y. Sasaki, M. Suzuki, S. Mori, and M. Sugiura, *Chem. Pharm. Bull.* (Tokyo), **20**, 632 (1972).

due to saturation of the signal. The signal intensities of ring and amino proton reported are the means of 4 or 5 measurements.

Proton Distribution——The α-value was estimated from the following equation:

$$\alpha_{[NH_2]_t} = \frac{[NH_2]_t}{[NH_2]_t[ortho]_t[para]_t[meta]_t} \times 100$$

Where $[NH_2]_t$, $[ortho]_t$, $[para]_t$, and $[meta]_t$ are the integrated intensities of the amino-, *ortho*-, *para*-, and *meta*-proton, respectively, at the optional stage.

Preparation of Deutero-aniline——1) Deutero-nitrobenzene from d_6-Benzene: Deutero-nitrobenzene was prepared from commercial d_6-benzene by the ordinary method.

2) Deutero-aniline from Deutero-nitrobenzene: Deutero-nitrobenzene (4.0 g) was dissolved in MeOH (180 ml), mixed with freshly prepared Raney-nickel catalyst (2.0 g), and reduced in an H_2 atmosphere. After 2100 cm^3 of H_2 gas had been absorbed, the catalyst was removed by filtration, and the solvent was evaporated off under reduced pressure. The residue was dissolved in 5% HCl. The resulting acid layer was washed with ether, made alkaline with aq. NH_4OH and saturated with NaCl. Then it was extracted with ether. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was distilled off to give a pale yellow oil (2.9 g). This was identified with an authentic sample of aniline by thin-layer chromatography (TLC) (Si_2O_3/ether (1) + C_6H_6 (1)) and by its nuclear magnetic resonance (NMR) spectrum (*cf.* Fig. 1).

Deuteration of N,N-Dimethylaniline——A mixture of N,N-dimethylaniline (2.0 ml), D_2O (6.0 ml) and 20% DCl (1.0 ml) was sealed in a glass tube and heated at —150° for 70 hr. After cooling, the product was dissolved in 5% HCl and washed with ether. Then it was made alkaline with aq. NH_4OH and saturated with NaCl. The base liberated was extracted with ether and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed and the residue was purified by ether/Al_2O_3 chromatography. Deuteration of the *ortho*- and *para*-positions was confirmed from the NMR spectrum (*cf.* Fig. 2).

H-D-Exchange Reaction of Deutero-aniline with $Cl_2CHCHCl_2$——A mixture of deutero-aniline (1.015 g) and $Cl_2CHCHCl_2$ (0.140 g) under a long air condenser was heated on an oil bath at 157°. Every 10 min, the NMR spectrum of the reaction products was measured, and the α-values of protons on the ring and amino groups were estimated (*cf.* Fig. 3 and Fig. 4).

Reaction of Deutero-aniline without $Cl_2CHCHCl_2$——Neat deutero-aniline was heated on an oil bath at 160° under a long air condenser. After 30 min and 1 and 3 hr, the NMR spectrum was measured. The signal intensity ratio did not alter during the reaction.

Reaction of Deutero-N,N-dimethylaniline with $Cl_2CHCHCl_2$——A mixture of deutero-N,N-dimethylaniline (1.301 g) and $Cl_2CHCHCl_2$ (0.141 g) was heated on an oil bath at 160° for 3 hr. Under these conditions, the ring-proton distribution did not alter. Moreover, on heating at —200° for 6 hr the mixture become brown, but the NMR spectrum did not change.

H-D-Exchange Reaction of Deutero-aniline with Hydroquinone——A mixture of deutero-aniline (0.273 g), $Cl_2CHCHCl_2$ (0.038 g) and hydroquinone (0.021 g) was heated on an oil bath at 155° for 1 hr. The NMR spectrum was similar to that observed on heating without hydroquinone.

H-D-Exchange Reaction of Deutero-aniline with Aniline·HCl——A mixture of deutero-aniline (0.486 g) and aniline·HCl (0.003 g) was heated on an oil bath at 150°. Every 10 min, the NMR spectrum of the mixture was measured, and the α-values of protons on the ring and amino groups were estimated (*cf.* Fig. 5).

Cross-reaction of Deutero-aniline and Deutero-N,N-dimethylaniline with $Cl_2CHCHCl_2$——Mixtures of deutero-aniline (0.498 g), deutero-N,N-dimethylaniline (0.539 g) and $Cl_2CHCHCl_2$ (0.188 g) were heated on an oil bath at 140°. Every 10 min, the NMR spectra of the reaction mixture were measured, and the α-values were estimated (*cf.* Fig. 7 and Fig. 8).

Identification of Cl^- in the H-D-Exchange Reaction of Aniline with $Cl_2CHCHCl_2$——Mixtures of aniline (0.979 g) and $Cl_2CHCHCl_2$ (0.175 g) were heated on an oil bath at —150° for 30 min. After cooling, the product was poured into H_2O with vigorous shaking. Saturated aq. $AgNO_3$ was added to the aqueous layer and a white precipitate was deposited.

Reaction of Aniline and $Cl_2CHCHCl_2$——A mixture of aniline (0.099 g) and $Cl_2CHCHCl_2$ (0.168 g) was heated on an oil bath at —150° for 4 hr. After precipitate was separated by filtration, washed with ether, and recrystallized from EtOH, 5 mg of white needles, mp 190—193 were afforded, and identified with aniline·HCl by mixed melting point determination.

From the filtrate, the new peak was detected by gas chromatography,[10] and identified with an authentic sample of $Cl_2C=CHCl$ by comparing the retention time.

In the similar condition without aniline, $Cl_2CHCHCl_2$ did not afford $Cl_2C=CHCl$.

10) Gas chromatography: Shimazu Type 4B, 50°, carrier gas; N_2, column; OV-101.

Result and Discussion

When deutero-aniline is prepared from d_6-benzene, the ring protons are almost entirely replaced by deuterium, except in the amino group (*cf.* Fig. 1).

When deutero-aniline is heated with a small amount of $Cl_2CHCHCl_2$ for several minutes, the signal intensities of the *ortho*- and *para*-hydrogens increase, while those of the amino hydrogens decrease. On the contrary, the signal intensity of *meta*-hydrogen is not altered during the reaction (*cf.* Fig. 3), but the signal becomes broader by virtual coupling due to increased amounts of hydrogen at *ortho*-, and *para*-positions.

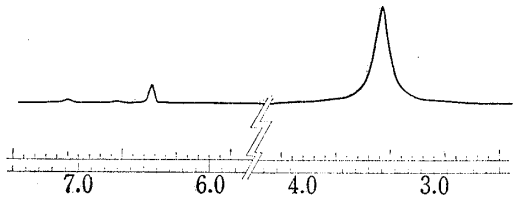


Fig. 1. NMR Spectrum of Deutero-aniline (Reference, TMS)

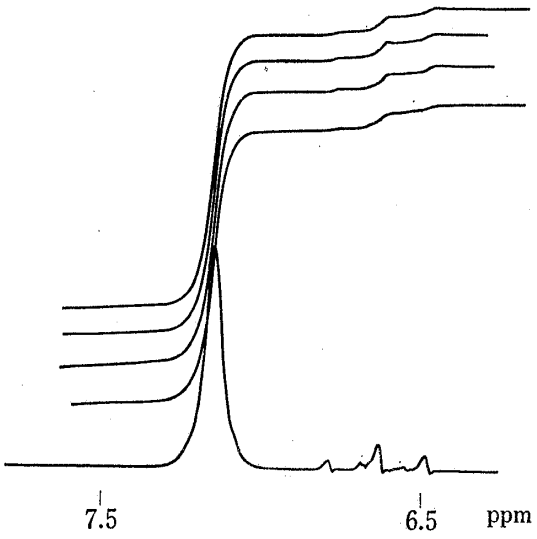


Fig. 2. Ring Proton NMR Spectral Patterns of Deutero-N,N-dimethylaniline (Reference, TMS)

This H-D-exchange reaction is catalysed by aliphatic halides: *i.e.* $Cl_2CHCHCl_2$, $CHCl_3$, CCl_4, Cl_3CCCl_3, *etc.*, whilst aromatic halides: *i.e.* C_6H_5Cl, $C_6H_2Cl_4$, *etc.* are inert. In the absence of the aliphatic halides cited above, this exchange reaction does not occur. The similar reaction of deuterated N,N-dimethylaniline, where *ortho*- and *para*-hydrogens are deuterated, does not alter the proton distribution in the presence of aliphatic halides. These experimental results show that this reaction is an inter- or intramolecular H-D-exchange reaction without proton transfer out of the reaction system.

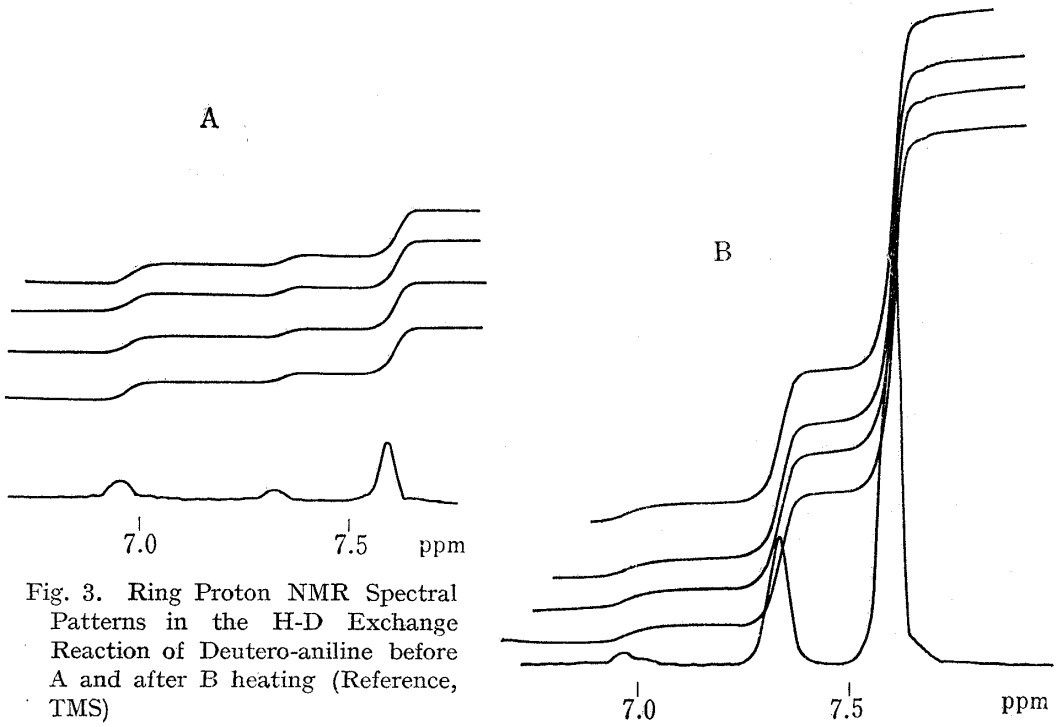


Fig. 3. Ring Proton NMR Spectral Patterns in the H-D Exchange Reaction of Deutero-aniline before A and after B heating (Reference, TMS)

The average values of the observed proton scrambling ratios in the NMR spectrum of the H-D-exchange of deutero-aniline with $Cl_2CHCHCl_2$ (*cf.* Fig. 4) at equiliblium, are 2: 2: 1 for the *ortho*- and *para*-positions and amino group.

Moreover, as show in Table I, the H-D-exchange reaction rates of deutero-aniline showed a dependency on the concentration of $Cl_2CHCHCl_2$.

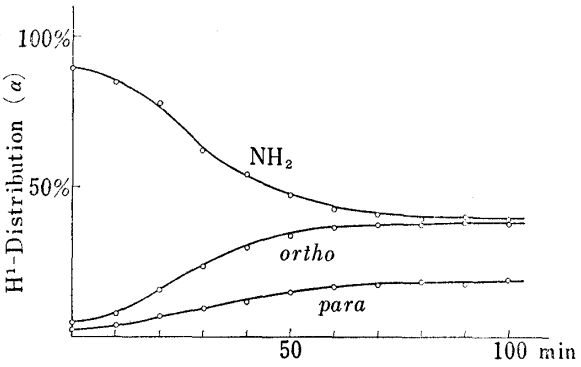


Fig. 4. Time-dependence of α-Values in the H-D Exchange Reaction

0.08 mole $Cl_2CHCHCl_2$/1 mole deutero-aniline

Table I. α-Value of the Amino Group after 10, 30 and 80 min on Addition of Various Amounts of $Cl_2CHCHCl_2$

$Cl_2CHCHCl_2$			
1 mole deutero-aniline	$\alpha_{(NH_2)_t}$		
	10 min	30 min	80 min
(mole)			
0.01	90.2	88.9	78.8
0.04	90.1	80.9	54.3
0.07	89.6	75.0	50.6
0.1	89.2	72.0	46.4
0.3	87.4	66.9	42.6

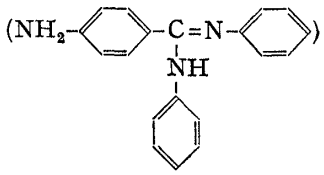
To see whether this reaction proceeded by an ionic or radical process, hydroquinone, which inhibits radical reactions, was added, but it did not inhibit the reaction. Thus the reaction does not seem to proceed by a radical mechanism. Moreover, the aromatic halide is very inert and is resistant to ionic cleavage of the C-halogen bond, and this is consistent with an ionic mechanism.

When a mixture of deutero-aniline and a small amount of $Cl_2CHCHCl_2$ was heated, Cl^- was liberated into the aqueous layer, but without heating, this qualitative test was negative. Similar results were observed on reaction of deutero-aniline with aliphatic halides: *i.e.* CCl_4, $CHCl_3$, CCl_3CCl_3, *etc.*

And when the equimolar mixture of aniline and $Cl_2CHCHCl_2$ was heated —150° for 4 hr, crystals of aniline·HCl were separated out, and a small quantity of $Cl_2C{=}CHCl$ was also detected by gas chromatography. This results support the following reaction scheme.

$$Cl_2CHCHCl_2 + \bigcirc\!\!-NH_2 \longrightarrow Cl_2C{=}CHCl + \bigcirc\!\!-NH_2\cdot HCl \qquad (1)$$

When only $Cl_2CHCHCl_2$ was heated —150°, $Cl_2C{=}CHCl$ was not detected, and then reaction (1) requires the presence of aniline. In the similar reaction of aniline and CCl_4, aniline·HCl and the compound seemed N,N′-diphenyl *p*-aminobenzamidine[11]



were produced.

Above results indicate that aniline·HCl from the reaction of aniline and a small amount of $Cl_2CHCHCl_2$ participates catalytically in this H-D-exchange reaction of deutero-aniline, and then this H-D-exchange reaction seems to be H^+ catalysed reaction.

To confirm futhermore above results, deutero-aniline was heated with 3×10^{-3} mole % aniline·HCl. Under these conditions no change in signal intensity in the NMR spectrum was observed in the initial state. The exchange rate under these conditions is as shown in

11) Y. Mori and T. Tsuji, *Tetrahedron*, **27**, 3811 (1971).

Fig. 5, and is consistent with first order kinetics (*cf.* Fig. 6). Comparison of Fig. 4 and Fig. 5 indicates that there is a time lag in the initial stage of the reaction on addition of an aliphatic halide, unlike on addition of aniline·HCl. From the reaction process observed in Fig. 4, following mechanisms is supported; H^+ (HCl) produced in the initial stage of the reaction seems to accelate the H-D-exchange of deutero-aniline catalytically.

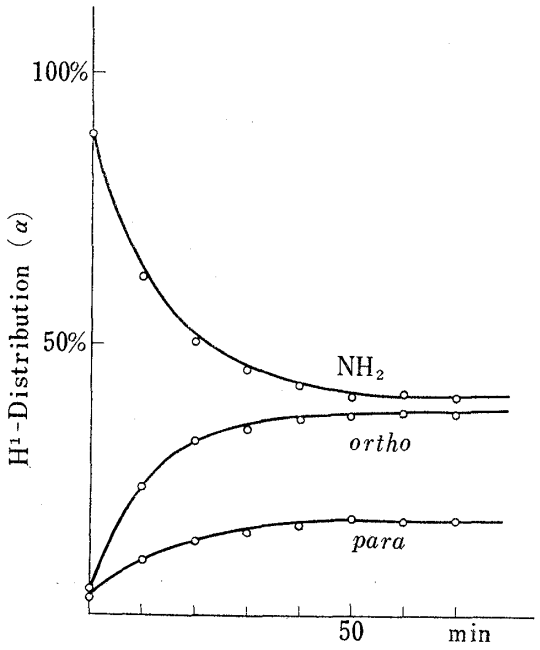


Fig. 5. Time-dependence of α-Values in the H-D Exchange Reaction

0.003 mole $C_6H_5NH_2$·HCl/1 mole deutero-aniline

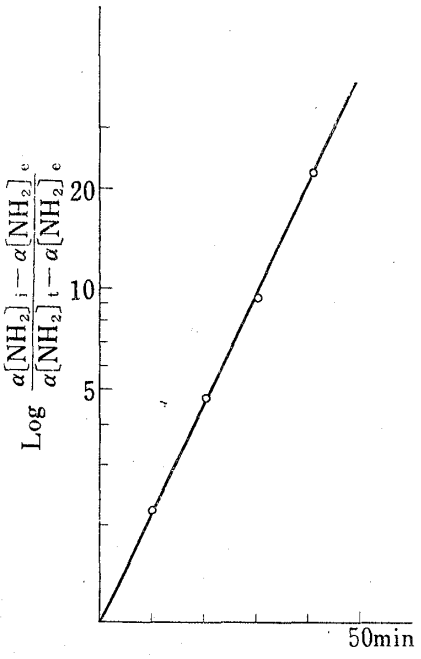


Fig. 6. First Order Linear Plot of the H-D Exchange Reaction

0.003 mole $C_6H_5NH_2$·HCl/1 mole deutero-aniline

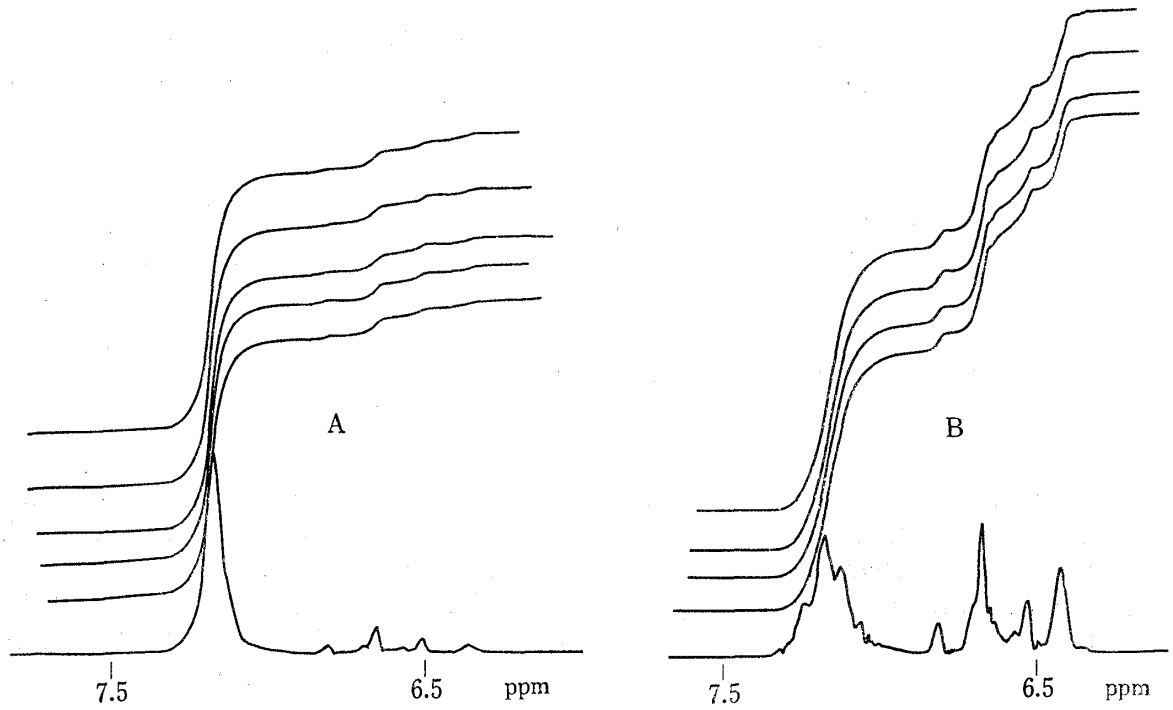


Fig. 7. Ring Proton NMR Spectral Patterns in the Cross Reaction of Deutero-aniline and Deutero-N,N-dimethylaniline before A and after B heating (Reference TMS)

To determine whether this reaction process is inter- or intra-molecular, the cross reaction between deutero-aniline and deutero-N,N-dimethylaniline was carried out. The results are shown in Fig. 7 and 8. The decrease in the signal intensity of NH_2 was accompanied by increase in the signal intensity of the *ortho*- and *para*-protons of deutero-aniline and deutero-N,N-dimethylaniline.

In this case the signal of *meta*-proton is converted to multiplets due to increase of protons at the *ortho*- and *para*-positions. These results indicate that the mechanism of the H-D-exchange reaction is intermolecular.

This results consistent with the conclusion that this reaction is H^+ catalysed reaction.

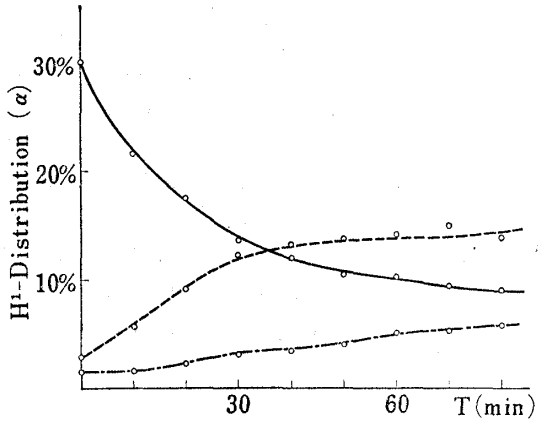


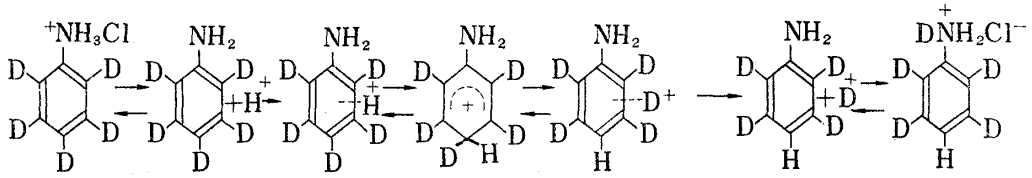
Fig. 8. Time-dependence of α-Values in a Mixture of Deutero-aniline and Deutero-N,N-dimethylaniline

———: NH_2/aniline
----------: *ortho* and *para*/N,N-dimethylaniline and *para*/aniline
———: *ortho*/aniline

Conclusion

The H-D-exchange reaction of deutero-aniline between the amino group and ring deuterium proceeds by addition of a small amount of aliphatic halides. This reaction was confirmed to be intermolecular mechanism by the cross reaction of deutero-aniline and deutero-N,N-dimethylaniline. And this reaction was showen to be initiated by H^+ produced from deutero-aniline and aliphatic halides (*e.g.* reaction (1)).

Results suggest the following scheme.



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The Ring Contraction of Pyridazinones to Pyrazoles. VII[1]

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Recent investigation in this laboratory has shown an unusual ring contraction of 4,5-dichloro-3(2*H*)-pyridazinone (I: R=Cl) leading to 1-phenyl-3-hydroxypyrazole-5-carboxylic acid (II) by alkaline treatment.[3] It has also noted that 2-phenyl-4-chloro-5-methylsulfonyl

1) Part VI: Y. Maki and M. Takaya, *Chem. Pharm. Bull.* (Tokyo), **20**, 747 (1972).
2) Location: *Mitahora, Gifu.*
3) Y. Maki, G.P. Beardsley, and M. Takaya, *Tetrahedron Letters*, **1971**, 1507.