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FLAME-INDUCED CARBOXYLATION OF UNSATURATED AMINES IN AN AQUEOUS FORMIC ACID SOLUTION

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When a hydrogen-oxygen flame was kept in contact with an aqueous formic acid solution of unsaturated amines, carboxylation onto a double bond took place. This reaction revealed to be initiated by addition of a hydrogen atom to the double bond followed by coupling of the resulted substrate radical with a carboxyl radical.

The use of plasmas to initiate chemical reactions has received an increasing amount of attention in recent years,$^{1-14)}$ whereas a few reports have appeared describing applications of plasmas to organic reactions in a liquid phase.$^{10-14)}$ Previously we reported that flames, in contact with an aqueous solution of organic compounds, were successfully employed as a radical source which could supply radicals effectively and continuously into the water phase.$^{15,16)}$ Flame, a plasma, produced by combustion, is most readily available compared with plasmas produced by high temperatures, electric fields, or high-energy radiations. This technique would be unique in view of the fact that radicals generated in a gas phase react directly with compounds in a liquid phase. However, the flame-induced reactions so far reported were mainly vigorous oxidation of substrates by the action of hydroxyl radicals and were hardly controlled to provide simple reactions.$^{15-17)}$ In the present study, we demonstrated that a hydrogen-oxygen flame could bring about direct carboxylation of carbon-carbon double bonds in an aqueous formic acid solution and also that oxidation of products could be almost completely suppressed owing to the presence of formic acid, an effective scavenger of hydroxyl radicals.

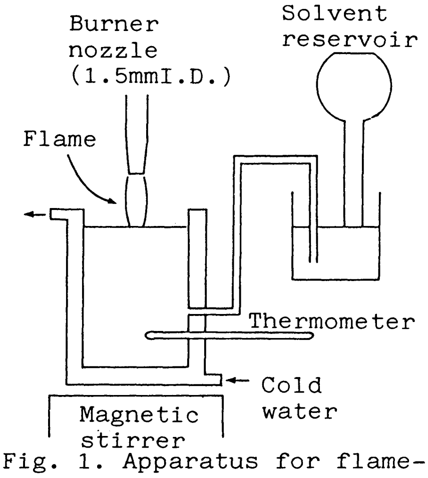


Fig. 1. Apparatus for flame-induced reaction.

A hydrogen-oxygen flame was kept in contact with the surface of an aqueous formic acid solution (250 ml) of several unsaturated aliphatic amines (ca. 1 mmol/l) by using an apparatus depicted in Fig. 1. The experimental procedure was essentially identical with that reported earlier.$^{15,18)}$

The products identified after a 30% formic acid solution of allylamine was exposed to a hydrogen-oxygen flame (H_2: 4 l/min, O_2: 0.8 l/min) are shown in Fig. 2. The substrate gave car-

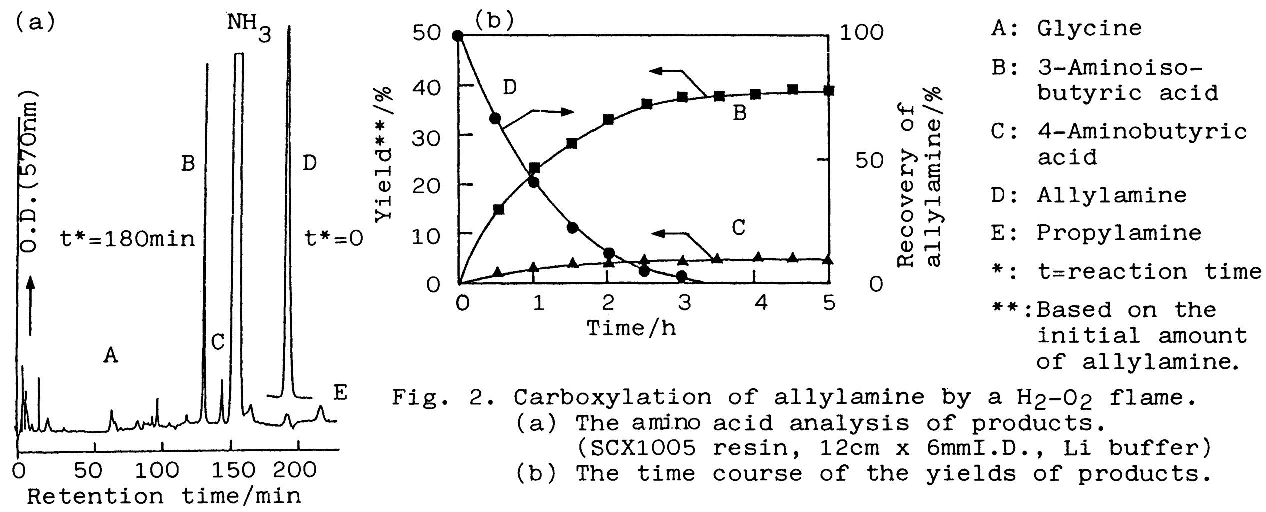
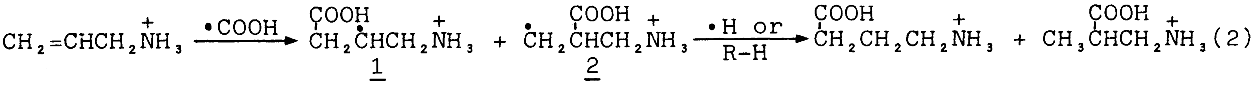


Fig. 2. Carboxylation of allylamine by a H_2-O_2 flame.
(a) The amino acid analysis of products.
(SCX1005 resin, 12cm x 6mmI.D., Li buffer)
(b) The time course of the yields of products.

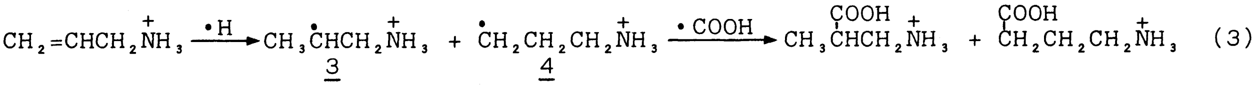
boxylated products, 3-aminoisobutyric acid and 4-aminobutyric acid, in a moderate combined yield, together with small amounts of propylamine, β-alanine, glycine, and several unidentified products. On exposure to the same flame in the absence of formic acid, allylamine gave the complex mixture of products, namely an amine (propylamine), amino alcohols, amino aldehydes, and amino acids (β-alanine and glycine), which were further decomposed on prolonged reaction. It is noteworthy that in the presence of formic acid oxidative degradation of the products was almost completely suppressed as shown in Fig. 2b. The suppression of oxidation would be attributed to the hydroxyl radical-scavenging effect of formic acid. The negligible formation of β-alanine and the low yield of glycine may indicate that the substrate was also little oxidized in spite of its high radical reactivity based on the double bond. The moderate total yield of analyzable products would be mainly due to radical oligomerization occurring in competition with the carboxylation. In fact, polyamino compounds were detected in the reaction mixture by paper electrophoresis, although not identified.

Another remarkable feature of this reaction is the high regioselectivity of carboxylation (3-aminoisobutyric acid : 4-aminobutyric acid = 8 : 1). The predominant formation of 3-aminoisobutyric acid should exclude the mechanism presented by Eq. 2, which involves addition of a carboxyl radical produced from formic acid (Eq. 1) to allylamine like a conventional radical addition to an olefin (Eq. 5) and affords 4-aminobutyric acid as a main adduct because of the higher stability of intermediate radical $\underline{1}$ than that of radical $\underline{2}$ (Eq. 2). Hydrogen atoms are known to exist in a hydrogen flame and expected to

$$HCOOH + {\bullet}OH \longrightarrow {\bullet}COOH + H_2O \qquad (1)$$



$$CH_2{=}CHCH_2\overset{+}{N}H_3 \xrightarrow{\bullet COOH} \underset{\underline{1}}{\overset{COOH}{CH_2}\overset{\bullet}{C}HCH_2\overset{+}{N}H_3} + \underset{\underline{2}}{\overset{\bullet}{C}H_2\overset{COOH}{CH}CH_2\overset{+}{N}H_3} \xrightarrow[R\text{-}H]{\bullet H\ or} \overset{COOH}{CH_2}CH_2CH_2\overset{+}{N}H_3 + CH_3\overset{COOH}{CH}CH_2\overset{+}{N}H_3 \qquad (2)$$



$$CH_2{=}CHCH_2\overset{+}{N}H_3 \xrightarrow{\bullet H} \underset{\underline{3}}{CH_3\overset{\bullet}{C}HCH_2\overset{+}{N}H_3} + \underset{\underline{4}}{\overset{\bullet}{C}H_2CH_2CH_2\overset{+}{N}H_3} \xrightarrow{\bullet COOH} CH_3\overset{COOH}{CH}CH_2\overset{+}{N}H_3 + \overset{COOH}{CH_2}CH_2CH_2\overset{+}{N}H_3 \qquad (3)$$

$$CH_3\overset{\bullet}{C}HCH_2\overset{+}{N}H_3 \xrightarrow{\bullet H\ or\ R\text{-}H} CH_3CH_2CH_2\overset{+}{N}H_3 \qquad (4)$$

$$R\text{-}CHO \xrightarrow{peroxide\ etc} R\text{-}\overset{\bullet}{C}O \xrightarrow{CH_2=CH\text{-}R} R\text{-}CO\text{-}CH_2\overset{\bullet}{C}H\text{-}R \xrightarrow{R\text{-}H} R\text{-}CO\text{-}CH_2CH_2\text{-}R \qquad (5)$$

react with compounds in solution under the conditions used here.[19)] By considering addition of a hydrogen atom to allylamine followed by coupling of the resulted radical (3) with a carboxyl radical (Eq. 3), the mechanism of this reaction is well explained. The main product expected in this mechanism is 3-aminoisobutyric acid on the basis of the stability of radical 3. The formation of propylamine clearly indicates the existence of intermediate 3 (Eq. 4), namely the participation of hydrogen radicals in this reaction. Radical 3 would also react with allylamine to afford oligomers.

Experiments were carried out to investigate the influences of flame composition and formic acid concentration on products. From the results illustrated in Figs. 3 and 4, the most suitable conditions for the carboxylation are determined as stated above (H_2/O_2: 5, solvent: 30% aq. HCOOH). When flames were used with the flow rate ratio H_2/O_2 up to 2, no carboxylated products were obtained (Fig. 3) and oxidation of allylamine proceeded. It is to be noted that formation of propylamine accompanies the carboxylation and that both of the reactions are induced only by flames with a large excess of hydrogen, which are considered rich in hydrogen atoms. These facts indicate that hydrogen atoms are essential for the carboxylation and strongly support the mechanism proposed above. With decreasing formic acid concentration in solvent, the rate of carboxylation became faster as shown in Fig. 4, but the products were rapidly decomposed by oxidation. On the other hand, the concentration of glycine in the reaction mixture constantly increased throughout the reaction for 5 hours and its formation rate was maximal in 3% aqueous formic acid. Glycine revealed to be formed not only by oxidation of the substrate but mainly from formic acid and ammonia[20)] by the action of flame.

The table summarizes the results of carboxylation of several unsaturated amines. All of the substrates gave the corresponding carboxylated products in moderate yields. Crotylamine showed no regioselectivity, since there is no difference in stability between two intermediate radicals formed by addition of a hydrogen atom to crotylamine (cf. Eq. 3). The relatively low yield of carboxylation of cinnamylamine would be due to decomposition of a phenyl ring under the reaction conditions. In this case, the yields of the products decreased slowly on prolonged reaction.

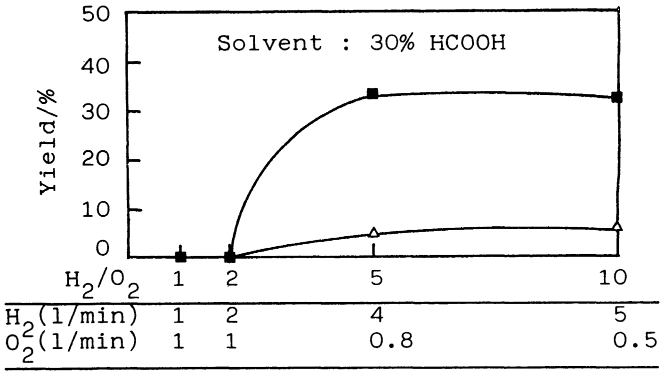


Fig. 3. Effect of flame composition on products. ■–■ :3-aminoisobutyric acid, △–△ :propylamine.

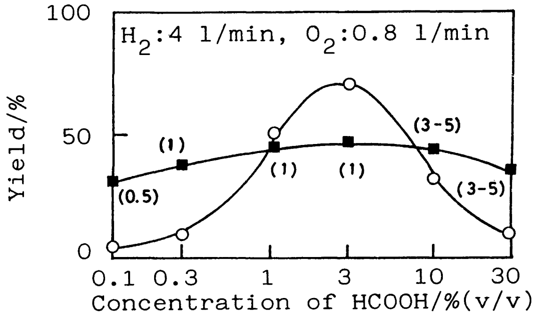


Fig. 4. Effect of formic acid concentration on products. ■–■: 3-aminoisobutyric acid, ○–○: Gly. Reaction time (h) at maximum yield is shown in parentheses.

Table 1. Carboxylation of unsaturated amines

Substrate	Reaction time/h	Product (yield/%)			
$CH_2{=}CHCH_2NH_2$	3.0	$CH_3\overset{COOH}{C}HCH_2NH_2$	(38)	$\overset{COOH}{C}H_2CH_2CH_2NH_2$	(5)
$CH_2{=}CHCH_2CH_2NH_2$	3.0	$CH_3\overset{COOH}{C}HCH_2CH_2NH_2$	(38)	$\overset{COOH}{C}H_2CH_2CH_2CH_2NH_2$	(4)
$CH_3CH{=}CHCH_2NH_2$	3.0	$CH_3\overset{COOH}{C}HCH_2CH_2NH_2$	(19)	$CH_3CH_2\overset{COOH}{C}HCH_2NH_2$	(17)
$\phi\text{-}CH{=}CHCH_2NH_2$	2.5	$\phi\text{-}\overset{COOH}{C}HCH_2CH_2NH_2$	(16)	$\phi\text{-}CH_2\overset{COOH}{C}HCH_2NH_2$	(5)
$CH_2{=}CH\overset{COOH}{C}HNH_2$	2.5	$CH_3\overset{COOH}{C}H{-}{-}\overset{COOH}{C}HNH_2$	(40)	$\overset{COOH}{C}H_2CH_2\overset{COOH}{C}HNH_2$	(3)
$CH_2{=}CHCH_2\overset{COOH}{C}HNH_2$	3.0	$CH_3\overset{COOH}{C}HCH_2\overset{COOH}{C}HNH_2$	(32)	$\overset{COOH}{C}H_2CH_2CH_2\overset{COOH}{C}HNH_2$	(3)

The carboxylation reported here will offer a first experimental evidence of introduction of hydrogen atoms from a flame into a water phase as well as a rare example of reaction in which hydrogen radicals play an important role. On account of the contribution of hydrogen atoms, the carboxylation is a new type of radical reaction which can introduce a functional group into an internal carbon atom of a terminal carbon-carbon double bond (cf. Eqs. 3 and 5). By the use of an appropriate flame composition and a radical scavenger, this study has enabled selective utilization of hydrogen atoms ($H_2/O_2 > 5$, 30% HCOOH) or hydroxyl radicals ($H_2/O_2 < 2$) from among many radicals that exist in the flame.

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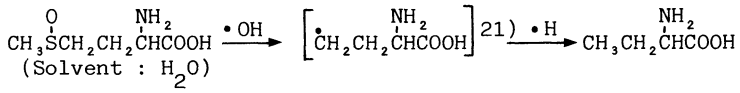
18) The temperature of the solution was kept at 40 - 55 °C by circulating cold water (1 °C) through the jacket of the reaction vessel.
19) In the following reaction, hydrogen atoms in the flame ($H_2/O_2=5$) are considered to react directly with compounds in solution. The details of this reaction will be reported elsewhere.



$$CH_3\overset{O}{S}CH_2CH_2\overset{NH_2}{C}HCOOH \xrightarrow{\bullet OH} \left[\overset{\bullet}{C}H_2CH_2\overset{NH_2}{C}HCOOH\right]^{21)} \xrightarrow{\bullet H} CH_3CH_2\overset{NH_2}{C}HCOOH$$

(Solvent : H_2O)

Flame composition	Yield/%
$H_2/O_2=5$	8.9
$H_2/O_2=1$	0

20) The reaction mixture, which is acidic, takes up ammonia from the atmosphere.
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