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REVIEW COMMENTARY

HOMOGENEOUS, UNIMOLECULAR, GAS-PHASE ELIMINATION OF LEAVING GROUPS AT THE ALKOYL SIDE OF CARBOXYLIC ACIDS

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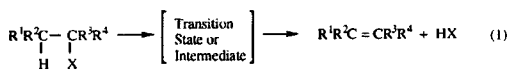
The molecular gas-phase elimination kinetics of the series $Cl(CH_2)_nCOOH$ ($n = 1-4$), show changes in mechanisms from polar five-centered intramolecular displacement of the Cl leaving group by the acidic hydrogen of the COOH to neighboring group participation of the oxygen carbonyl of the COOH group. The mechanisms for the series 2-, 3- and 4-chlorobutyric acids are explained similarly as above. The leaving chloride at the 2-position of acetic, propionic, and butyric acids is displaced by the hydrogen of the COOH group through a prevaling path of a five- centered cyclic transition-state mechanism. This type of mechanism is also described for the pyrolysis of 2-hydroxy-, 2-alkoxy-, 2-phenoxy-, and 2-acetoxycarboxylic acids. The ease with which the groups at the 2-position of acetic and propionic acids are displaced by the H of COOH give rise the sequences AcO > OH > PhO > EtO > MeO > Cl and AcO > PhO > Br > EtO > MeO > MeO > OH > Cl, respectively. These two sequences differ only in the OH leaving group position. Additional work on glycolic acid pyrolysis is needed to explain the above differences.

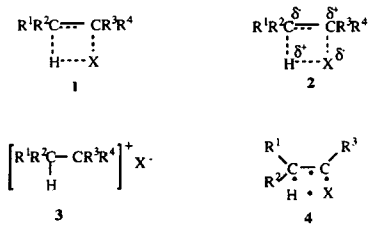
INTRODUCTION

It is well known that the homogeneous, unimolecular, gas-phase pyrolysis or elimination of simple alkyl halides leads to the formation of the corresponding olefin and hydrogen halide, respectively [equation (1)].



(1)

Before 1953, and in spite of the few kinetic investigations, the generally accepted mechanism consisted in a concerted four-membered cyclic transition state reaction (**1**). For molecular dehydrohalogenation, the presence of an adjacent β-hydrogen to the C—X bond is necessary.



In 1955, Maccoll and Thomas[1] suggested that activation consisted mainly of an elongation of the C—X bond with subsequent polarization, in the sense $C^{\delta+} \cdots X^{\delta-}$, with some assistance from an adjacent also polarized C—H bond (**2**). In 1967, Maccoll and Thomas[2] considered the very polar transition state in terms of an intimate ion-pair intermediate (**3**) and they offered evidence in support of this assumption. However, this theory was immediately questioned seriously. In 1963, Benson and Bose[3] suggested a semi-ion-pair transition state for gas-phase elimination as represented in **4**. Four years later, using this model, O'Neal and Benson[4,5] calculated energies and entropies of activation which agreed remarkably well with the experimentally reported values for their four- centered transition state reaction.

When our laboratory started to study the gas-phase elimination kinetics of organic molecules, our endeavour was to establish whether an intimate ion-pair mechanism is feasible in the pyrolyses of organic halogen compounds. This type of mechanism was believed to be possible if the said molecules could be stabilized through neighboring group participation, by means of an intramolecular solvation or 'autosolvation,' then *trans*-elimination and possibly intramolecular migration or rearrangement may take place. Along these

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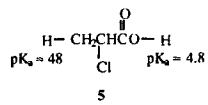
lines, and in order to appreciate the nature of the transition state for alkyl halide pyrolyses, we examined the substituent effects in the homogeneous, unimolecular eliminations of primary,[6] secondary[7] and tertiary[8] alkyl chlorides in the gas phase.

HALO ACIDS

When the substituent Z = COOH is considered as one of the possible candidates in the correlation of α-substituted ethyl chloride,[7] CH_3CHZCl, we kept in mind that 2-chloropropionic acid, $CH_3CHClCOOH$, may undergo an intramolecular competition (**5**) between the hydrogen of the COOH ($pK_1 = 4{\cdot}8$) for a five-membered cyclic transition state and the hydrogen of the CH_3 ($pK_a = 48{\cdot}0$) for the usual four-membered cyclic transition state in dehydrochlorination of alkyl halide pyrolyses.[9]



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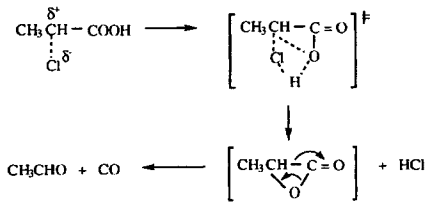
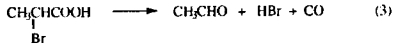
The actual pyrolysis products are acetaldehyde, carbon monoxide and hydrogen chloride. On the basis of this result, the mechanism is believed to proceed in terms of a polar five-membered cyclic transition state, as described in equation (2).



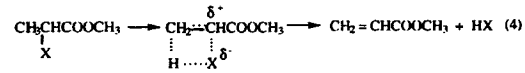
(2)

To verify the above result, the gas-phase pyrolytic elimination of 2-bromopropionic acid was undertaken.[10] The experiments support the previous one, as shown in equation (3).



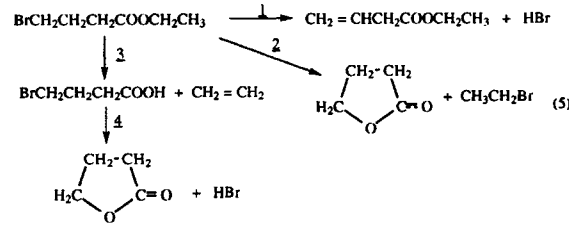
(3)

The mechanism is interpreted in the same terms as that for 2-chloropropionic acid [equation (2)]. Table 1 indicates that when the H of the COOH is replaced by the CH_3 group, the elimination of the hydrogen halide proceeds through the usual four-membered cyclic transition-state mechanism [equation (4)]. Moreover, the five-membered conformation through the assistance of the acidic H of the COOH appears to be more favored than the four-membered conformation for elimination. In addition the Br atom appears to be a better leaving group than the Cl atom, as is already known in the process of molecular dehydrohalogenation of organic halogen compounds in the gas-phase.



(4)

Among the studies questioning the intimate ion-pair intermediate is a reaction which involves neighboring group participation and ionic intermediates in solutions, namely the lactonization of ethyl 4-bromobutyrate.[11] It was reported that no reaction occurred in the gas- phase, and that only HBr elimination was detected at the very high temperature of 450 °C. This information was surprising, since the ethyl side of the ester should have been eliminated faster or easier than dehydrobromination. Consequently, the gas-phase elimination kinetics of ethyl 4-bromobutyrate were re-examined.[12,13] The pyrolysis of this substrate, under maximum inhibition and in the temperature range 354–375 °C, revealed that parallel and consecutive eliminations took place [equation (5)].



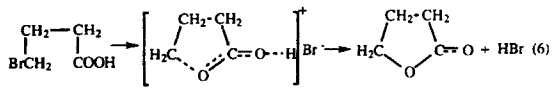
(5)

According to the kinetic parameters of the overall and partial rate, together with product analyses, the $COOCH_2CH_3$ substituent provided anchimeric assistance in the product formation via paths 1 and 2. The mechanism was explained in terms of an intramolecular solvation of the bromide ion through a common intimate ion-pair intermediate which decomposes in two different directions. The products 4-bromobutyric acid and ethylene (path 3), are the result of a normal six- membered cyclic transition state as generally occurs in the gas-phase pyrolysis of primary ethyl

Table 1. Kinetic parameters and comparative rates at 360 °C

Substrate	E_a (kJ mol^{-1})	Log[A (s^{-1})	$10^4 k_1$ (s^{-1})	Relative rate
$CH_3CHClCOOCH_3$	217·0 ± 7·4	12·22 ± 0·54	0·02	1
$CH_3CHClCOOH$	186·9 ± 3·0	12·53 ± 0·25	12·80	610
$CH_3CHBrCOOCH_3$	211·4 ± 4·4	13·01 ± 0·34	0·37	1
$CH_3CHBrCOOH$	180·3 ± 3·4	12·41 ± 0·29	33·88	92

esters. 4-Bromobutyric acid, which is known to be unstable at room temperature, decomposes rapidly to butyrolactone. The mechanism of the consecutive reactions of path 4 was explained in a similar manner as for path 2 (H instead CH_3CH_2,) where an intimate ion-pair intermediate leads through COOH participation to the exclusive formation of butyrolactone [equation (6)].

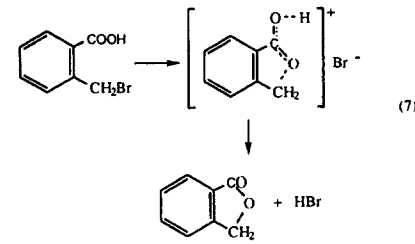


An additional study of a 2-bromo acid involved the elimination kinetics of 2-bromo-3-methylbutyric acid in the gas-phase.[14] Since the electron release of the isopropyl group in RCHBrCOOH (Table 2) increases the C—Br bond polarization more than methyl in 2-bromopropionic acid, a higher elimination rate must be obtained. This work ratifies the mechanism of 2-halopropionic acids,[9,10] where the polar five-membered cyclic transition state appears to be preferred in HX elimination [equation (2)].

In association with the unstable 4-bromobutyric acid, where the Br atom is insulated by three carbon atoms from the COOH group, the gas-phase pyrolysis kinetics of α-bromo-*o*-toluic acid[15] were examined. The interest in this substrate, where the Br is also insulated by a three carbon chain to the COOH group, arises from the high stabilization of the benzylic part of the molecule favouring the C—Br bond polarization in the transition state. Consequently, the COOH participation must be more effective. The reaction shown in equation (7) and the data in Table 3 support the previous generalization with regard to the occurrence of neighboring group participation in gas-phase reactions of organic molecules.[16] This phenomenon was thought to be effective when the transition state is highly polar. Since the benzylic C—Br bond in α-bromo-*o*-toluic acid is very polar and rate determining, the assistance of the neighhoring carbonyl oxygen of the COOH group leads to an elimination faster than lactone formation, as compared with 4-bromobutyric acid (Table 3). The pyrolysis of bromotoluic acid suggest an intimate ion-pair type of mechanism through neighboring COOH group participation [equation (7)], which, on collision, proceeds to the formation of phthalide by intramolecular solvation or autosolvation of the bromide ion.

Table 2. Comparative rates for RCHBrCOOH pyrolysis at 350° C

R	Log[A (s^{-1})]	E_a (kJ mol^{-1})	$10^4 k_1$ (s^{-1})
CH_3	12·41 ± 0·29	180·3 ± 3·4	19·64
$(CH_3)_2CH$	12·72 ± 0·25	181·8 ± 2·9	30·02



By analogy with 4-bromobutyric acid the pyrolysis kinetics of 4-chlorobutyric acid, which is stable at room temperature, yielded quantitatively γ-butyrolactone.[17] The mechanism is similar to that for 4-bromobutyric acid described in equation (6).

Because of the several mechanisms described previously, in which 4-chlorobutyric acid gives butyrolactone, 2-chloropropionic acid produces acetaldehyde [equation (2)], and the fact that the pyrolyses of ethyl 2-haloacetates, ($XCH_2COOCH_2CH_3$, X = F, Cl, Br) yielded the corresponding halocarboxylic acid, which decomposes further to CH_2O and little CH_3X [equation (8)],[18–20] it was necessary to establish a clear knowledge of the mechanism of pyrolysis occurring when the halogen leaving group, in our case chlorine, is at different position along the carbon chain in aliphatic carboxylic acids, that is, $Cl(CH_2)_nCOOH$ ($n = 1–4$). Also the series 2-, 3- and 4- chlorobutyric acids and the 2-chlorocarboxylic acids, RCHClCOOH (R = H, CH_3, CH_3CH_2), had to be examined.

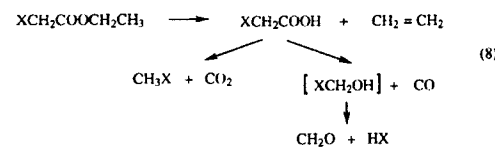


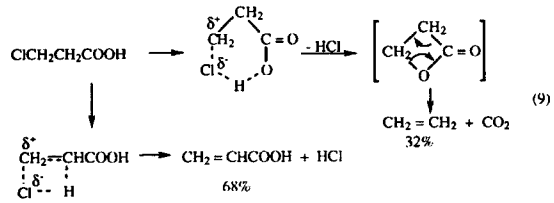
Table 3. Arrhenius parameters and comparative rates at 380 °C

Substrate	Log [A (s^{-1})]	E_a (kJ mol^{-1})	Relative rate
$BrCH_2CH_2CH_2COOH$	12·97 ± 0·31	210·3 ± 3·8	1
o-$BrCH_2C_6H_4COOH$	11·69 ± 0·13	182·1 ± 1·6	10

ω-CHLOROCARBOXYLIC ACIDS

According to the experimental results in Table 4, several mechanisms may take place, from intramolecular displacement of the chlorine leaving group by the acidic hydrogen of the COOH (chloroacetic acid and 3-chloropropionic acid) to the anchimeric assistance of the carbonyl COOH group to the C—Cl bond polarization of 4-chlorobutyric acid and 5-chlorovaleric acid.[21]

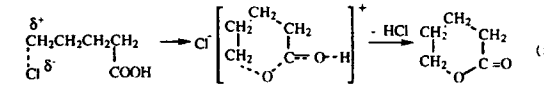
The five-membered conformation of the chlorine displacement appears to be less assisted by the acidic hydrogen of the COOH for dehydrochlorination than the six-membered conformation in 3- chloropropionic acid [equation (9)]. The mechanistic explanations of these eliminations have been considered by comparison with that of 2-chloropropionic acid [equation (2)].



(9)

Consideration that β-propiolactone is the intermediate described in equation (9) finds support in the pyrolysis kinetics of this compound[22,23] to give only $CH_2{=}CH_2$ and CO_2.

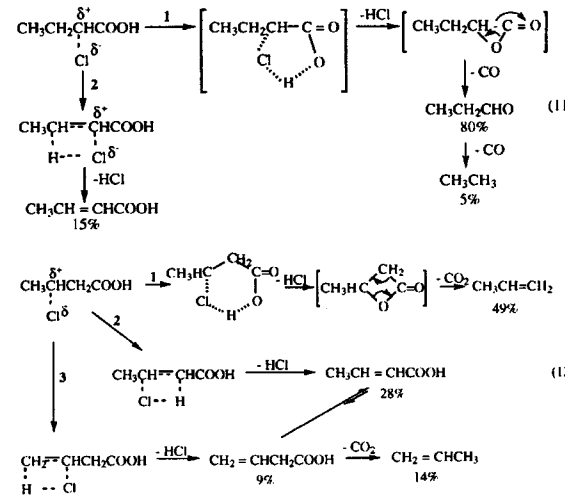
The data in Table 4 suggest that the five-membered conformation of neighboring group participation in 4-chlorobutyric acid is more favored than the six-membered conformation in 5-chlorovaleric acid [equation (10)]. As a result, the high C—Cl bond polarization through anchimeric assistance of the oxygen carbonyl enhances the rate of HCl elimination more than the direct intramolecular displacement by the acidic hydrogen of the COOH group.



(10)

ω-CHLOROBUTYRIC ACIDS

The mechanistic interpretations derived from product formation and the data in Table 4 appear to be strengthened by the comparative results of the leaving chlorine from position 2 to position 4 in ω-chlorobutyric acids (Table 5).[21] The neighboring carbonyl group of 4-chlorobutyric acid assists the leaving Cl better than direct participation of the acidic hydrogen of the COOH of 2- and 3-chlorobutyric acids. The mechanisms of the latter two substrates are rationalized in equations (11) and (12).



(11)

(12)

Table 4. Comparative rates at 340 °C

Substrate	Lactone formation	$10^4 k_1$ (s^{-1})	Relative rate
$ClCH_2COOH$	Lactone[a]	0·12	1
$ClCH_2CH_2COOH$	β-Propiolactone[a]	1·47	12
$ClCH_2CH_2CH_2COOH$	γ-Butyrolactone	19·05	159
$ClCH_2CH_2CH_2CH_2COOH$	δ-Valerolactone	8·42	70

[a] Unstable lactone under reaction conditions.

Table 5. Kinetic parameters and comparative rates at 350 °C

Substrate	Lactone formation	Log[A (s^{-1})]	E_a (kJ mol^{-1})	$10^4 k_1$ (s^{-1})[a]
$CH_3CH_2CHClCOOH$	α-Butyrolactone[b]	11·25	170·4	7·75
$CH_3CHClCH_2COOH$	β-Butyrolactone[b]	14·48	206·0	7·95
$ClCH_2CH_2CH_2COOH$	γ-Butyrolactone	12·32	176·5	33·11

[a] k_1 = Rate of lactone formation.
[b] Unstable lactone.

The formulation that β-butyrolaclone is an intermediate of path 1 in equation (12) may find support from the pyrolysis of this compound at 209–250 °C, which gives only propene and CO_2.[24]

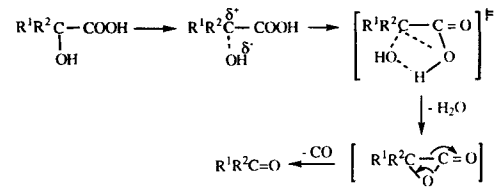
2-CHLOROCARBOXYLIC ACIDS

The results in Table 6, where the chlorine leaving atom is at the 2-position of several carboxylic acids, indicate that the secondary C—Cl bond is more readily displaced than the primary C—Cl bond. Apparently the electron release of alkyl groups, R in RCHClCOOH, increases the stabilization of the C—Cl bond in the transition state. Consequently, both 2-chloropropionic acid [equation (2)] and 2- chlorobutyric acid [equation (11)] give faster HCl elimination than chloroacetive acid.

In conclusion regarding the intramolecular displacement of the leaving chlorine by hydrogen in halocarboxylic acids, the usual four-centered transition state of HCl elimination is better assisted than the six- centered transition state, as shown by the results for 3-chloropropionic acid [equation (9)] and 3-chlorobutyric acid [equation (12)]. However, the five-centered transition state eliminates HCl mole easily than the four-centered transition state as shown in 2-chlorobutyric acid pyrolysis [equation (11)]. In addition to these considerations, neighboring group participation must greatly stabilize the C—Cl bond polarization in the transition state, thus leading to faster elimination. Consequently, the oxygen of the carbonyl of the COOH assists the Cl leaving group better than direct displacement by the acidic H of the COOH group.

2-HYDROXYCARBOXYLIC ACIDS

In association with the results on the HCl elimination of 2-halocarboxylic acids, the elimination of primary, secondary and tertiary 2-hydroxy acids were studied.[25,26] The data in Table 7 imply that the greater the basicity of the OH of alcohols in the gas-phase, the faster is the dehydration process through the assistance of the acidic H of the COOH. In this respect, the rates increase from primary to tertiary 2-hydroxycarboxylic acids. According to these results, the mechanism was considered to proceed via a semi-polar five-centered transition state where the C—OH bond polarization, in the sense $C^{\delta+}\cdots OH^{\delta-}$, is rate determining [equation (13)].



(13)

The transmission of the electronic effects of the alkyl groups appears to be responsible for the rate increase. The steric acceleration factor was not underestimated. Because of this, additional work on the elimination kinetics of DL-mandelic acid[27] showed that the greater stabilization of the benzylic carbocation in the transition state gives a faster dehydration process. Consequently, the above result confirms the polar nature and not the steric factor, when the secondary OH leaving group of mandelic acid is compared with the secondary OH leaving group of lactic acid: at 340 °C, $10^4 k_1 = 4{\cdot}57$ and $88{\cdot}98\ s^{-1}$ for

Table 6. Kinetic parameters and comparative rates at 370 °C

Substrate	Log[A (s^{-1})]	E_a (kJ mol^{-1})	$10^4 k_T$ (s^{-1})[a]	$10^4 k_1$ (s^{-1})[b]
$ClCH_2COOH$	11·21	189·2	0·69	0·69
$CH_3CHClCOOH$	12·53	186·9	22·39	22·39
$CH_3CH_2CHClCOOH$	11·25	170·4	25·70	21·85

[a] k_T = Overall rate.
[b] k_1 = Rate of lactone formation.

Table 7. Arrhenius parameters and comparative rates at 340 °C

Substrate	Log[A (s^{-1})]	E_a (kJ mol^{-1})	$10^4 k_1$ (s^{-1})	Relative rate
$HOCH_2COOH$	14·03	209·3	1·58	1
$CH_3CHOHCOOH$	12·24	182·8	4·57	3
$(CH_3)_2COHCOOH$	12·91	174·7	104·71	66
$CH_3CH_2(CH_3)COHCOOH$	12·87	171·2	190·50	121
$(CH_3CH_2)_2COHCOOH$	12·13	159·4	346·70	219

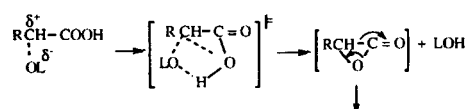
Table 8. Comparative elimination rates of the leaving groups L in LCH_2COOH and $CH_3CHLCOOH$

	$10^4 k_1$ (s^{-1})	
L	LCH_2COOH (380 °C)	$CH_3CHLCOOH$ (350 °C)
Cl	1·20	7·24
Br	—	19·50
HO	19·50	8·13
CH_3O	4·37	15·49
CH_3CH_2O	6·17	19·05
C_6H_5O	7·24	60·26
CH_3COO	234·40	354·81

$CH_3CHOHCOOH$ and $C_6H_5CHOHCOOH$, respectively, i.e. relative rates of 1:20.

RESEARCH WORK IN PROGRESS

Further studies on leaving groups at the 2-position of carboxylic acids, such as alkoxy, phenoxy and acetoxy, are at present in progress to obtain more detailed and complete experimental data.[28] Nevertheless, the mechanism of these eliminations involving a lactone intermediate may be considered in a similar manner as described before [equation (14)].



(14)

(i) R = H, L = CH_3
(ii) R = CH_3, L = CH_3
(iii) R = H, L = CH_3CH_2
(iv) R = CH_3, L = CH_3CH_2
(v) R = H, L = C_6H_5
(vi) R = CH_3, L = C_6H_5
(vii) R = H, L = CH_3CO
(viii) R = CH_3, L = CH_3CO

Partial results of these eliminations lead to the conclusion that the five-membered intramolecular displacement of leaving groups at the 2-position may be a reasonable type of mechanism. In considering this type of mechanism as probable, then a sequence in rates of these leaving groups at the 2-position in acetic and propionic acids is suggested (Table 8).

According to Table 8, the order of leaving ability of substituents at the 2-position where their departure may be assisted by the acidic hydrogen of the COOH group is as follows:

for LCH_2COOH: $CH_3COO > OH > C_6H_5O > CH_3CH_2O > CH_3O > Cl$;

for $CH_3CHLCOOH$: $CH_3COO > C_6H_5O > Br > CH_3CH_2O > CH_3O > OH > Cl$.

These two sequences differ only in the OH leaving group. Apparently, the higher prolysis rate for dehydration of glycolic acid suggests an exception from the five-centered transition state type of mechanism. Consequently, another process may well be operating during this elimination. It seems that the primary C—OH has a small bond polarization which may cause a different dehydration path. In this respect, additional thorough examination of glycolic acid pyrolysis is needed in order to clarify the above difference.

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