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Formic Acid Reduction. XVI.[1] Mechanism of the N-Methylation of *p*-Phenylenediamine Derivatives with Formates

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Mechanistic investigation on the previously reported N-methylation of formanilides effected by the constant-boiling liquid of the formates composed of formic acid and trialkylamine has been made by introducing isotopic tracer method into the representative reaction of *p*-phenylenediamine derivatives. In accord with the isotopic tracer results a mechanism of this formate reaction has been proposed. It has been revealed that the formate reagents affect the conversion of N-formyl, which suffers interchange in the formate medium, into N-methyl acting as reducing agent.

It has been reported in the preceding paper[1] that, on heating with formate reagents composed of trialkylamine and formic acid or with formic acid alone, the N-methylation and the N,N-dimethylation of formanilides possessing varied substituents are effected.

$$\mathrm{ArNHCHO} \xrightarrow[\text{in formate or formic acid}]{175\text{—}180^\circ} \mathrm{ArN}\begin{matrix}\diagup\mathrm{CH_3}\\ \diagdown\mathrm{CHO}\end{matrix} + \mathrm{ArN}\begin{matrix}\diagup\mathrm{CH_3}\\ \diagdown\mathrm{CH_3}\end{matrix}$$

The N-methyl formed has been deduced[1] to be derived from the N-formyl of the substrate compounds or formic acid component of the formate reagents. This study was initiated in order to elucidate the mechanism of this reaction. Investigation on this subject was made by employing isotopic tracer method by carrying out the reactions using ^{14}C-labelled and non-labelled N,N′-diformyl-*p*-phenylenediamine (I), N,N′-diformyl-N,N′-dimethyl-*p*-phenylenediamine (II) and TBAF,[3] which is composed of formic acid and tributylamine, as substrates and formate reagent, respectively.

Result

On referring to the preceding paper,[1] because of easy isolation of the products as crystals, for mechanistic study of the N-methylation of formanilides and N-methylformanilides with formates, we selected, as models, the previously reported reaction of I and II with the formate TBAF. It has been shown in the preceding paper[1] that after 90 hour's reaction period at 175—180°, the TBAF reaction of II resulted in the formation of N-formyl-N,N′,N′-trimethyl-*p*-phenylenediamine (III) in 15% yield and that of I resulted in the formation of N,N′-diformyl-N-methyl-*p*-phenylenediamine (IV) and II in 24% and 2% yield, respectively, where the substrates to TBAF (as HCO_2H) molar proportion used were 1 : 25. Our object was to determine radiochemical yields of the N-methylated products by carrying out the reactions between the radioactive substrate, I′ or II′, which expresses I or II possessing N-formyl-^{14}C, and TBAF and between non-radioactive substrate, I or II, and TBAF composed of formic acid-^{14}C. On understanding theoretical radiochemical yields, there were con-

1) Part XV: M. Sekiya, S. Takayama, K. Ito, J. Suzuki, K. Suzuki, and Y. Terao, *Chem. Pharm. Bull.* (Tokyo), **20**, 2661 (1972).
2) Location: *2-2-1 Oshika, Shizuoka.*
3) A distillable liquid formate, bp 108—109° (20 mmHg), which may be given by $7HCO_2H \cdot 3N(C_4H_9)_3$ (see ref. 1).

sidered two problems to be solved preliminarily. One was a possible exchange of the N-formyls of the substrate by the influence of formic acid in TBAF and the other was the decomposition of formic acid in TBAF during the course of the reaction.

In order to follow exchange of the N-formyls of the substrates, preliminary experiments were conducted for measurement of radioactivities of the recovered substrates for increasing period of the reaction under the previously reported condition: substrate to TBAF (as HCO_2H) molar proportion of 1:25 and temperature of 175—180°. Rather rapid exchange of the N-formyl was recognized with both types of the substrates. Percentage of the N-formyl exchange obtained at each increasing time during the reactions are shown in Table I. Let A and B be decreasing radioactivities of I′ and II′ during their reactions with TBAF and

Table I. Variation of Radioactivities of the Substrate for Increasing Reaction Period

Time (min)	Percentage of radioactive variation of the substrate			
	A	A′	B	B′
30	58.8	36.8	85.5	13.5
60	38.3	63.7	70.7	23.2
90	20.8	82.4	62.3	33.7
120	12.8	93.1	47.5	44.4
150	10.1	97.9	42.4	53.2
180	8.8	97.2	38.8	59.1
210	8.3	101.3	28.2	66.8
240	7.6	98.2	27.5	69.7

conditions: substrate to TBAF (as HCO_2H) molar proportion; 1:25, reaction temperature: 175—180°

A: $OH^{14}CHN$-C$_6$H$_4$-$NH^{14}CHO$ (I′)+TBAF

A′: OHCHN-C$_6$H$_4$-NHCHO (I)+TBAF-^{14}C

B: CH_3, CH_3, $OH^{14}C$, ^{14}CHO (II′)+TBAF

B′: CH_3, CH_3, OHC, CHO (II)+TBAF-^{14}C

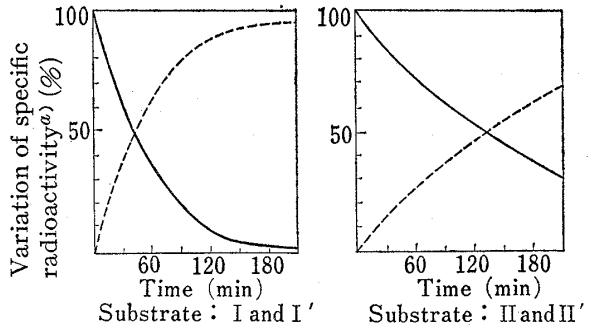


Fig. 1. Rates of Variation of Radioactivities of the Substrate in the Reactions

——: substrate possessing two N-formyl-^{14}C with TBAF
------: non-radioactive substrate with TBAF-^{14}C
conditions: substrate to TBAF (as HCO_2H) molar proportion, 1:25; reaction temperature: 175—180°
a) measured by assay for radioactivity of the recovered substrate

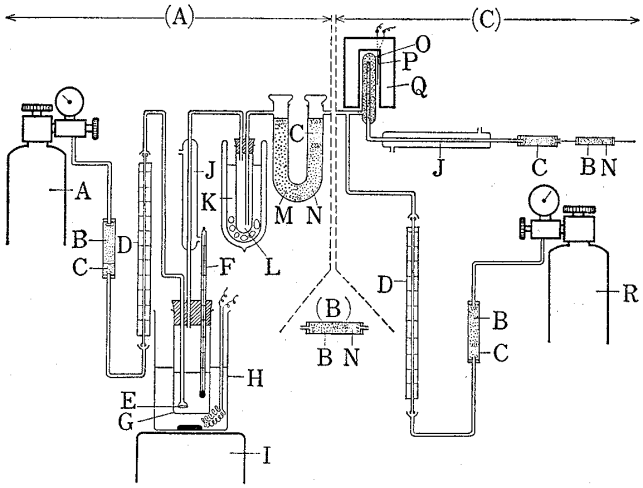


Fig. 2. Apparatus for Analysis of Decomposing Gas of TBAF

A: nitrogen cylinder; B: soda asbestos; C: granular P_2O_5; D: floating flow meter; E: glass filter; F: thermometer; G: reaction vessel (80 ml); H: oil bath; I: magnetic stirrer; J: Liebig condenser; K: dry ice-acetone; L: trap; M: silica gel-sulfuric acid; N: anhydrous magnesium perchlorate; O: silver permanganate; P: thermocouple; Q: electric furnace; R: oxygen cylinder

let A′ and B′ be increasing radioactivities of I and II during their reactions with TBAF-formic acid-^{14}C. Values A and B must be identical with values 100−A′ and 100−B′, respectively, in theory. Consequently, for the decrease of the radioactivities the two values should be averaged and are plotted against time as expressed by the curve lines in Fig. 1. By the same way the dotted lines in Fig. 1 can be drawn for the increase of the radioactivities.

Next, in order to determine loss of formic acid by decomposition during the TBAF reaction, proportion of formic acid decomposition of TBAF itself at 175—180° was measured for increasing period. The decomposition of formic acid in TBAF was shown to proceed in the following two ways and was measured as sum of carbon dioxide and carbon monoxide evolved.

$$HCO_2H \longrightarrow H_2 + CO_2$$
$$HCO_2H \longrightarrow H_2O + CO$$

The decompositions in these two ways were also measured separately by analyses of carbon dioxide and carbon monoxide. Methods and apparatus are shown in Fig. 2. These decompositions with increasing period are shown in Fig. 3. As can be seen in Fig. 3, the total decomposition of formic acid after 3.5 hr reaches *ca.* 15%, which comprises much greater decomposition to carbon monoxide than that to carbon dioxide. For the meaningful isotopic experiments decomposing loss of formic acid in TBAF in the presence of the substrate under the reaction conditions had to be measured. Under the conditions consistent with the isotope experiments the observed decomposing loss of formic acid in TBAF for increasing period is shown in Fig. 4. It is noticeable that decomposition of formic acid in TBAF is accelerated in the presence of the substrates, particularly I.

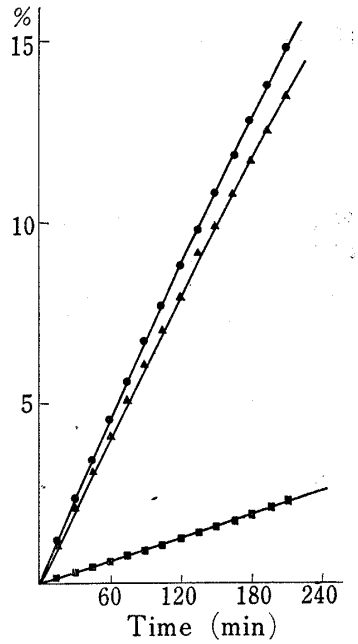


Fig. 3. Decomposition of TBAF

—●—: decomposition of formic acid component in TBAF
—▲—: decomposition of formic acid component in TBAF converting to CO
—■—: decomposition of formic acid component in TBAF converting to CO_2
reaction temperature: 175—180°

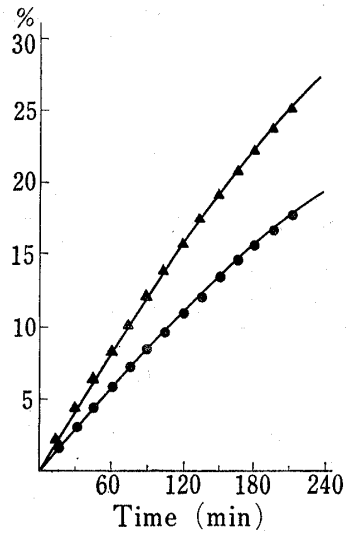
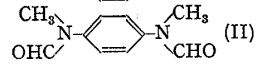


Fig. 4. Decomposition of TBAF in the Presence of I and II

reaction conditions: substrate to TBAF (as HCO_2H) molar proportion, 1:25; reaction temperature: 175—180°

—▲—: OHCNH–C$_6$H$_4$–NHCHO (I)

—●—:  (II)

After the N-formyl exchange of the substrates and the decomposition of formic acid in TBAF were determined, we then conducted the reactions of the radioactive I′ and II′ with

TBAF and the reactions of the non-radioactive I and II with TBAF-formic acid-^{14}C in order to obtain radiochemical yields of the N-methylated products, under the standardized conditions: 175—180° for 3.5 hr. Treatment of the reaction mixture gave the corresponding N-methylated radioactive product, IV or III, in 1—2% yield, which were hydrolyzed to N-methyl-*p*-phenylenediamine dihydrochloride (V) or N,N,N′-trimethyl-*p*-phenylenediamine dihydrochloride (VI), respectively. The purified dihydrochlorides were subjected to assay for radioactivity and the results are recorded in Table II.

Table II. Radioactive Assays Pertaining to the TBAF Reactions[a)]

Substrate	Activity (dpm/mole)	Formate	Activity (dpm/mole)	Product for assay	Measured activity (dpm/mole)
I′	4.85×10^9	TBAF		H_2N–C$_6$H$_4$–$NH^{14}CH_3\cdot2HCl$ (V)	3.77×10^8
I		TBAF-^{14}C	4.89×10^{8} [b)]	H_2N–C$_6$H$_4$–$NH^{14}CH_3\cdot2HCl$ (V)	4.36×10^8
II′	8.29×10^9	TBAF		CH_3NH–C$_6$H$_4$–$N(^{14}CH_3)(CH_3)\cdot2HCl$ (VI)	1.37×10^9
II		TBAF-^{14}C	4.89×10^{8} [b)]	CH_3NH–C$_6$H$_4$–$N(^{14}CH_3)(CH_3)\cdot2HCl$ (VI)	3.56×10^8

a) reaction conditions: substrate to formate (as HCO_2H) molar proportion; 1:25, 175—180°, 3.5 hr
b) activity based on HCO_2H

Discussion

From the results of the experiments described in the preceding section it is shown that the substrates I and II suffer exchange of their N-formyls by formic acid in the TBAF reaction medium before the conversion to the N-methylated products by interaction of formic acid. We will first discuss possible reaction mechanism on the basis of the chemical results.

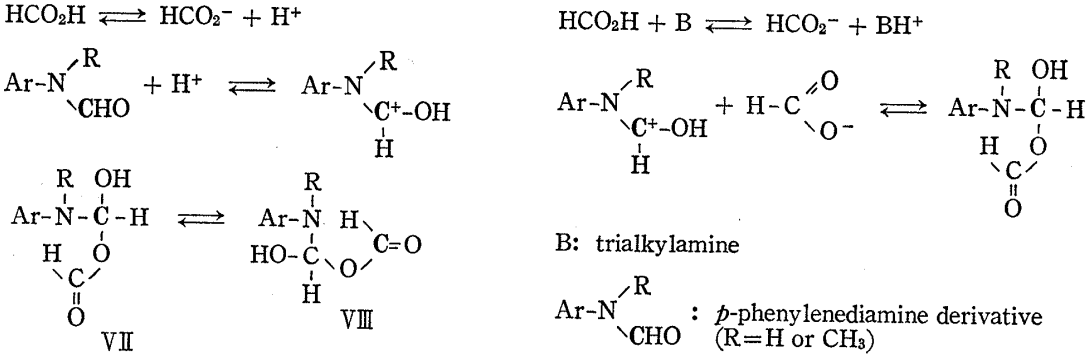


Chart 1

Pathway of the N-formyl exchange, which is reversible, is presumed as shown in Chart 1. That is, the N-formyl exchange proceeds through the unstable adduct formed from the protonated substrate and the formate ion. Nucleophilic attack of formate ion on amide carbonyl may be referred to as an usual reaction fashion similar to that of nucleophiles such

as hydroxide in the known hydrolysis of an amide.[4] The mechanism in Chart 1 is also analogous to that of the O-acetyl exchange reaction of *p*-nitrophenyl acetate proposed by Akahori.[5]

Next, course of the N-methylation of the substrate, which is suffering the above N-formyl exchange reaction, comes under consideration. It has been previously reported[6] that the reductive fission of the carbon-oxygen bond of the compound possessing the carbon attached to both oxygen and nitrogen is readily effected on heating with TMAF, being demonstrated with a variety of methylene and benzylidene derivatives and a number of 2-alkyl derivatives of oxazolidine. This reaction is referred to as a nucleophilic substitution attacked by formate ion, which eventually gives hydride by removal of carbon dioxide through an ester intermediate or ester-like transition state, as known for formic acid reduction.[7]

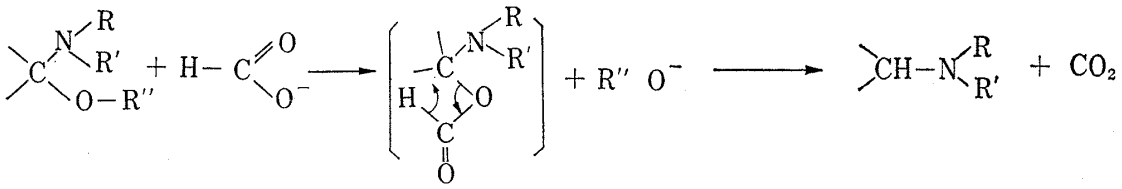
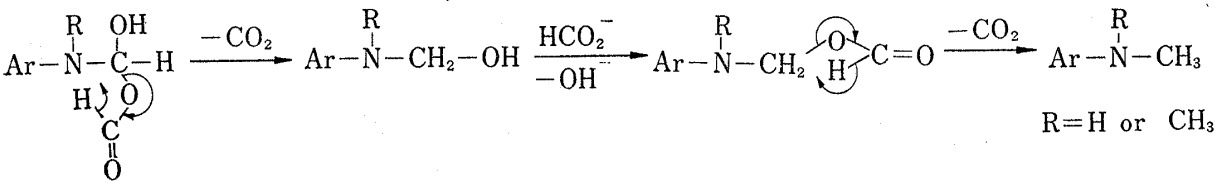


Chart 2

By referring to this reported formic acid reduction, a possible reaction mechanism of the N-methylation following the N-formyl exchange may be deduced as shown in Chart 3. It may be recognizable by analogy of the above formic acid reduction of the N,O-alkylidene compounds that the adduct, formic acid monoester of 1-amino-1,1-diol, formed in the course of the N-formyl exchange (see Chart 1), which is referred to as an intermediate analogous to one in the course of the formic acid reduction shown in Chart 2, undergoes decarboxylation to give 1-aminoalcohol and successively this suffers, in the same way shown in Chart 2, formic acid reduction to give the N-methylated amine. In the case of the substrate R=H in Chart 3, the resulting N-methylated amine would be successively formylated by formic acid to give the final N-formylated product. Throughout the reaction, trialkylamine in the formate reagents is considered to play a role in the formation of the formate ion from formic acid.



adduct intermediate

Chart 3

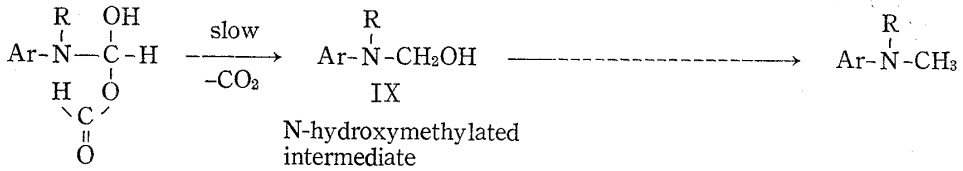
The above possible mechanism indicated by combination of Charts 1 and 3 would have to be consistent with the results of the isotopic tracer experiments shown in the preceding section. From the observed facts for the reaction, we begin by making the following three assumptions.

(i) Before the decarboxylation of the adduct in the course (Chart 3) of the conversion to the N-methylated product, the adducts, VII and VIII (Chart 1), exist as 1:1 equilibrium

4) R.A. Long and M.A. Paul, *Chem. Rev.*, **57**, 935 (1957); A.R. Katrizky and R.A.Y. Jones, *Chem. Ind.* (London), **1961**, 722; G. Fraenkel, A. Lowenstein, and S. Meiboon, *J. Phys. Chem.*, **65**, 700 (1961); C. O,Conner, *Quart. Rev.* (London), **1970**, 553.
5) Y. Akahori and S. Fukushima, *Chem. Pharm. Bull.* (Tokyo), **12**, 166 (1964).
6) K. Ito, H. Oba, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 2112 (1972).
7) R. Stewart, *Can. J. Chem.*, **35**, 766 (1957); S.T. Bowden, D.L. Clark, and W.E. Harris, *J. Chem. Soc.*, **1940**, 874; R.G.R. Bacon and J. Kochling, *ibid.*, **1964**, 5609.

mixture. As shown in the preceding section, after the 3.5 hour's reaction period, the yields of the N-methylated products are very low (yield based on the product isolated: 1.9% for the substrate I; 1.0% for the substrate II) against the great exchange of the N-formyl (96% for I; 69% for II). Thus, it can be said that rate of the N-formyl exchange is much greater than that of the succeeding formic acid reduction path. Therefore, it is very likely to presume that the adducts, VII and VIII, which exist in low concentration in the course of the rapid N-formyl exchange, attain an equilibrium before the succeeding reduction to the N-methylated product and, because of the isosteric structure of the two adducts, the equilibrium between them reaches 1:1 molar proportion.

(ii) In the stage converting to the N-methylated product from the adduct, the first decarboxylation stage leading to the possible N-hydroxymethylated intermediate IX is slower than the mutual conversion of the adducts and that the rate is first order with respect to the adduct.



(iii) In the course from the adduct the N-methylated product is formed only from the intermediate IX and not formed by another route. By this assumption the specific radioactivity of IX, calculated in theory, should be identical with that of the N-methylated product.

In the isotopic tracer reactions, specific radioactivity of IX depends on the proportion of ^{14}C at the carbon, connected to the nitrogen of the adduct, which comes from the N-formyl-^{14}C of the substrate or the formic acid-^{14}C in the TBAF. When the N-formyl carbon of the substrate and the formic acid carbon are expressed by Cs and Cf, respectively, the two adducts possessing Cs and Cf attached to the nitrogen should be formed in equivalent amount and should be converted into the two kinds of IX possessing Cs and Cf in equivalent amount in view of the foregoing assumptions (see Chart 4).

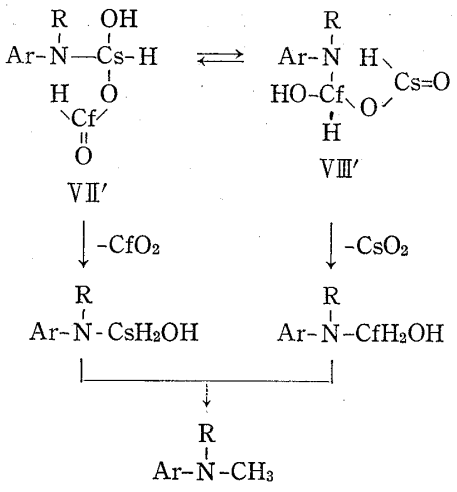


Chart 4

In the four isotopic tracer reactions, let Ss and Sf be specific radioactivities of the substrate and the TBAF reagent (as HCO_2H), respectively, in the reaction mixture at an arbitrary time. Specific radioactivity, Smt, of IX formed at this time can be calculated as in the following.

$$Smt = \frac{1}{2}\left(\frac{1}{2}Ss + Sf\right)$$

In this equation 1/2Ss is given by the reason that one of the two N-formyls of the substrate is converted through the monohydroxymethylated intermediate IX to the methyl group of the product, which, after converted into the hydrolyzed hydrochloride, is submitted to assay of specific radioactivity. Because Ss and Sf vary with increasing reaction period owing to the N-formyl exchange, specific radioactivity, Sm, of IX formed throughout the reaction can be calculated by integration.

$$Sm = \frac{1}{2}\int_0^t \left(\frac{1}{2}Ss + Sf\right)dt \qquad (1)$$

Let S be the initial specific radioactivity of the substrate or the TBAF (as HCO_2H). Ss and Sf are given as function of time.

$$Ss = S \cdot f(t) \qquad Sf = S \cdot g(t)$$

Values $f(t)$ and $g(t)$ mean varying proportion of specific radioactivities of the substrate and TBAF, respectively, with increasing reaction period. Insertion of these into Eq. (1) gives the following equation.

$$Sm = \frac{1}{2}\int_0^t \left\{\frac{1}{2}Sf(t) + Sg(t)\right\} dt = \frac{S}{2}\left\{\frac{1}{2}\int_0^t f(t)\,dt + \int_0^t g(t)\,dt\right\} \qquad (2)$$

Value $\int_0^t f(t)\,dt$ as to the substrates in the isotopic tracer experiments corresponds to the proportions of the lower areas of the four curve lines against the whole areas in Fig. 1. In order to obtain value $\int_0^t g(t)\,dt$ as to the TBAF variation of actual Sf for increasing reaction period must be measured, but there are difficulties in isolation of pure TBAF for measurement of its radioactivity during the course of the reaction. However, Sf for the increasing reaction period can be calculated from Fig. 1 and 4 by approximation. Fig. 1 means the corresponding transfer of radioactivity from the radioactive substrate to TBAF or from TBAF-formic acid-^{14}C to the non-radioactive substrate through the N-formyl exchange. Loss of radioactive formic acid by decomposition for increasing reaction period can be calculated from Fig. 4, which shows rate of decomposition of TBAF under the same reaction condition.

Let t_n and t_{n+1} be arbitrary two times of short interval in the course of the reaction, and let x_{tn} and x_{tn+1} be varying proportions of specific radioactivities of the substrate at t_n and t_{n+1} (see Fig. 5). Varying radioactivity of the substrate in the interval from t_n to t_{n+1} is given by $|x_{tn}-x_{tn+1}|\cdot S$, which transfers to TBAF or from TBAF-formic acid-^{14}C. In order to obtain real value of specific radioactivity in TBAF, it is necessary to consider the loss of formic acid in TBAF by decomposition based upon Fig. 4. Let y_{tn} and y_{tn+1} be proportions of decomposition of formic acid until t_n and t_{n+1}, respectively (see Fig. 5). In a short interval from t_n to t_{n+1}, varying radioactivity of TBAF can then be calculated approximately as in the following. As a period from t_n to t_{n+1} is very short, loss of radioactivity of TBAF by decomposition in this interval can be approximately given by $|x_{tn}-x_{tn+1}|\cdot S\cdot(y_{tn+1}-y_{tn})$. Loss of radioactivity

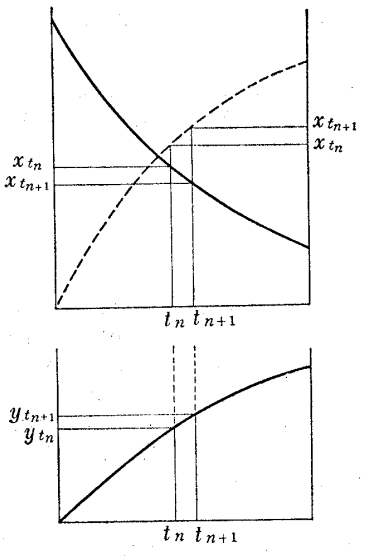


Fig. 5

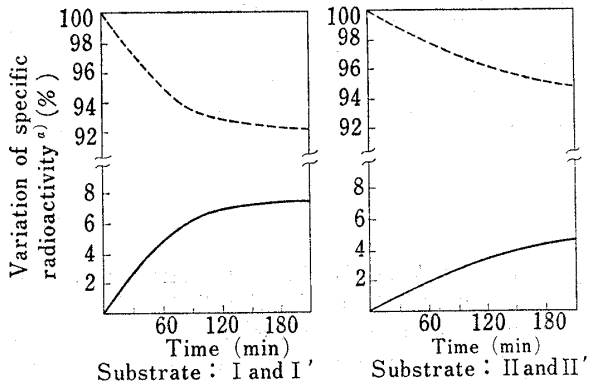


Fig. 6. Rates of Variation of Radioactivities of TBAF in the Reactions

——: substrate possessing two N-formyl-^{14}C with TBAF
------: non-radioactive substrate with TBAF-^{14}C
conditions: substrate to TBAF (as HCO_2H) molar proportion, 1:25; reaction temperature, 175—180°
a) variation of specific radioactivity calculated

incorporated into the N-methylated product is so small that it is neglected. Consequently, varying radioactivity of TBAF in the interval is expressed by $|x_{tn}-x_{tn+1}|\cdot S-|x_{tn}-x_{tn+1}|\cdot S\cdot(y_{tn+1}-y_{tn})$. Since $25(1-y_{tn+1})$ mole of TBAF (as HCO_2H) per one mole of the substrate exists at t_{n+1} (the initial molar proportion of the substrate to TBAF (as HCO_2H) is 1/25), varying specific radioactivity of TBAF in the interval from t_n to t_{n+1} can be expressed by the following.

$$\frac{|x_{tn}-x_{tn+1}|\cdot S-|x_{tn}-x_{tn+1}|\cdot S\cdot(y_{tn+1}-y_{tn})}{25(1-y_{tn+1})}=\frac{|x_{tn}-x_{tn+1}|\cdot[1-(y_{tn+1}-y_{tn})]\cdot S}{25(1-y_{tn+1})}$$

Sf at t_{n+1} is obtained by the following equation.

$$Sf=\sum_{n}\frac{|x_{tn}-x_{tn+1}|\cdot[1-(y_{tn+1}-y_{tn})]\cdot S}{25(1-y_{tn+1})}$$

According to this equation specific radioactivity, Sf, of the TBAF in the reactions at t_{n+1} is plotted by taking interval of each fifteen minutes as shown in Fig. 6.

Value of $\int_0^t g(t)\,dt$ as to TBAF in Eq. 2 is obtained as proportions of the lower areas of the four curve lines against the whole areas in Fig. 6. For each of the four isotopic tracer experiments the two values, $\int_0^t f(t)\,dt$ and $\int_0^t g(t)\,dt$ thus obtained, are inserted into Eq. 2 and then the theoretical specific radioactivity of the intermediate IX, Sm, is calculated.

Table III

Substrate	Formate	$\int_0^t f(t)dt$	$\int_0^t g(t)dt$	Radiochemical yield		
				Found (dpm/mole)	Calculated Sm (dpm/mole)	(Found/Calcd.) (%)
I′	TBAF	0.27	0.06	3.77×10^8	4.01×10^8	94.0
I	TBAF-^{14}C	0.73	0.94	4.36×10^8	4.09×10^8	106.6
II′	TBAF	0.65	0.03	1.37×10^9	1.41×10^9	97.2
II	TBAF-^{14}C	0.35	0.97	3.56×10^8	3.23×10^8	110.2

As listed in Table III, the values calculated above are in fair agreement with the experimental values observed for the N-methylated *p*-phenylenediamines.

Then the results of the isotopic tracer experiments are in accord with the theoretical expectations derived from the possible reaction path including the N-formyl exchange in Chart 1 and the reduction course in Chart 3. Consequently these mechanistic sequences are strongly supported.

In brief, it has now been revealed that the formate reagents affect the conversion of N-formyl, which suffers interchange in the formate medium, into N-methyl acting as reducing agent.

Experimental

Apparatus for Analysis of Decomposition of TBAF——The schematic of the apparatus for analysis of decomposing gas emitted on heating TBAF is shown in Fig. 2. Decomposing amount of formic acid in TBAF was analyzed as sum of forming carbon monoxide and carbon dioxide by the apparatus connecting (A) and (C) in Fig. 2, where carbon monoxide was oxidized to carbon dioxide through silver permanganate at 500° and total carbon dioxide was analyzed by absorbing in soda asbestos. Decomposing carbon dioxide was also analyzed separately by the apparatus connecting (A) and (B). Decomposing carbon monoxide was analyzed separately from carbon dioxide by the apparatus connecting (A), (B), and (C) in the order named. Speed of nitrogen current: 13 ml/min. Speed of oxygen current in the cases of connecting the apparatus (C): 45 ml/min.

TBAF Composed of Formic Acid-^{14}C——To 414 g (9.0 mole) of 99% formic acid, sodium formate-^{14}C containing 2 mCi was dissolved. After standing for 2 days 832 g (4.5 mole) of tributylamine was added

under cooling. The mixture was distilled under reduced pressure to give the formate distillate which was dried over anhydrous $MgSO_4$ and redistilled. TBAF fraction, bp 99—100° (13 mmHg), 1054 g, was assayed for radioactivity (4.89×10^8 dpm/mole of HCO_2H).

N,N′-Diformyl-^{14}C-*p*-phenylenediamine (I′)——A solution of sodium formate-^{14}C containing 1 mCi and 50.2 ml of 80% HCO_2H dissolved in 50 ml of dioxane was allowed to stand for 2 days. To this solution *p*-phenylenediamine, which was prepared from 34.6 g (0.25 mole) of *p*-nitroaniline by catalytic hydrogenation over Raney nickel catalyst under high hydrogen pressure, was added. The mixture was refluxed for 1 hr. On cooling, crystals that deposited in the solution were collected by filtration and recrystallized from H_2O. The crystals, mp 208—210°, weighing 28 g (73.5%), were assayed for radioactivity (4.85×10^9 dpm/mole).

N,N′-Diformyl-^{14}C-N,N′-dimethyl-*p*-phenylenediamine (II′)——A solution of sodium formate-^{14}C containing 1 mCi and 27.5 ml of 80% HCO_2H dissolved in 27.5 ml of dioxane was allowed to stand for 2 days. To this solution 40.4 g (0.39 mole) of triethylamine and 35.0 g (0.167 mole) of N,N′-dimethyl-*p*-phenylenediamine dihydrochloride prepared from II by hydrolysis was added. The mixture was refluxed for 1 hr. On cooling, crystals which deposited in the solution were collected by filtration and recrystallized from EtOH. The crystals, mp 200—201°, weighing 30.0 g (93.5%), were assayed for radioactivity (8.29×10^8 dpm/mole).

Reaction of N,N′-Diformyl-^{14}C-*p*-phenylenediamine (I′) with TBAF——In a flask provided with a long air condenser tube a mixture of 18.0 g (0.11 mole) of I′ containing 4.85×10^9 dpm/mole and 354 g (2.75 mole based on HCO_2H) of TBAF was heated with constant stirring at 175—180° for 3.5 hr. After evaporation of TBAF the residue was extracted with benzene. After removal of benzene the residue was washed with ether and recrystallized from EtOH to give 0.15 g of N,N′-diformyl-N-methyl-*p*-phenylenediamine which was hydrolyzed to N-methyl-*p*-phenylenediamine dihydrochloride by refluxing with 10% HCl solution. Pure material, which was checked by paper chromatography, was obtained by repeated recrystallizations from EtOH and was shown by assay to have 3.77×10^8 dpm/mole.

Reaction of N,N′-Diformyl-*p*-phenylenediamine (I) with TBAF Composed of Formic Acid-^{14}C——A portion of 18.0 g (0.11 mole) of I was heated along with 342 g (2.75 mole based on HCO_2H) of TBAF-^{14}C containing 4.89×10^8 dpm/mole of HCO_2H at 175—180° for 3.5 hr. Procedures were the same as described in the above experiment. Pure N-methyl-*p*-phenylenediamine dihydrochloride obtained was shown by assay to have 4.36×10^8 dpm/mole.

Reaction of N,N′-Diformyl-^{14}C-N,N′-dimethyl-*p*-phenylenediamine (II′) with TBAF——A portion of 19.2 g (0.1 mole) of II′ containing 8.29×10^9 dpm/mole was heated along with 313 g (2.5 mole based on HCO_2H) of TBAF at 175—180° for 3.5 hr. After evaporation of TBAF the residue was extracted with petr. ether. After removal of petr. ether the residue was recrystallized from ether to give 35.8 mg of N-formyl-N,N′,N′-trimethyl-*p*-phenylenediamine, which was hydrolyzed to N,N′,N′-trimethyl-*p*-phenylenediamine dihydrochloride. Pure material obtained by repeated recrystallizations from EtOH was shown by assay to have 1.37×10^9 dpm/mole.

Reaction of N,N′-Diformyl-N,N′-dimethyl-*p*-phenylenediamine (II) with TBAF Composed of Formic Acid-^{14}C——A portion of 19.2 g (0.1 mole) of II was heated along with 313 g (2.5 mole based on HCO_2H) of TBAF-^{14}C containing 4.89×10^8 dpm/mole of HCO_2H at 175—180° for 3.5 hr. Procedures were the same as described in the above experiment. Pure N,N,N′-trimethyl-*p*-phenylenediamine dihydrochloride obtained was shown to have 3.56×10^8 dpm/mole.

Radioactive Determination——Counting: the radioactivity was measured by Tri-Carb Liquid Scintillation Spectrometer 314 (Packard Instrument Co.).

A few miligram of the dried sample were weighed into a counting vial and dissolved in 15 ml of the scintillator solution, then cooled in a refrigerator for 3 hr prior to counting.

The efficiency of counting under the conditions described above were shown to be 25.7—51.5% using standard toluene-^{14}C.

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