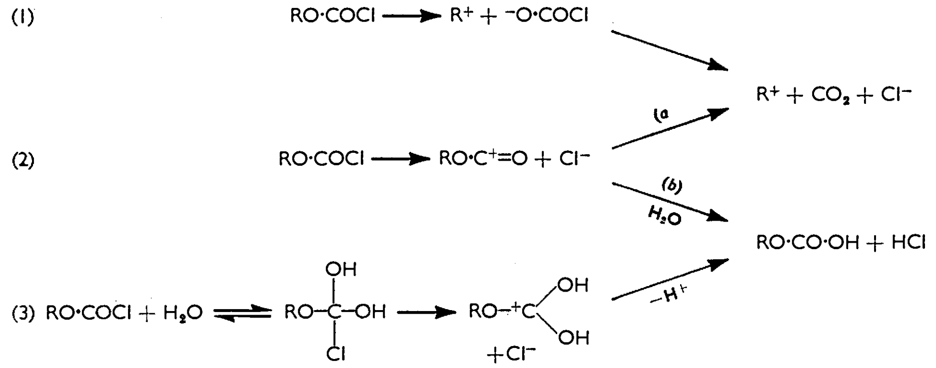
200. *The Mechanism of Hydrolysis of Acid Chlorides. Part VIII.*[1] *Chloroformates of Secondary Alcohols.*

By M. Green and R. F. Hudson.

The rates of solvolysis of cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl chloroformate are similar in formic acid and in 65% aqueous acetone, increasing in this order. This shows that the reactions do not proceed by a mechanism involving rate-determining ionisation of the C–O bond. In all cases, 35—60% yields of olefin were obtained in water. (—)-1-Methylheptyl chloroformate gave 30% of olefin and 70% of (—)-1-methylheptanol with 90% retention of configuration. No olefin was detected in the hydrolysates of *trans*-4-t-butylcyclohexyl chloroformate, which shows that a free carbonium ion is not formed. These observations are interpreted by assuming a rate-determining ionisation to give the acylium ion RO·CO⁺.

In a previous paper,[1] it was suggested that secondary chloroformates are solvolysed by a rate-determining ionisation, and the alternative mechanisms (1—3) were considered.



In formic acid, alkyl–oxygen fission was observed, since *D*(+)-1-methylheptyl chloroformate gave *L*(+)-1-methylheptyl formate,[*] but this product could have been formed by a process following rate-determining C–Cl bond fission.

To investigate this mechanism further, the reactivities and products of reaction of a series of chloroformates of cyclic alcohols, both in aqueous solution and in formic acid, have been determined. Owing to strain in the cyclic systems, the rate of ionisation leading directly to carbonium ions is very sensitive to the size of the ring,[2] as proved for solvolysis of sulphonates[3] and halides,[4] and the rate order $C_5 > C_6 < C_7 < C_8$ for S_N1 ionisation is now well established (cf. Figure). The transition state of an S_N2 reaction adopts the same configuration, but steric hindrance affects the rate sequence, which becomes[5] $C_5 \gg C_6 < C_7 > C_8$.

The characteristic S_N1 order has recently been used[6] to support an ionisation mechanism for the hydrolysis of ketals which is similar to mechanism (2) given above.

---

[*] *D* and *L* are used in the sense defined by Linstead, Lunt, and Weedon (*J.*, 1950, 3333).

[1] Part VII, *J.*, 1961, 3748.

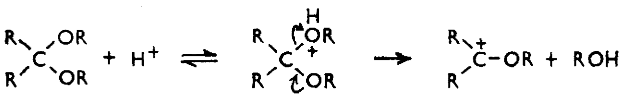
[2] Baeyer, *Ber.*, 1885, **18**, 2269; Prelog, *J.*, 1950, 420; Brown and Ichikawa, *Tetrahedron*, 1957, **1**, 221.

[3] Roberts and Chambers, *J. Amer. Chem. Soc.*, 1951, **73**, 5034; Brown and Ham, *ibid.*, 1956, **78**, 2736.

[4] Brown, Fletcher, and Johannesen, *J. Amer. Chem. Soc.*, 1951, **73**, 212; Brown and Borkowski, *ibid.*, 1952, **74**, 1894.

[5] Fierens, *Bull. Soc. chim. belges*, 1952, **61**, 427, 609.

[6] Kreevoy, Morgan, and Taft, *J. Amer. Chem. Soc.*, 1960, **82**, 3064.



The present results (Table 1) show a gradual increase in reactivity from C_5 to C_8, in both solvents. These results suggest that the mechanisms are similar in the two solvents and do not involve a rate-determining fission of the C–O bond. The small rate increase with ring size may be due to an increase in electron release to the oxygen atom.

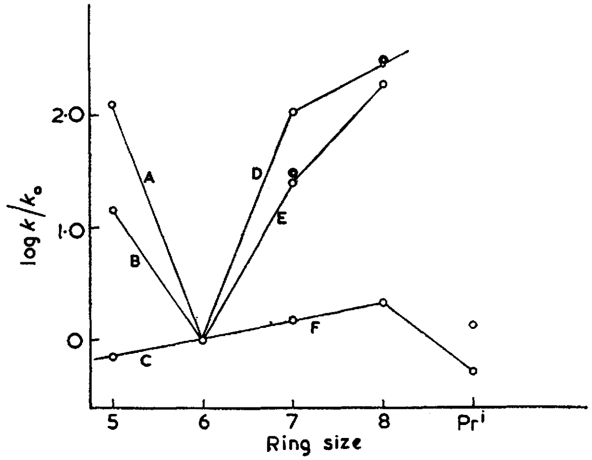
TABLE 1.

Rates of solvolysis of cyclic chloroformates in formic acid (*a*) and in 65% v/v aqueous acetone * (*b*).

	C_5	C_6	C_7	C_8	Pr^i
(*a*) 10^4k (sec.$^{-1}$), 24°	3·55	5·02	7·80	10·8	2·60
(*b*) 10^4k (sec.$^{-1}$), 25°	4·91	6·82	9·90	14·55	4·35

* In this paper *x*% v/v aqueous acetone denotes *x* ml. of water mixed with 100 − *x* ml. of acetone.

Analysis of the products disclosed high yields of olefin (Table 2) which varied with ring size rather as in the solvolysis of sulphonates [3] and halides.[4] This suggests that the olefin is produced either from a carbonium ion itself produced after the rate-determining stage (mechanism 2a), or from the acylium ion (mechanism 2b) which may be regarded alternatively as a stabilised carbonium ion. Olefin would not be produced by mechanism (3), since H–O fission is extremely fast compared with R–O fission and affords the alkyl hydrogen carbonate. This was found to give no olefin in neutral or acid conditions (see p. 1080).



Change in reactivity relative to the cyclohexyl compound, k/k_0, with ring size: (A, D) solvolysis of 1 chloro-1-methylcycloalkanes in 80% aqueous ethanol (Brown and Borkowski [4]); (B, E) acetolysis of cycloalkyl toluene-*p*-sulphonates (Brown and Ham [3]); (C, F) solvolysis of cycloalkyl chloroformates in 65% aqueous acetone, and in formic acid.

TABLE 2.

Amount (%) olefin formed at pH 6·0, determined by two methods.

	C_6H_7·CHMe	C_5	C_6	C_7	C_8
By bromination *	31·5, 30·8	36·7, 37·0	50·2,† 51·3	43·4,‡ 44·4	54·3, 58·7
By isolation	30	—	49	—	—

* Duplicate expts. † At pH 4·0. ‡ No buffer used.

(—)-1-Methylheptyl chloroformate, when hydrolysed at pH 7 in 85% aqueous acetone, gave (—)-1-methylheptanol. From the specific rotation, the reaction was found to proceed with 90·5% retention of configuration. Since a free carbonium ion with this structure normally leads to racemisation or predominant inversion,[7] the high degree of retention observed in the present case indicates that a carbonium ion is not formed in any stage of the reaction. The partial but high degree of retention is readily explained by simultaneous attack of water molecules on the alkyl and the acyl groups of the intermediate cation:

$$R^{*}O{\cdot}C^{+}{=}O \xrightarrow{H_2O} R^{*}O{\cdot}CO_2H + H^{+} \quad \text{(Retention)}$$

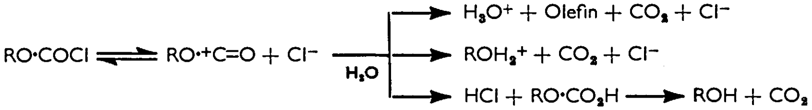
$$R^{*}{-}{}^{+}O{=}C{=}O \xrightarrow{H_2O} R^{*}OH + CO_2 + H^{+} \quad \text{(Inversion)}$$

It is interesting that this stereochemical result differs from that of formolysis.[1] The cause may lie in the different nucleophilic reactivities of water and formic acid, the less basic reagent reacting preferentially at the less electrophilic centre. (We have found[8] that reactions at the $C^{+}{=}O$ group are more sensitive to changes in the basicity of the nucleophile than are those at a saturated carbon atom.) The cause may, however, alternatively lie in the mode of decomposition of the mixed anhydride which could be formed in formic acid,[1] and no definite conclusion can yet be drawn.

The changes in optical activity also suggest that the reaction does not proceed by mechanism (3), since the formation of the alkyl carbonate would lead to complete retention of configuration.[9] It is possible that most of the reaction (~90%) proceeds by way of mechanism (3), and the remainder by bimolecular hydrolysis involving alkyl–oxygen fission, but this is unlikely since we have shown[10] that strong nucleophiles towards the saturated carbon atom (*e.g.*, I^{-} and CNS^{-}) are unreactive towards ethyl chloroformate. It follows *a fortiori* that a very weak nucleophile (water) would be very unreactive towards the less reactive secondary carbon atom.

The absence of a free carbonium ion is also shown by the products of solvolysis of *trans*-4-t-butylcyclohexyl chloroformate, in which the chloroformate group is in an equatorial position. It is well known that an E_2 elimination is greatly retarded when the leaving group assumes this configuration.[11] A similar stereochemistry will prevail in the acylium ion, so that olefin will be produced only if a carbonium ion is formed (mechanism 2a). No olefin was detected in the hydrolysates (aqueous acetone at pH 6·0), so that mechanisms (1) and (2a) may be discounted. The olefin which is found in the hydrolysates of the other chloroformates in which there is no conformational control is therefore produced by an E_2 mechanism on the acylium ion or on the original compound.

All these observations may be explained by assuming rate-determining formation of the acylium ion, followed by its rapid decomposition, *viz.*:



$$RO{\cdot}COCl \rightleftharpoons RO{\cdot}{}^{+}C{=}O + Cl^{-} \xrightarrow{H_2O} \begin{cases} H_3O^{+} + \text{Olefin} + CO_2 + Cl^{-} \\ ROH_2^{+} + CO_2 + Cl^{-} \\ HCl + RO{\cdot}CO_2H \longrightarrow ROH + CO_2 \end{cases}$$

The alternative possibility of simultaneous hydrolysis by mechanism (3) and bimolecular elimination (E_2), namely:

$$H_2O + Me{\cdot}CHR{\cdot}O{\cdot}COCl \longrightarrow H_3O^{+} + CH_2{:}CHR + CO_2 + Cl^{-}$$

---

[7] Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, New York, 1953, p. 386; Streitwieser, *Chem. Rev.*, 1956, **56**, 571.

[8] Hudson and Loveday, unpublished results.

[9] Garner and Lucas, *J. Amer. Chem. Soc.*, 1950, **72**, 5497.

[10] Green and Hudson, *Proc. Chem. Soc.*, 1959, 149.

[11] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.

is thought to be unlikely for the general reason given above in discussion of the optical activity changes. Bimolecular elimination and substitution of primary and secondary alkylating agents normally proceed at comparable rates in aqueous solution.[12] We have shown [10] that bimolecular displacement reactions at the saturated carbon atom of ethyl chloroformate are very slow compared with the alternative hydrolysis involving reaction at the carbonyl group. By analogy, therefore, bimolecular elimination should be very slow and unable to compete with the rate-determining ionisation (2b or 3) leading to the alcohol.

EXPERIMENTAL

Materials.—The following chloroformates were prepared by adding a solution of the corresponding alcohol (1 mol.) in ether to liquid carbonyl chloride (*ca.* 5 mol.) at −60°, the mixture being kept overnight at room temperature and then distilled: cyclopentyl, b. p. 65°/23 mm. (lit.,[13] b. p. 69—70·5°/25 mm.); cyclohexyl, b. p. 47°/4 mm. (lit.,[14] b. p. 38—44°/2 mm.); *cycloheptyl*, b. p. 46—48°/0·2 mm. (Found: C, 54·5; H, 7·5; Cl, 19·9. $C_8H_{13}ClO_2$ requires C, 54·5; H, 7·35; Cl, 20·0%); *cyclo-octyl*, b. p. 76—77°/0·2 mm. (Found: C, 57·0; H, 8·0; Cl, 18·7. $C_9H_{15}ClO_2$ requires C, 56·75; H, 7·85; Cl, 18·65%); trans-4-*t-butylcyclohexyl*, b. p. 76—77°/0·2 mm. (Found: C, 60·6; H, 8·8; Cl, 16·35. $C_{11}H_{19}ClO_2$ requires C, 60·6; H, 8·7; Cl, 16·25%); (−)-1-methylheptyl, b. p. 60—61°/5 mm. (lit.,[1] b. p. 60—61°/5 mm.), $[\alpha]_D^{22}$ −24·0° (homogeneous), from (−)-1-methylheptanol, $[\alpha]_D^{20}$ −10·5° (*c* 13·0 in MeOH).

trans-4-t-Butylcyclohexanol, m. p. 80·5—81° (lit.,[15] m. p. 81—82°), was prepared through the hydrogen phthalate, m. p. 145·5—146·5°, by the method of Winstein and Holness.[15]

Sodium cyclohexyl carbonate was prepared by passing carbon dioxide into a solution of sodium hydroxide (12 g.) in cyclohexanol (75 g.) until one equivalent had been absorbed. Dry ether (200 ml.) was added, and the product filtered off, washed with dry ether, and estimated acidimetrically (96% purity).

Kinetic Results.—The rates of solvolysis in formic acid were followed conductometrically by the method described previously,[16] a Phillips bridge of type GM 4249 with "magic-eye" detector being used. A given quantity of the chloroformate (1 ml.) was added from a safety-pipette to anhydrous formic acid (50 ml.) in the conductivity cell at the temperature of the thermostat. The conductivity was shown to be proportional to the concentration of hydrochloric acid produced over the concentration range employed, although small deviations were noted in very dilute solutions. The first-order rate constants given in Table 3 were obtained graphically from the relation $\log R_t/(R_t - R_\infty) = k_1t/2{\cdot}303 + \log R_0/(R_0 - R_\infty)$, where R_0, R_∞, and R_t are the measured resistances at the beginning and end of the reaction and at time t, respectively. The initial concentration was obtained from a calibration graph of $1/R_\infty$ against concentration.

TABLE 3.

Rates of solvolysis of chloroformate in formic acid at 24°.

Cyclo-alkyl	$1/R_\infty$	[Ester] (N)	10^4k_1 (sec.$^{-1}$)	Mean	Cyclo-alkyl	$1/R_\infty$	[Ester] (N)	10^4k_1 (sec.$^{-1}$)	Mean
(Pr^i) ……	11·70	0·0488	2·60	2·60	C_7 ……	9·52	0·0368	7·80	
C_5 ………	17·24	0·0673	3·64			8·93	0·0348	7·82	7·81
	10·75	0·0424	3·53	3·55	C_8 ……	8·00	0·0316	11·10	
	9·43	0·0372	3·48			5·88	0·0237	10·92	
C_6 ………	11·76	0·0468	4·98	5·02		5·63	0·0224	10·40	10·8
	9·61	0·0380	5·06			5·21	0·0217	11·10	

Two methods were used to follow the rates of reaction in aqueous acetone: (*a*) Samples (5 ml.) of the reaction mixture were titrated to lacmoid with a 0·01N-solution of triethylamine in acetone (30 ml.); the results for a pair of experiments were plotted on the same graph, and the rate constants given in Table 4 are the mean values.

---

[12] Ref. 7, p. 420.

[13] Nakanishi, Myers, and Jensen, *J. Amer. Chem. Soc.*, 1955, **77**, 3099.

[14] Saunders, Slocombe, and Hardy, *J. Amer. Chem. Soc.*, 1951, **73**, 3796.

[15] Winstein and Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562.

[16] Crunden and Hudson, *J.*, 1956, 501.

TABLE 4.

Rates of hydrolysis of chloroformates in aqueous acetone at 25°, followed acidimetrically.

Cyclo-alkyl	Concn. (N)	H_2O in $COMe_2$	10^4k_1 (sec.$^{-1}$)	Cyclo-alkyl	Concn. (N)	H_2O in $COMe_2$	10^4k_1 (sec.$^{-1}$)
C_5	0·013	50 g. in 100 ml.	1·22	C_5	0·0137	40% v/v	0·713
	0·0095				0·0114		
C_6	0·0114	,, ,,	1·60		0·0153	50% v/v	1·38
	0·0090				0·0143		
C_7	0·0097	,, ,,	2·24		0·0157	60% v/v	2·86
	0·0104				0·0129		
C_8	0·0098		3·47	C_6	0·0131	50% v/v	1·66
	0·0086				0·0113		
				C_7	0·0107		2·57
					0·0121		
				C_8	0·0094		3·91
					0·0087		

(*b*) In the faster runs the rates were followed colorimetrically by the Schoeneman method.[17] The reaction mixture (1 ml.) was added to the analytical reagent (23 ml.), and the mixture made up to 25 ml. The colour intensity was measured after 10 min. by means of a Unicam spectrophotometer, at 4350 Å. The concentration of chloroformate was obtained from a calibration curve. Results are in Table 5.

TABLE 5.

Rates of hydrolysis of chloroformates in 65% aqueous acetone at 25°, followed colorimetrically.

Ester	Concn. (10^{-3}N)	10^5k_1 (sec.$^{-1}$)	Ester	Concn. (10^3N)	10^5k_1 (sec.$^{-1}$)
Isopropyl	2·80	4·22	Cycloheptyl	3·36	10·1
	2·92	4·47		2·48	9·45
Cyclopentyl	2·97	4·97	Cyclo-octyl	1·78	14·73
	2·52	4·87		1·61	14·38
Cyclohexyl	2·88	6·82			

Estimations of Olefins.—(a) *By isolation*. Cyclohexyl chloroformate (6·55 g.) was boiled for 4 hr. with a M-phosphate buffer solution (100 ml.) of pH 6·0. The cold solution was extracted several times with ether and then fractionally distilled through a 12″ packed column, giving cyclohexene (1·61 g., 49%), b. p. 83°, n_D^{20} 1·4443 (lit.,[18] n_D^{22} 1·4450). In a similar experiment, (−)-1-methylheptyl chloroformate (4 g.) gave 0·7 g. (30%) of olefin.

(b) *By bromination*. The chloroformate (1 ml.) was boiled in a M-phosphate solution (100 ml.) of pH 6·0 for 30—40 min. The condenser was rinsed with carbon tetrachloride (20 ml.), and the cold mixture titrated to a pale-yellow end-point with a 0·1M-solution of bromine in carbon tetrachloride. A portion (10 ml.) was then acidified with 6N-nitric acid (3 ml.), and the chloride estimated by the Volhard method, with nitrobenzene to aid flocculation. This method was used because the chloroformate partially dissolves in the layer of olefin and alcohol produced, and the reaction does not always proceed to completion, even on prolonged boiling. Owing to the volatility of cyclopentene, a second condenser (−70°) was used. The results of the analyses are given in Table 2.

In six further experiments, weighed amounts of cyclohexyl carbonate (*ca.* 1·0 g.) were boiled with buffer solution (100 ml.) of pH 4·0 and then the mixture was analysed. No olefin was detected. A more acidic buffer was used owing to the alkalinity of the carbonate. The pH of the solution at the end of the reaction was 5—5·5. Similarly, no olefin was detected in the hydrolysates (pH 6·0) of *trans*-4-t-butylcyclohexyl chloroformate in three experiments.

CYANAMID EUROPEAN RESEARCH INSTITUTE, 91, ROUTE DE LA CAPITE,
COLOGNY, GENEVA, SWITZERLAND.
[*Received*, *July* 31*st*, 1961.]

---

[17] Marsh and Neale, *Chem. and Ind.*, 1956, 494.

[18] Brühl, *J. prakt. Chem.*, 1900, **49**, 240.