

Reaction of Potassium Fluoride with Organic Halogen Compounds.
(Part I) Reactions of Potassium Fluoride with Organic Halides, Acids,
and Esters in presence of Dimethyl Formamide and their Pyrolytic
Decarboxylation in presence of Potassium Fluoride

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有機 할로젠 化合物과 弗化加里의 反應 (第 1 報)
有機 할라이드, 酸 및 에스테르와 弗化加里의 디메틸 호름아마이드 溶媒系
反應 및 高溫-脫炭酸-熱分解反應

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Abstract

Reactions between potassium fluoride with organic halogen-containing carboxylic acids in dimethyl formamide solvent gave a decarboxylation reaction for the case of fluoro carboxylic acids of the type of CF_3COOH , C_6F_7COOH , and C_2F_5COOH , whereas an additional partial fluorination together with dimerization reaction occurred for the chlorine containing acids of the type of $CH_2ClCOOH$, $CH_3CHClCOOH$, $CHCl_2COOH$ and $o\text{-Cl-C}_6\text{H}_4\text{-COOH}$. The phenyl halides showed no reactivity, but the halides with two electron attracting substituents on the benzene ring gave mainly dimerization reaction. The esters and alcohols gave an usual fluorination reaction. The same reactions in absence of the solvent at the elevated temperature increase the yield of the dimerized product and gave the cyclized product, fluorenone, in case of *o*-chlorobenzoic acid. It was found that the fluorination usually precede the decarboxylation reaction by checking the stiochemical sequence of reaction. Catalytic influence of potassium fluoride were discussed and the mechanism of the reaction was considered.

要 約

「디메틸 호름아마이드」 溶媒系에서 有機할로젠化合物을 弗化加里와 反應시켜 본 結果 CF_3COOH , C_6F_7COOH , C_2F_5COOH 와 같은 含弗素有機酸에서는 脫炭酸反應이 일어나며, 含氯素有機酸, $CH_2ClCOOH$, $CH_3CHClCOOH$, $CHCl_2COOH$ 및 $o\text{-Cl-C}_6\text{H}_4COOH$ 은 一部 弗化反應이 일어나고 變合(dimerization) 反應이 隨伴된다는 것을 究明하였다. 芳香族할라이드類에서는 反應度를 나타내지 않았으나 芳香環에 誘電子置換基가 二個있는 試藥에서는 主로 變合反應을 일으켰다. 알콜 및 에스테르類는 通常의 弗化反應을 잘 일으켰다. 같은 反應을 溶媒를 使用치 않고 高溫에서 進行시켜 본 結果 變合反應物의 收率을 增加시켰고 $o\text{-Cl-C}_6\text{H}_4COOH$ 에서는 環化物(fluorenone)을 少量生成하였다. 反應段階中의 各 試藥의 消耗 및 生成에 對한 化學量的關係를 比較檢討한 結果 酸의 反應에서는 普通 脫炭酸反應보다 弗化反應이 優先 進行됨을 究明하였다. 弗化加里의 反應觸發作用 및 反應機構에 關하여서도 論議하였다.

Introduction

Numerous reports were appeared in the literature on the fluorination of organic chloro compounds with potassium fluoride.¹⁾ The reaction conditions of potassium fluoride fluorination are varied in regards to reaction temperature,²⁾ solvent³⁾, and the type of compounds⁴⁾. Recently Du pont workers found that

the dimethyl formamide is an effective solvent for KF fluorination⁵⁾. The use of this solvent for a nucleophilic reaction was also reported in the case of Ullmann reaction⁶⁾. The catalytic influence of potassium fluoride in the decarboxylative cyclization reaction of adipic acid⁷⁾ and other acids⁸⁾ were reported in the recent publications. A Skelton rearrangement

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caused by KF was also observed.⁹⁾ The role of KF as a Lewis base which catalyzes a carbanion reaction is well experienced by many workers. Present investigation, a part of synthetic study of the preparation of multiple halogen containing insecticidal attractants, was concentrated to find the role of KF in the reaction system of organic halogen containing acids, esters, and halides, which have reactive functional species towards potassium fluoride. The reaction of halogen exchange by KF and the additional reaction of KF with the functional group other than halogen both in a solvent system and a pyrolytic procedure may give a multiple reaction sequence, which would be helpful to elucidate the role of KF in the reaction system of acids and esters. Further interest may be concerned to the structural influence of the reactant and reaction conditions. A gas chromatographic technique and infrared spectrophotometric determinations for the elucidation of reaction may be adapted for clarifying the present interest.

Experimental*

Starting Materials.

The reagents used in the present investigation were mainly obtained from commercial source. Chlorobenzene (Wako Chemical), Bromobenzene (Wako Chemical), Iodobenzene (Eastman Kodak), Fluoro-acids (Fisher Chemicals), Chloro acids (Fisher Chemical), Potassium fluoride (Merck), 2, 4-dinitro-1-chloro-benzene (Merk), Dimethyl formamide (Merk), Ethyl chlorohydrin (Merk) were obtained from commercial reagents grade as indicated. Ethyl chloroacetate was prepared by Fisher esterification of chloro acetic acid. p-Iodoaniline was prepared by iodination of aniline in presence of sodium carbonate¹³⁾.

Reaction of halogen containing acids with anhydrous potassium fluoride in dimethyl formamide.

General Procedures...Potassium fluoride(0.1~0.05 mole) and the equivalent quantity of the acid

*All melting and boiling points in this experimental were not corrected. The infrared spectra was taken at this Institute using Beckman IR-4. The gas chromatogram was taken using GC-2 Beckman model at this Institute.

were placed in a 100 ml. three necked round bottomed flask equipped with a stirrer, thermometer, and condenser. The mixture was refluxed under vigorous stirring for 4~6 hours.

The reaction mixture was filtered and the solid from the filtration was examined for the presence of potassium chloride using silver nitrate and dilute nitric acid. The filtrate was diluted to 100 ml. with dimethyl formamide, and the aliquot of the diluted solution was examined by quantitative gas chromatography in case of volatile acids. (Fluoro acids). Gas chromatographic analysis was made by means of peak area comparison of the reaction mixture and standard solution which contained equivalent quantity of the acid in the reaction in dimethyl formamide solvent. The solid acid and high boiling acids were isolated from the reaction mixture by distillation and the structure was confirmed by infrared spectrophotometry. The amount of acid consumed in case of chloro acids were measured by titration.

The quantitative comparison of the acids before and after reaction was attempted by means of a standard Na-Cl cell of Beckman IR-4 wherever possible. All products from the reaction was checked by gas chromatography, infrared spectrophotometry, and physical and chemical separation respectively. The result of the reaction was summarized in Table 2. The solid from the reaction contained unreacted acids, potassium salt of the acid, unreacted potassium fluoride, and potassium chloride. The solid was dissolved in ethanol or water in order to separate the unreacted acids and potassium salt or potassium fluoride. The separated product was dried under vacuum and weighed. The amount of the original solid and separated product was compared and the stoichiometrical relation was summarized in the Table 3.

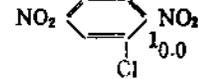
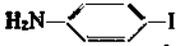
Reaction of phenyl halides with potassium fluoride in dimethyl formamide.

General procedure... 0.1 mole of phenyl halides and the equivalent quantity of potassium fluoride in 50 ml. of dimethyl formamide were placed in a three necked round bottomed flask equipped with a stirrer, condenser, and thermometer. The reac-

tion mixture was refluxed during the course of 8~5 hours under vigorous stirring. The reaction mixture was filtered and the filtrate was diluted to 100 ml. using dimethyl formamide. The solid from the filtration was examined for the presence of potassium chloride as described previously. The diluted reaction mixture was then examined by means of gas chromatography in order to measure the amount of reagents reacted and fluorinating product. In case of nitrochloroderivative the gas chromatography was not feasible for measurement because of the high boiling point of the reagent or

overlapping the peak of the reagent with solvent peak. Therefore, reaction mixture from 2,4,-dinitro-1-chloro-benzene was triturated by means of solvent evaporation and the examination of the solid residue by checking melting point, fluorine test, and infrared spectrophotometry. The reaction mixture from p-iodo aniline was triturated by solvent distillation and the conversion of the residue from the distillation to the corresponding amine hydrochloride. The amine hydrochloride was checked for melting point and fluorine test. There result of the reaction was summarized in Table 1.

Table 1. Reaction of potassium fluoride with organic halogen containing phenyl derivatives in dimethyl formamide.

Reactant	Amount g.	KF g.	Reaction temp.	Reaction time	Halides consump- tion	Type of reaction and product	Product identification
 -Cl	11.3	5.8	reflux	8 hrs.	none	—	*G.C.
 -I	15.9	5.8	reflux	8 hrs.	none	—	G.C.
 -Br	20.4	5.8	reflux			—	G.C.
 -NO ₂ Cl	10.0	2.9	reflux	8 hrs. 5 hrs.	none donot measure	dimerized product. m.p. 165°, (yield 32.6%) Residue, oil, containing fluorine(trace)	distillation
 -H ₂ N I	6.8	2.9	reflux	5 hrs.	none	none reactivity recovered acid. m.p. 58°.	distillation

* Beckman GC-2 Gas chromatography; A 3 silicon and a 6' carbowax 1,000 column was used, respectively.

Reaction of ethyl chlorohydrin and ethyl chloro-acetate with potassium fluoride in dimethyl formamide solvent.

9.1 g of ethyl chlorohydrin and 5.8 g of potassium fluoride dissolved in 50 ml. of dimethyl formamide were placed in a 100 ml. three necked round bottomed flask equipped with a stirrer, condenser, and thermometer. The reaction mixture was refluxed during the course of 5 hours under vigorous stirring. The reaction mixture was filtered to give solid which dissolved in water and gave white precipitate by adding silver nitrate solution and dilute nitric acid. (indicate the presence of KCl.) The filtrate was diluted to 100 ml. using dimethyl formamide. The diluted reaction mixture was exa-

mined for ethyl fluorohydrin and unreacted chlorohydrin by means of gas chromatography. (6' column, temp. 130°C). The gas chromatogram showed two peaks at retention time of 2.1 and 3.1 min. and the relative ratio of the two peaks was 0.56:1.0. The yield of fluorohydrin measured by this method was about 48%.

4.5 g of ethyl monochloro-acetate and 2.2 g of potassium fluoride in 50 ml. of dimethyl formamide were placed in a 100 ml. three necked round bottomed flask. The reaction mixture was refluxed during the course of 5 hours and triturated as described above. Gas chromatogram of the reaction mixture indicated that major peaks at 2.8 and 3.4 min. (6' column) The comparison of standard chloro-acetate

solution with the reaction mixture by gas chromatography indicated that 3.6 g chloro-acetate was consumed by the reaction. There were no other peaks than that of the solvent. The formation of

fluoro-acetate was identified by the peak at retention time of 2.8 min. The results are summarized in Table 2.

Table 2. Reaction of potassium fluoride with organic halogen containing carboxylic acid, alcohol, and ester.

Reactant	Amount g	KF Amount g	Reaction temp.	Reaction time	Acid consumption	Type of reaction	Product	Method of identification
CH ₃ COOH	9.0	5.8	110°C	5hrs.	62.0%	Salt formation and decarboxylation	Potassium salt	G.C.* and crystallization
CF ₃ COOH	11.4	5.8	60	5	17.8	//	//	//
C ₂ F ₅ COOH	15.4	5.8	110	5	49.0	//	//	//
C ₂ F ₇ COOH	22.4	5.8	60	5	65.2	//	//	//
CH ₂ ClCOOH	9.8	5.8	reflux	5	49.4	Fluorination, decarboxylation dimerization	Trace solid m.p. 210° and tar	I.R.** and physical separation
$\begin{array}{c} \text{H} \\ \\ \text{CH}_3-\text{C}-\text{COOH} \\ \\ \text{Cl} \end{array}$	10.9	5.8	reflux	5	24.4	//	//	//
CHCl ₂ COOH	12.8	5.8	reflux	5	53.9	Decomposition	Tar, carbonized product.	//
$\begin{array}{c} \text{C}_6\text{H}_4 \\ \\ \text{Cl} \\ \\ \text{COOH} \end{array}$	15.8	5.8	reflux	5	48.0	Fluorination decarboxylation, dimerization	4.1g of mix. of chloro acid and fluoro-acid.(m.p.124°)	I.R. [characteristic frequency. 1680, 1690, 1728, (50)]
ClCH ₂ CH ₂ OH	9.1	5.8	reflux	5	—	Fluorination	Fluoro hydrin 48%	G.C.
ClCH ₂ COOCH ₃	4.5	2.2	110	5	—	Fluorination	Fluoro acetate 80%	//

* Gas chromatography. Beckman GC-2. 6' carbowax 1,000, and 3' silicon column.

** Infrared spectrophotometry. NaCl prism. Beckman IR-4.

Table 3. Stoichiometrical relations of solid product from the reaction of acids.

Acids	Amount of acids used	Acid consumption %	Estimated consumption based on acid consumption		Amount of solid formed except KF or acid salt (g)	
			KF (g)	KCl or RCOOK (g)		
Acetic	(0.1 mole)	62.0	2.2	16.1	} → RCOOK	7.4
Caproic	(//)	55.0	2.6	0.2		5.7
Benzoic	(//)	32.0	3.7	5.2		4.0
Succinic	(//)	45.0	6.4	8.6*(7.1)		4.4
Adipic	(//)	82.0	2.0	18.2(15.1)		13.7
Mono-chloroacetic	(//)	49.4	2.5	3.7	} → KCl	0.7
α-Chloro-propionic	(//)	24.4	4.4	1.8		1.5
Dichloro acetic	(//)	53.9	2.7	4.0		0.8

* Based on mono acid salt.

Pyrolytic decarboxylation reaction in presence of KF

(a) Monochloroacetic Acid

Into a 500 ml. of round bottomed flask were pla-

ced 58.8 g of monochloroacetic acid and 34.8 g of anhydrous potassium fluoride, and the mixture was well shaken. The reaction mixture was heated under reflux for 1 hour. The reaction mixture was

then dissolved in methanol and the insoluble residue was taken in water. The methanol solution was distilled to give tarry residue which does not contain fluorine but chlorine. The aqueous solution was evaporated to give 28.5 g of solid. The solid suspended in water was heated to eliminate potassium fluoride and chloride. The filtration of the solid suspension gave 12.6 g of solid, which contain trace of inorganic chlorine and does not melt above 300°C. The infrared spectra in nujol mull indicated the formation of the corresponding acid potassium salt.

(b) Dichloroacetic Acid

Into a 500 ml of round bottomed flask equipped with a distilling head, cooler, and receiver were placed 76.8 g of dichloro acetic acid and 34.8g of potassium fluoride. The reaction mixture was heated to reflux. The reaction proceeded violently liberating gas, and the content of the flask was carbonized seriously. The reaction contents were washed with methanol and the methanol solution was examined to give positive inorganic chlorine but no fluorine. The evaporation of methanol gave an unidentified brownish tars. The residue from methanol washing was dissolved in water. The water solution gave a slight fluorine and chlorine test. The water insoluble black mass, decomposition product, weighed 10.0g. The recovery of unreacted fluoride was trace.

(c) α -chloropropionic Acid

Into a 500 ml. round bottomed flask was placed 65.4 g of acid, 34.8 g of potassium fluoride and the mixture was well shaken. The reaction mixture was then heated under reflux for an hour. The reaction mixture was triturated with methanol and the resulting methanol solution was evaporated to give brownish tarry material which contains chlorine and fluorine. The tar was distilled under reduced pressure to give a white solid which melt at 123°, (0.8 g) after recrystallization.

The infrared spectra of the solid indicated the formation of dimethyl succinic acid (characteristic frequency: 1760, 1250, 1150, 1100, 990, cm^{-1}). The insoluble residue from methanol washing was dissolved in water. The insoluble solid which indicated

the formation of potassium salt of the acid weighed 6.3g. The solid composed of trace of KCl, mono acid salt, and diacid salt.

The tarry distillation residue was a polymerized product. Infrared spectra gave an intense peak at 1760-50 cm^{-1} .

(d) *o*-chlorobenzoic Acid

(A) Into a 500 ml, round bottomed flask equipped with a distilling head, cooler, and receiver was placed 31.3 g of acid and 11.3 g of potassium fluoride. The reaction mixture was heated under reflux for 4 hours and it was distilled under reduced pressure to give a brownish, aromatic smelling oily distillate. The distillate was triturated with methanol and the insoluble solid was separated and dried, which melted at 158°, and weighed 2.9 g. The methanol solution was evaporated to dryness to give 6.5 g of brownish solid. The solid was washed with 5 % sodium hydroxide solution and the insoluble solid (2.5 g) was dried, which melted at 165°C. The sodium hydroxide solution was neutralized with dilute hydrochloric acid to give unreacted *o*-chlorobenzoic acid which melted at 136°C. (amount 4.0 g). The solid residue from methanol treatment of the flask content was washed with methanol and the insoluble solid was washed water. There obtained a solid after evaporating methanol. This solid was treated with 5% solution of sodium hydroxide. The sodium hydroxide solution was neutralized with acid to give the unreacted acid. (amount 2.0 g). From the insoluble portion of solid in methanol, 1.0g of solid melted at 228° was obtained. The water washing of the flask residue was evaporated to give unreacted KF and KCl weighed 6.3 g. The water insoluble black mass, which was decomposition product, weighed 6.5 g. The solids separated at each separating scheme were purified and the infrared spectra were examined. Total yield based on the infrared identification was 6.0 g of the unreacted acid, 6.4 g of the diphenic acid, 6.5 g. of decomposition product, and 6.3 g. of unreacted KF and KCl. The solid obtained from the methanol solution of the distillate was washed with carbon tetrachloride and the solution was examined by infrared spectrophoto-

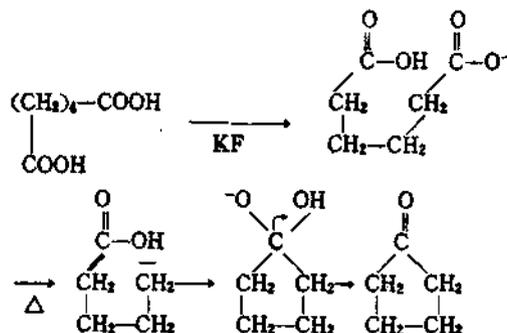
ometric method to indicate the formation of fluorenone. There was a trace quantity of *o*-fluorobenzoic acid.

Characteristic frequency (cm ⁻¹)						
diphenic acid.	1.670	1.610	1.390	1.150	758	in nujol mull
fluorenone	1.740	1.560	1.320	935		in CCl ₄
	(1.490)	1.420				

Results and Discussion

It was known that fluorination of organic chlorine compounds by means of potassium fluoride mainly proceeds at elevated temperature because of high melting point of potassium fluoride and unavailability of a suitable solvent. Acetamide⁹⁾, ethylene glycol,³⁾ and other high boiling solvents were adapted to dissolve the potassium fluoride and to maintain an elevated reaction temperature. Dimethyl formamide which boils at 153-54° cannot be comparable to the prementioned solvents in regards to the refluxing temperature, but the solvating property of the solvent is excellent in the case of Ullmann reaction which involves an insoluble organometallic intermediate⁶⁾. The reaction of potassium fluoride with *o*-chloro-nitrobenzene in dimethyl formamide gave a 60% yield of fluorinated product by refluxing the reaction mixture for four hours⁵⁾. The application of dimethyl formamide as solvent in the present research was based on the above facts. The solubility of potassium fluoride in dimethyl formamide was again experienced. In each reaction carried at lower temperature than the boiling point of the solvent, potassium fluoride was dissolved considerably, which was checked by the examination of the residue from the distillation of the reaction mixture. The fluorination reaction of chloroester, and chlorohydrin were as usual. The reaction gave the corresponding fluoride in 50-80% yield which was measured by gas chromatographic technique. (see Table 2). However, a different reaction path was observed in case of acids. The role of potassium fluoride other than fluorination was recently experienced by other workers^{7, 8)}. Potassium fluoride acts as a catalyst for the formation of Dieckman condensation reaction of adipic

acid. The reaction proceeded in good yield in presence of potassium fluoride. The initial abstraction of proton by potassium fluoride from the carboxylic group of the acid and formation of subsequent carboxylate anion were the reaction path.



Other catalytic effect of potassium fluoride in the reaction of decarboxylation of acids⁹⁾, addition dehydration reaction of active methylene containing compounds⁹⁾, and Hoffman reaction of *N*-chloro benzamide¹⁰⁾ were experienced by other workers. In each case the role of potassium fluoride was a Lewis base. In the prementioned Dieckman reaction the rate was slower and the yield was increased when the amount of potassium fluoride was decreased, which was explained by the fact that potassium fluoride was acted as a base for abstracting proton from the acid, but the acid is still retain bonding. The KF is not enough to react with α -hydrogen. Results obtained in the present research of fluoro acids was in accord with the prementioned result. Fluoro-acids which are strong enough to form hydrate gave a rapid decarboxylation reaction at lower temperature (60-110°). The evolution of carbon dioxide from the reaction system was observed and the decrease of acids after reaction was noticed by gas chromatography. The relative ease of the decarboxylation was in order of acidity of the acid itself as summarized in Table 2. However, the reaction of chloroacid gave a different reaction path. Potassium fluoride catalyzed the decarboxylation of the acids, but the fluorine displacement of chlorine in the molecule was slight.

The reaction resulted in the formation of salt and dimerization product. The dimerization reaction was increased when the acidity of the acid was

decreased. The dimerization reaction was also observed in case of phenyl halide with reactive chlorine. (Table 1). The dimerization of organic halides were also reported by other workers¹¹⁾. In a separate research done at this laboratory the dimerization of *p*-chlorobenzoic acid, ethyl 1, 2, -dichloro-2-phenyl propionate and acid in dimethyl formamide solvent was observed in presence of zinc, and a slight reactivity of the dimerization of the above reactants was also observed under mixed U.V. irradiation¹²⁾. Therefore, the reactivity of chlorine atoms in the prescribed type of compounds towards dimerization or substitution was not surprising. However, the role of potassium fluoride in the present system of acids and reactive chlorophenyl derivative of benzene caused the present interest. As summarized in the Table 2 the yield of fluorination and dimerization reactions were low in the reaction condition described. Therefore a stoichiometrical sequence of the reaction of acid, diacid, and chloroacid were checked by examining the solid residue of the reaction product. It was found that in the reaction of potassium fluoride with non chlorinated acids, and diacids, the relative amount of the acid consumed during the reaction and the unreacted potassium fluoride, or the formation of potassium salt indicated decarboxylation is not major process of the reaction. The degree of the decarboxylation was in order of the acidity of the acid. In case of chloroacid, however, the formation of potassium salt was slight as compared with the formation of potassium chloride and the product analysis indicated that the formation of decarboxylation product was not stoichiometrically counterbalanced. This consideration showed that the reaction proceed in favor of fluorination or dimerization at the expense of the reactivity of the carboxylic function. Since the data from the reaction of non chlorinated acid indicated that the decarboxylation process in the present reaction is not major process, further reaction was carried using dry condition and at elevated reaction temperature to effect decarboxylation. Monochloro acid and α -chloro acid gave mainly the corresponding potassium salt and the decarboxylation product,

which would be an unstable three membered cyclic propanone, could not be identified. In case of α -chloro propionic acid a considerable amount of a polymerized tar and 1.0% of the dimerized diacid together with the potassium salt were obtained. The formation of the unstable three membered cyclic ketone at an elevated temperature will probably be hindered by decomposition. The investigation was therefore extended to the reaction of *o*-chloro benzoic acid which will give a stable five membered cyclic ketone after the decarboxylation of the dimerized product. In a reaction run carried at above 350° the formation of fluorenone was identified in trace quantity and about 10.0% of the dimerized diacid together with fluoro acid were reaction obtained. The reaction was repeated varying the temperature between 250-350°. In each case the formation of fluoro acid, diacid, and salt were observed, but the formation of fluorenone was not identifiable at the reaction temperature below 350°C. The reaction of dichloro acid at elevated temperature gave exclusively decomposition product which indicated the enhanced reactivity of chlorine in the molecule. In conclusion the reaction of potassium fluoride with phenyl halide gave no reactivity in case of inert halides, but the reactive chloride gave a dimerized product. The reaction of non chlorinated acid and diacid in dimethyl formamide gave a slight decarboxylation, but the same reaction with chlorine containing acid gave fluorination or chlorine displacement predominantly. The use of high reaction temperature resulted the decomposition of the product with formation of fluoro acid, diacid, and cyclic ketone in trace. The formation of dimerization product during the reaction path probably proceeds in the following route. Potassium fluoride abstracts initially a proton from acid and forms a carboxylate anion. In case of the strong acid the formation of carboxylate anion is rapid and condensable amount which cause decarboxylation. (Fig. 1) The chloro acid and non chlorinated acid the acidity was markedly decreased and hence the resulting carboxylate anion is not stabilized enough to effect decarboxylation and formed mainly potassium salt. The reactive chlorine

