Neighboring Group Participation by Carbonyl Oxygen

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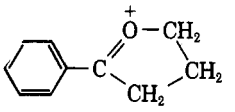
Participation by numerous functional groups in carbonium ion processes has received much attention. Notably lacking from the list of functional groups studied, and yet perhaps one of the more interesting with respect to the electronic factors involved, is the carbonyl group of simple ketones. The present study reveals that the silver ion assisted solvolysis of chloro ketones in 80% ethanol occurs with assistance from the carbonyl oxygen as evidenced by product and kinetic studies. This study indicates that the p–π bonding pair of electrons is not involved in the interaction in the transition state of the ionization process.

Introduction

Participation in solvolytic (SN1 processes) and nucleophilic displacements by a nucleophilic functional group within the reacting molecule, termed neighboring group participation, has been observed with many functional groups including singly and doubly bonded atoms.[1] Studies involving participation by functional groups containing a doubly bonded oxygen include neighboring acetoxyl[2] and benzamido[3] groups.

The participation by the carbonyl group of a ketone has not been subjected to a complete study although scattered reports have indicated that such a participation does occur. Oae[4] observed that bromo ketones in which the bromine was in the γ-position were remarkedly more reactive than the other homologs. Oae postulated that stabilization of the carbonium ion occurred by carbonyl oxygen participation as illustrated in **1**. A similar participation by a ketone carbonyl is apparent in the unimolecular solvolysis of the bromo ketone **2** in aqueous acetone to give the vinyl ether **3**.[5]



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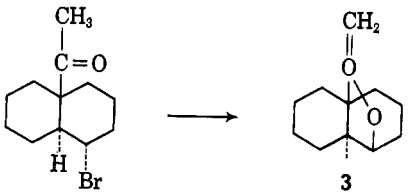
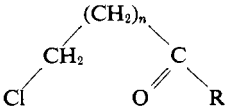


2 **3**

A number of nucleophilic displacements involving substituted ketones, in which the carbonyl group participates in the displacement, have been reported. In the majority of these cases the nucleophilic reagent adds to the carbonyl carbon–oxygen double bond and the oxide anion thus formed undergoes the nucleophilic displacement.[6] The participation by the carbonyl group in carbonium ion formation reactions and in pure nucleophilic displacement reactions is electronically two basically different processes. At the present time we will consider only the interaction of a carbonyl group with an incipient carbonium ion. The interaction of a carbonyl group with an incipient carbonium ion can occur in three possible manners. Electronically the carbonyl group is composed of a p–π bonding pair of electrons and highly s- and highly p-hybridized nonbonding pairs of electrons.[7] The highly s-hybridized nonbonding pair is firmly held, and would not be expected to take part in bond formation processes, whereas the highly p-nonbonding pair is much less firmly held.[7] Depending on the type of interaction, distinctly different cations could result, the differences being in the electron hybridization of the system. Whether or not a distinction can be made between the three possible modes of interaction on a chemical basis is a challenging problem. The present publication establishes the occurrence of neighboring group participation involving the carbonyl group of a ketone and sheds some light on the nature of this interaction although many questions still remain to be answered.

Discussion

Preparation of Starting Materials. A series of chloro ketones of the general structure **4** was prepared. Most of the synthetic sequences involve the use of well



4, R = isopropyl (n = 2,3,4); phenyl (n = 0–4); p-substituted phenyl (n = 4)

known reactions; however several synthetic steps will merit further discussion of the mechanisms involved at the end of this article.

3-Chloropropiophenone was prepared by the Friedel–Crafts acylation of benzene with β-chloropropionyl chloride.[8] 4-Chlorobutyrophenone and 5-chlorovalerophenone were prepared in a sequence of steps beginning with the acylation of benzene with succinic and glutaric anhydrides, respectively. The keto acids were converted to the corresponding ethyl esters and sub-

(1) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, Chapter 14.

(2) S. Winstein and R. E. Buckels, *J. Am. Chem. Soc.*, **64**, 2780, 2787 (1942); S. Winstein, H. V. Hess, and R. E. Buckels, *ibid.*, **64**, 2796 (1942); S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

(3) S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950); S. Winstein, R. Boschan, and L. Goodman, *ibid.*, **72**, 2311 (1950).

(4) S. Oae, *ibid.*, **78**, 4030 (1956).

(5) G. Baddeley, E. K. Baylis, B. G. Heaton, and J. W. Rasburn, *Proc. Chem. Soc.*, 451 (1961).

(6) M. L. Bender and M. S. Silver, *J. Am. Chem. Soc.*, **84**, 4589 (1962); L. I. Smith and J. R. Holum, *ibid.*, **78**, 3417 (1956); J. R. Holum, D. Jorenby, and P. Mattison, *J. Org. Chem.*, **29**, 769 (1964).

(7) R. S. Mulliken, *J. Chem. Soc.*, **3**, 564 (1935). See also G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 282.

(8) E. P. Kohler, *Am. Chem. J.*, **42**, 375 (1909).

Table I. Solvolysis Products of the Phenyl Chloro Ketones

4, R = phenyl	Recovered starting material, %	O ‖ $C_6H_5C(CH_2)_{n+1}OH$, %	O ‖ $C_6H_5C(CH_2)_{n+1}OC_2H_5$, %	$(CH_2)_n$ / CH_2 C OC_2H_5 / O C_6H_5, %
$n = 0$	23	...	51[a]	..
$n = 1$	..	33[b]	45[c]	..
$n = 2$	..	24[d]	...	47
$n = 3$[e]	15	17[f]	...	32
$n = 4$	16	52[g]	...	..

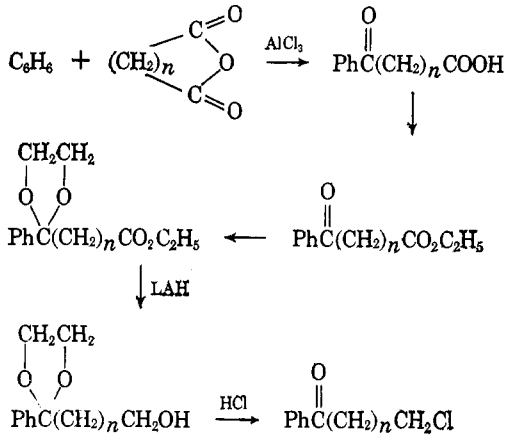
[a] Identified by its infrared spectrum (5.83 and 9.10 μ) and $n^{20}D$ 1.5255 ($n^{20}D$ 15250: N. E. Rigler and H. R. Henze, *J. Am. Chem. Soc.*, **58,** 475 (1936)). [b] Identified by conversion to the 2,4-dinitrophenylhydrazone with m.p. 187–189° (m.p. 189°: M. Ohara, K. Yamamoto, K. Kamitai, and K. Tanaka, Japanese Patent 17,716 (1961), *Chem. Abstr.*, **29,** 4599*h* (1962)). [c] Identified by conversion to the phenylhydrazone with m.p. 84–86° (lit.[8] m.p. 86°). [d] Identified by its infrared spectrum (2.92 and 5.93 μ) and m.p. of 32–33° (m.p. 32–33°: C. V. Chelintzev and E. D. Osetrova, *Compt. rend. acad. sci. URSS*, **2,** 251 (1935); *Chem. Abstr.*, **29,** 6223_8 (1935)). [e] In addition to the cited products a 15.6% yield of 6-phenyl-3,4-dihydro-2H-pyran was isolated with $n^{20}D$ 1.5708 and 2,4-dinitrophenylhydrazone with m.p. 142–144° ($n^{20}D$ 1.5700 and 2,4-dinitrophenylhydrazone, m.p. 145°: H. Normant, *Compt. rend.*, **231,** 909 (1950)). [f] Identified by its m.p. of 40–41° (m.p. 40–41°: F. S. Kipling and W. H. Perkin, *J. Chem. Soc.*, **57,** 311 (1890)) and 2,4-dinitrophenylhydrazone with m.p. 142–144°. [g] Identified by its m.p. of 32–33° (m.p. 32–34°: K. Kwant and R. T. Keen, *J. Am. Chem. Soc.*, **81,** 947 (1959)).

Table II. Solvolysis Products of the Isopropyl Chloro Ketones

4, R = isopropyl	Recovered starting material, %	O ‖ $i\text{-PrC}(CH_2)_{n+1}OH$, %	O ‖ $i\text{-PrC}(CH_2)_{n+1}OC_2H_5$, %	Cyclic enol ether, %
$n = 2$	25	25	10	8.5[a]
$n = 3$[b]	18	23	..	13.5[c]
$n = 4$	27	48	..	..

[a] This olefin appeared to be a mixture of 2-isopropyl-4,5-dihydrofuran and 2-isopropyl-2,5-dihydrofuran from its nuclear magnetic resonance spectrum. [b] An additional compound (8.3%) was isolated which is tentatively identified as 6-methyl-5-ketoheptyl nitrate. [c] This material had b.p. 135–138° with $n^{20}D$ 1.4377 (b.p. 142.5° and $n^{25}D$ 1.4308: J. Colonge and A. Girantel, *Compt. rend.*, **254,** 498 (1962)).

sequently to the ethylene ketal esters. Lithium aluminum hydride reduction produced the ketal alcohols which were converted to the desired chloro ketones on mild heating with hydrochloric acid. The final step in this sequence will receive further comment later in this article.



6-Chlorocaprophenone was prepared *via* rearrangement of 1-phenylcyclohexyl hypochlorite. The *para*-substituted 5-chlorovalerophenones were prepared by addition of the *para*-substituted phenylmagnesium bromides to 5-chlorovaleronitrile followed by hydrolysis of the imime and purification with Girard's T reagent.

2-Methyl-6-chloro-3-hexanone and 2-methyl-7-chloro-3-heptanone were prepared by rearrangement of dimethyl(2-tetrahydrofuranyl)- and dimethyl(2-tetrahydropyranyl)carbinol, respectively, in concentrated hydrochloric acid. 2-Methyl-8-chloro-3-octanone was prepared by rearrangement of 1-isopropylcyclohexyl hypochlorite.

Identification of Solvolysis Products. The above chloro ketones, excepting the *para*-substituted 5-chlorovalerophenones, were subjected to solvolysis in 80% by volume ethanol in the presence of silver nitrate. The products were separated by column chromatography and identified by comparison of physical properties with literature values, by their infrared and nuclear magnetic resonance spectra, and by comparison with authentic compounds. The results are presented in Tables I and II.

The isolation of the cyclic enol ethers in the cases of the aliphatic chloro ketones and the isolation of the cyclic ketals in the cases of the aromatic chloro ketones provides evidence for carbonyl–oxygen interaction during the ionization process. The formation of these products will be considered later in this article.

Kinetic Measurements and Mechanistic Interpretation of the Silver Ion Assisted Solvolysis of the Chloro Ketones. To facilitate the ionization process silver ion was added to the reaction solutions. Attempts to utilize silver nitrate and follow the disappearance of silver ion by the addition of a precipitation agent and back titration of this agent gave very erratic results. The use of silver perchlorate as the source of silver ion[9] with the titrimetric analysis of the perchloric acid formed in the reaction gave very satisfactory and reproducible second-order kinetic results. The reactions were protected from light, and no catalytic effect by the precipitated silver chloride was observed.

(9) M. F. Hawthorne and R. D. Strahm, *J. Am. Chem. Soc.*, **79,** 2515 (1957).

The rate constants were determined at three temperatures and are tabulated in Table III. The rate of solvolysis of **4** (R = isopropyl) decrease as n increases

Table III. Rates of Solvolysis of ω-Chloro Ketones with Silver Perchlorate in 80% Aqueous Ethanol

Compd.	$k \times 10^3$ l. mole^{-1} min.$^{-1}$ 25.00 ± 0.05°	40.00 ± 0.05°	56.20 ± 0.05°
n-Butyl chloride	...	...	0.211
2-Methyl-6-chloro-3-hexanone	8.55	31.6	114
	8.48[a]	...	...
	8.66[b]	...	...
2-Methyl-7-chloro-3-heptanone	0.195	0.978	4.54
2-Methyl-8-chloro-3-octanone	0.029	0.150	0.755
Phenacyl chloride	0.041	0.105	0.265
3-Chloropropiophenone	0.0499	0.321	1.66
4-Chlorobutyrophenone	9.13	38.8	161
5-Chlorovalerophenone	0.157	0.704	4.52
6-Chlorocaprophenone	0.041	0.159	0.567
4′,5-Dichlorovalerophenone	0.104	0.475	2.17
4′-Methyl-5-chlorovalerophenone	0.222	1.31	6.07
4′-Methoxy-5-chlorovalerophenone	0.299	1.84	8.29

[a] 2-Methyl-6-chloro-3-hexanone concentration was 0.0050 mole in 25 ml. of 80% aqueous ethanol. [b] 2-Methyl-6-chloro-3-hexanone concentration was 0.010 mole in 25 ml. of 80% aqueous ethanol. In each case the silver perchlorate concentration was kept at 0.00517 mole in 25 ml. of 80% aqueous ethanol.

from 2 to 4. This is as expected if the ionization process involves the formation of a cyclic intermediate, the ring sizes being 5-, 6-, and 7-membered, respectively. The solvolysis rates of the aliphatic chloro ketones are all greater than the rate of the silver ion assisted solvolysis of *n*-butyl chloride at 56.2°.

Two members of the more complete phenyl-substituted chloro ketone series require comment in greater detail. The over-all solvolysis rates increase as n goes from 0 to 2 and decreases as n then increases to 4, and are all greater than the solvolysis rate of *n*-butyl chloride at 56.2°. This rate enhancement is again consistent with neighboring group participation.

The relative rate (*n*-butyl chloride as 1.00) of the solvolysis of phenacyl chloride is 1.3. If no participation were possible, the rate of solvolysis would be expected to be drastically decreased due to the powerful inductive effect of the benzoyl group decreasing the stability of the carbonium formed during the ionization process. Oae has observed that the rate of mercuric ion assisted solvolysis of 2-bromoethylbenzene is less than one-half the rate of solvolysis of *n*-butyl bromide (see Table IV).[10] The net decrease in the rate of solvolysis of 2-bromoethylbenzene is due to a decrease caused by the inductive effect of the phenyl group (more appropriately for comparison the inductive effect of the benzyl group should be used) and an increase due to any phenyl participation which may have occurred. The greater inductive effect of the benzoyl group with respect to the benzyl group would be expected to cause a truly significant decrease in the rate of solvolysis of phenacyl chloride relative to *n*-butyl chloride. The observed relative rate of solvolysis of phenacyl chloride however is 1.3, indicating a very significant rate enhancement which can be attributed to carbonyl group participation. Further evidence in support for this view will be provided by the entropy of activation.

(10) S. Oae and C. A. Vanderwerf, *J. Am. Chem. Soc.*, **75**, 5038 (1953)

Table IV. Solvolysis of Alkyl Bromides with Mercuric Ion in 70% Aqueous Dioxane at 50°[a]

Compd.	$k \times 10^4$ l. mole^{-1} sec.$^{-1}$
n-Butyl bromide	11.2
2-Bromoethylbenzene	5.02
3-Bromopropylbenzene	4.48
4-Bromobutylbenzene	7.53
5-Bromopentylbenzene	7.87
6-Bromohexylbenzene	7.80

[a] See ref. 10.

The rate of solvolysis of 3-chloropropiophenone is consistent with an acceleration due to carbonyl group participation. However, the activation parameters indicate otherwise. The remaining members of the phenyl-substituted series are consistent with neighboring group participation.

The rate data presented in Table III was used to calculate the enthalpies and entropies of activation employing the Eyring equation.[11] These parameters along with the relative rate constants at 56.2° (*n*-butyl chloride as 1.00) are presented in Table V. In the

Table V. Comparison of Rates of Solvolysis of ω-Chloro Ketones with Silver Perchlorate in 80% Aqueous Ethanol at 56.2°

Compd.	Relative rate	ΔH^*, kcal./mole[a]	ΔS^*, e.u.
n-Butyl chloride	1.00	...	...
2-Methyl-6-chloro-3-hexanone	537	16.2	−18.2
2-Methyl-7-chloro-3-heptanone	21.5	18.7	−20.8
2-Methyl-8-chloro-3-octanone	3.6	19.3	−22.6
Phenacyl chloride	1.3	11.7	−45.3
3-Chloropropiophenone	7.9	20.9	−16.0
4-Chlorobutyrophenone	759	18.0	−15.8
5-Chlorovalerophenone	21.3	20.5	−20.4
4′,5-Dichlorovalerophenone	10.3	19.2	−20.5
4′-Methyl-5-chlorovalerophenone	28.7	19.4	−17.9
4′-Methoxy-5-chlorovalerophenone	39.2	19.0	−18.5
6-Chlorocaprophenone	2.7	19.1	−23.1

[a] The rate measurements were reproducible with a precision of better than 2%; in most cases the precision was approximately 1%. The probable error in the calculated activation parameters is therefore approximately ±0.4 kcal./mole and ±1.2 e.u. for the enthalpy and entropy of activation, respectively.

isopropyl chloro ketone series the entropy becomes more highly negative as one increases the ring size of the transition state from the five-membered ring (generally the ring formed with the least negative entropy) as expected. In the phenyl-substituted chloro ketone series the entropy of activation for phenacyl chloride (n = 0) is quite large, −45 e.u. The entropy

(11) S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 14.

of activation becomes less negative as the ring size of the transition state increases to the five-membered ring ($n = 2$) and then becomes more negative again as one approaches the seven-membered ring ($n = 4$).

The relatively large negative entropy of activation for phenacyl chloride indicates a highly ordered transition state. Comparison of the present values with those reported by Winstein[12] for the unimolecular solvolysis of methoxy brosylates of general structure **5** (see Table VI) reveals a greater difference in the entropy of activation for the first member of both series, 22 e.u., than for

Table VI. Activation Parameters Found for the Solvolyses of ω-Methoxy-1-alkyl *p*-Bromobenzenesulfonates in Absolute Ethanol[a]

Compd.	ΔH^*, kcal./mole	ΔS^*, e.u.
$CH_3(CH_2)_3CH_2OBs$	23.7	−17.4
$CH_3OCH_2CH_2OBs$	23.0	−22.1
$CH_3OCH_2CH_2CH_2OBs$	23.8	−17.9
$CH_3OCH_2(CH_2)_2CH_2OBs$	22.0	−10.4
$CH_3OCH_2(CH_2)_3CH_2OBs$	21.6	−15.1
$CH_3OCH_2(CH_2)_4CH_2OBs$	23.9	−16.4

[a] See ref. 12.

$$CH_3O(CH_2)_nCH_2OBs$$
5

the higher homologs of both series, approximately 5 to 7 e.u. This latter difference in the entropies of activation can be attributed to one, or both, of the two following factors. An increase in the entropy of activation should be apparent on going from a first-order solvolysis (Winstein's work) to a second-order assisted solvolysis (present work). This increase in the entropy of activation should remain reasonably constant throughout the entire series. The second factor is the effect on the entropy of activation due to the presence of a doubly bonded system (the carbonyl group, see later discussion on the mechanism) in the cyclic transition state. This effect should be relatively small in the larger membered rings but should be quite large in the smaller cyclic transition states. If one assigns the entire difference in the entropies of activation in the higher homologs as being due to the difference in kinetic order, this still leaves a 15–17-e.u. d fference to be rationalized in the phenacyl chloride solvolysis with respect to **5** ($n = 1$). Should the participation proceed *via* carbonyl oxygen interaction, a three membered transition state including a carbon–oxygen double bond is involved. This could wel. lead to the increase in the entropy of activation. Another equally reasonable explanation, at the present time, to explain this entropy of activation difference would be a more intimate involvement of a molecule of solvent by addition to the carbonyl group destroying the carbon–oxygen doubly bonded system. In this case the acceleration would be due to participation by this added molecule of solvent. At the present time a distinction cannot be made between these alternatives which are illustrated below.

The entropy of activation for the solvolysis of 3-chloropropiophenone is not wholly consistent with neighboring group participation by the carbonyl group. The expected entropy of activation should be decidedly more negative than the observed value of −16 e.u., perhaps in the −25 e.u. region. A more consistent mechanism for the silver ion assisted solvolysis of 3-chloropropiophenone might be described as a Lewis acid catalyzed (silver ion) α,β-elimination of HCl without involving the carbonyl oxygen. However it is not possible to completely rule out the partial operation of a participation mechanism on the basis of this evidence. The solvolysis products isolated from 3-chloropropiophenone are also consistent with this proposal as the initial product benzoylethylene is known to undergo a rapid addition of solvent.[8]

Although the products, solvolysis rates, and thermodynamic activation parameters all indicate participation by the carbonyl group in the transition state for the ionization in both the isopropyl and phenyl chloro ketone series, a more careful analysis of the rate data presented in Table III reveals an interesting fact. If one views the mechanism of the ionization process as proceeding *via* a transition state which might be naively described as **6**, a substantial rate increase of the phenyl chloro ketone solvolysis should be observed due to stabilization of the partial positive charge on the carbonyl carbon atom by interaction with the phenyl group. Inspection of the rate data presented in Table III shows that the phenyl chloro ketone series does *not* in general react at a rate greater than the isopropyl chloro ketone series. These data are *not* consistent with the direct p–π interaction, leading to a direct placement of the positive charge on the carbonyl carbon atom, or the substantial contribution of **6** to the transition state formed by involving s- or p-nonbonded pair interaction. It appears that **7** is the principal contributor to the transition state of the ionization process.

6 **7**

Additional evidence in support of the above statements is provided by the rate data for the *para*-substituted valerophenones. The Hammett plot of log k/k_0 does *not* correlate well at all with δ^+ (Figure 1) but does correlate quite well with δ (Figure 2). These facts also indicate that direct resonance stabilization of the transition state contributor **6** by the phenyl group does not occur and that the transition state is best described as **7**.

The difference between the observed and expected behavior of the phenyl chloro ketones cannot be ascribed to steric factors, by inspection of Dreiding models, in the transition state forcing the phenyl group out of the plane of the carbonyl group reducing the

(12) S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, 3, 1 (1958).

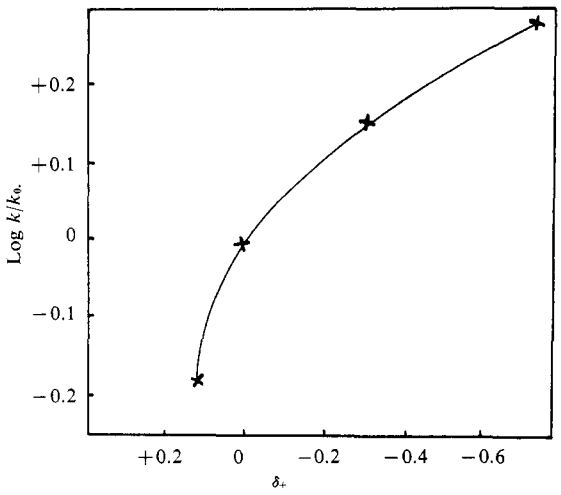


Figure 1. Solvolysis of *para*-substituted 5-chlorovalerophenones.

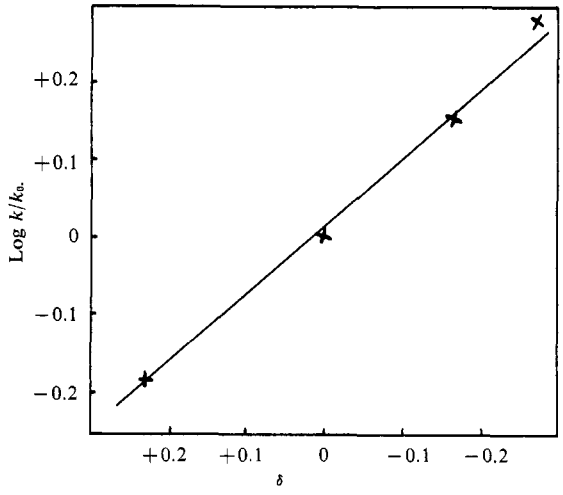
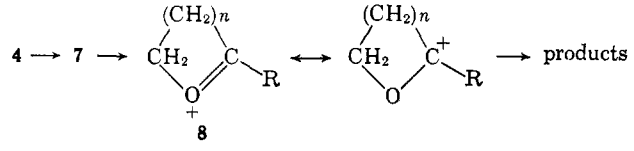


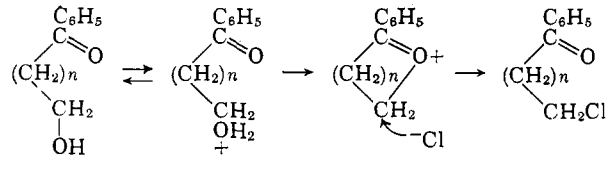
Figure 2. Solvolysis of *para*-substituted 5-chlorovalerophenones.

possibility of favorable overlap. Likewise the difference cannot be attributed to significant differences in the solvation of the transition states of the two series of chloro ketones. Differences in solvation should be reflected in the entropies of activation but inspection of Table V reveals that the values are nearly identical for each ring size.

The most consistent mechanism which can be put forward at the present time for the carbonyl group participation, except possibly in the case of phenacyl chloride, involves the initial formation of ion **8** *via* a transition state resembling **7** involving participation of one of the nonbonded pairs.



The mechanism involving the conversions of the ketal alcohols to the chloro ketones can be rationalized on the basis of carbonyl oxygen participation in the elimination of water. The first step of this over-all process must be the hydrolysis of the ketal alcohols to the keto alcohols. The conversion of the primary alcohol to the primary chloride under the relatively mild conditions employed (concentrated hydrochloric acid at 60° for 3 hr.) is not typical for the normal replacement of a primary hydroxyl by chlorine. The conversion is pictured as occurring *via* loss of water with carbonyl oxygen participation with subsequent attack by chloride on the cyclic cation. A similar mechanism can be written for the conversion of 2-methyl-6-hydroxy-3-hexanone to 2-methyl-6-ethoxy-3-hexanone in acidic ethanol. These reactions also demonstrate the synthetic utility possible with this type of reaction.



Experimental

Preparation of 3-Chloropropiophenone. To a mixture of 30 g. (0.22 mole) of aluminum chloride in 100 ml. of benzene at 0° was added 25.4 g. (0.20 mole) of 3-chloropropionyl chloride. The mixture was heated on a steam bath for 1 hr. and hydrolyzed with ice water. The hydrolyzed mixture was extracted with ether. The extract was washed with water and dried over magnesium sulfate. Evaporation of the solvent produced a solid which when recrystallized from petroleum ether (b.p. 30–60°) gave 3-chloropropiophenone (70%) with m.p. 56–57° (lit.[8] m.p. 57–58°).

Preparation of 4-Chlorobutyrophenone. 3-Benzoylpropionic acid was prepared by acylation of benzene with succinic anhydride in the presence of aluminum chloride.[13] The 3-benzoylpropionic acid (10 g.) was esterified in methanolic sulfuric acid (15 ml. of concentrated sulfuric acid in 300 ml. of methanol) at reflux for 1 hr. The reaction mixture was cooled and added to 800 ml. of water and extracted with ether. The extract was washed with 10% sodium bicarbonate and dried, and the solvent was removed. Distillation of the residue gave 8.8 g. (82%) of methyl 3-benzoylpropionate, b.p. 138–140° at 2.2 mm. and n^{20}D 1.5255 (lit.[14] b.p. 119–120° at 0.4 mm. and n^{20}D 1.5260).

Methyl 3-benzoylpropionate (9.0 g., 0.038 mole), ethylene glycol (6.2 g., 0.10 mole), and *p*-toluenesulfonic acid (0.5 g.) were placed in 150 ml. of benzene and refluxed until an equivalent amount of water had been collected in a Dean–Stark trap. The reaction mixture was cooled, washed with 10% sodium bicarbonate, and dried over sodium sulfate. The benzene was removed under reduced pressure leaving a viscous liquid (single carbonyl band at 5.75 μ) which was not purified but was used directly in the next step.

An ethereal solution of the ketal ester was added dropwise to a suspension of 2.22 g. (0.06 mole) of lithium aluminum hydride in 100 ml. of ether. The reaction mixture was stirred at room temperature for 8 hr. and hydrolyzed with water. The ether layer was removed and the ether was evaporated. The crude ketal alcohol was heated at 60° with 35 ml. of con-

(13) L. F. Sommerville and C. F. Allen, *Org. Syn.*, **13**, 12 (1933).
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centrated hydrochloric acid for 3 hr. After cooling, the reaction mixture was extracted with ether. The ether extract was washed with 10% sodium bicarbonate and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was distilled giving 4.0 g. (58% over-all) of chlorobutyrophenone (5.92 μ), b.p. 106–107° at 1.1 mm. and $n^{20}D$ 1.5488.

Anal. Calcd. for $C_{10}H_{11}ClO$: C, 65.75; H, 6.07; Cl, 19.41. Found: C, 66.08; H, 6.08; Cl, 19.23.

Preparation of 5-Chlorovalerophenone. 4-Benzoylbutyric acid was prepared as described above with m.p. 124–125° (lit.[15] m.p. 125–126°). The acid was esterified as described above giving methyl 4-benzoylbutyrate, b.p. 135–136° at 1.8 mm. (lit.[16] b.p. 147–148 at 8 mm.).

The methyl 4-benzoylbutyrate was converted to the ketal and reduced with lithium aluminum hydride. The ketal alcohol was heated at 60° with hydrochloric acid for 3 hr. giving 5-chlorovalerophenone (14.5% overall) with m.p. 48–49° from petroleum ether (lit.[17] m.p. 49–50°).

Preparation of 4'-Methoxy-5-chlorovalerophenone. To an ethereal solution of *p*-methoxyphenylmagnesium bromide (prepared from 27 g. (0.12 mole) of *p*-methoxybromobenzene and 2.4 g. (0.10 mole) of magnesium in 200 ml. of ether) was added 11.2 g. (0.10 mole) of 5-chlorovaleronitrile in 50 ml. of ether. The reaction mixture was stirred at room temperature for 10 hr. and hydrolyzed by the addition of 200 ml. of 15% hydrochloric acid. The ether layer was decanted and the aqueous layer was washed with ether. The ether layers were combined and washed with 10% sodium bicarbonate and dried over sodium sulfate. Removal of the ether gave an oily substance which was dissolved in 95% ethanol (150 ml.) and treated with Girards' T reagent (12.0 g.) and acetic acid (5 ml.) and refluxed for 2 hr. The mixture was cooled and poured into 500 ml. of water and washed with 200 ml. of ether. The aqueous layer was heated on a steam bath for 15 min. with 50 ml. of concentrated hydrochloric acid. After cooling, the reaction mixture was extracted with ether. The ether extract was washed with 10% sodium bicarbonate and dried over sodium sulfate. Removal of the ether gave a solid material which on recrystallization from petroleum ether gave 4.4 g. (17.7%) of 4'-methoxy-5-chlorovalerophenone, m.p. 82–84°.

Anal. Calcd. for $C_{12}H_{15}ClO$: C, 63.57; H, 6.67; Cl, 15.64. Found: C, 63.62; H, 6.53; Cl, 15.73.

Preparation of 4',5-Dichlorovalerophenone. Using the above described procedure, *p*-chlorophenylmagnesium bromide and 5-chlorovaleronitrile gave 4',5-dichlorovalerophenone (29.6%) as a yellowish liquid with b.p. 140–142° at 0.8 mm., $n^{20}D$ 1.6981.

Anal. Calcd. for $C_{11}H_{12}Cl_2O$: C, 57.16; H, 5.24; Cl, 30.68. Found: C, 56.94; H, 5.43; Cl, 30.69.

Preparation of 4'-Methyl-5-chlorovalerophenone. To an ethereal solution of 4-methylphenylmagnesium bromide (prepared from 60.0 g. (0.35 mole) of *p*-bromotoluene and 7.2 g. (0.30 g.-atom) of magnesium in 400 ml. of ether) was added 25.4 g. (0.30 mole) of cyclopentanone. The mixture was stirred at room temperature for 3 hr. and hydrolyzed with saturated ammonium chloride solution. The ether layer was decanted and dried over sodium sulfate. After distilling off the ether the 1-*p*-tolylcyclopentanol (67%) was distilled at 110–112° at 1.0 mm., $n^{20}D$ 1.5510 (lit.[18] b.p. 98–99° at 0.2 mm., $n^{18}D$ 1.5518).

To a mixture of 35.6 g. (0.20 mole) of 1-*p*-tolylcyclopentanol and 800 ml. of 0.75 *M* sodium hypochlorite at 0° was added a solution of 80 ml. of glacial acetic acid in 60 ml. of carbon tetrachloride. The mixture was stirred at 0° for 6 hr. The carbon tetrachloride layer was removed and the aqueous layer was extracted three times with carbon tetrachloride. The extracts were combined and washed with 10% sodium bicarbonate and dried over magnesium sulfate.

The carbon tetrachloride layer was refluxed under nitrogen for 12 hr., during which time nitrogen was continually bubbled through the solution. The solvent was removed by distillation and the brown oily residue was taken up in petroleum ether and treated three times with Norit. Upon cooling a white solid precipitated which on recrystallization from petroleum ether gave 4'-methyl-5-chlorovalerophenone (25%) with m.p. 75–76° (lit.[19] m.p. 75–76°).

Preparation of 6-Chlorocaprophenone. 6-Chlorocaprophenone was prepared as described for 4'-methyl-5-chlorovalerophenone *via* 1-phenylcyclohexyl hypochlorite with m.p. 29–30° (lit.[17] 29–30°) in 59% yield.

Preparation of 2-Methyl-6-chloro-3-hexanone. To a solution of 102 g. (1.00 mole) of tetrahydrofuran-2-methanol in 500 ml. of reagent grade acetone at 0° was slowly added a solution of 125 g. (1.25 mole) of chromium trioxide in sufficient 30% sulfuric acid. After stirring for 5 hr. the reaction mixture was poured into 1000 ml. of water and extracted with four 200-ml. portions of ether. The extract was dried over sodium sulfate and the solvent was removed by distillation. Distillation of the residue gave 38 g. (29%) of tetrahydrofuran-2-carboxylic acid with b.p. 97–100° at 1.05 mm., $n^{22}D$ 1.4626 (lit.[20] b.p. 131° at 14 mm., $n^{19}D$ 1.4585).

Tetrahydrofuran-2-carboxylic acid was esterified in acidic ethanol, as described for 3-benzoylpropionic acid, giving ethyl 2-tetrahydrofurancarboxylate, b.p. 80° at 2.5 mm., $n^{21}D$ 1.4441 (lit.[21] 51° at 1 mm., $n^{18}D$ 1.4455).

Ethyl 2-tetrahydrofurancarboxylate was converted to dimethyl-2-tetrahydrofuranylcarbinol, by treatment with methylmagnesium iodide in ether, with b.p. 46–48° at 4.0 mm. and $n^{25}D$ 1.4445 (lit.[22] b.p. 32° at 0.6 mm. with $n^{25}D$ 1.4482).

A mixture of dimethyl-2-tetrahydrofuranylcarbinol (5 g., 0.0385 mole) and concentrated hydrochloric acid (40 ml.) was heated at 60° for 3 hr. After cooling, 10 ml. of saturated sodium chloride was added and the mixture was extracted with ether. The extract was washed with 10% sodium bicarbonate and dried over

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sodium sulfate. The ether was removed by distillation and the product, 2-methyl-6-chloro-3-hexanone (74%) was purified by distillation at 82° at 0.55 mm., $n^{25}D$ 1.4243. The infrared displayed carbonyl absorption at 5.87 μ.

Anal. Calcd. for $C_7H_{13}ClO$: C, 56.62; H, 8.81; Cl, 23.76. Found: C, 56.67; H, 8.86; Cl, 23.72.

Preparation of 2-Methyl-7-chloro-3-heptanone. Tetrahydropyran-2-methanol was oxidized as above giving tetrahydropyran-2-carboxylic acid with b.p. 91–93° at 0.55 mm., $n^{20}D$ 1.4661 (lit.[23] b.p. 110° at 5 mm. with $n^{20}D$ 1.4665).

Methylation of ethyl 2-tetrahydropyranylcarboxylate with methylmagnesium iodide, as described above, gave dimethyl(2-tetrahydropyranyl)carbinol with b.p. 54° at 2.4 mm. and $n^{25}D$ 1.4490.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.19. Found: C, 66.44; H, 11.43.

A mixture of 5.0 g. (0.034 mole) of dimethyl(2-tetrahydropyranyl)carbinol and 30 ml. of concentrated hydrochloric acid was heated at 65° for 4 hr. Distillation of the crude product, following work-up as described above, gave 2-methyl-7-chloro-3-hexanone with b.p. 40° at 1.8 mm., $n^{25}D$ 1.4565. The infrared spectrum displayed carbonyl absorption at 5.83 μ.

Anal. Calcd. for $C_8H_{15}ClO$: C, 59.06; H, 9.29. Found: C, 58.93; H, 9.32.

Preparation of 2-Methyl-8-chloro-3-octanone. 1-Isopropylcyclohexanol was prepared by treatment of cyclohexanone with isopropylmagnesium bromide, giving b.p. 81–83° at 20 mm., $n^{20}D$ 1.4681 (lit.[24] b.p. 76–78° at 18 mm. with $n^{20}D$ 1.4683).

1-Isopropylcyclohexanol was converted to the corresponding hypochlorite and rearranged to 2-methyl-8-chloro-3-octanone (14.5%) as described for 4′-methyl-5-chlorovalerophenone, with b.p. 79° at 0.75 mm., $n^{25}D$ 1.4571. The infrared spectrum displayed carbonyl absorption at 5.82 μ.

This material decomposed on standing or if left open in air. The material was freshly distilled before use in the kinetic runs.

Reaction of Chloro Ketones with Silver Nitrate in 80% Ethanol. The chloro ketone and silver nitrate (approximately 10% excess of the latter) in 80% by volume ethanol was heated at 60° for varying lengths of time depending on the observed rate of reaction. The reaction mixtures were poured into saturated aqueous calcium chloride and extracted with ether. The extracts were dried over sodium sulfate and the solvent was removed under reduced pressure. The product mixture was separated by chromatography on activated alumina. The product analyses are given in Tables I and II. The products were identified by comparison with physical constants reported in the literature or by characterization or preparation of authentic compounds described as follows.

2-Phenyl-2-ethoxytetrahydrofuran. 2-Phenyl-2-ethoxytetrahydrofuran was purified by molecular distillation under reduced pressure. The infrared spectrum was transparent in the 2–3- and 5–6-μ regions. The nuclear magnetic resonance spectrum (n.m.r.) displayed a triplet and distorted quartet at τ 8.98 and 6.05, respectively, characteristic of the ethoxyl group.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.78; H, 8.55.

2-Phenyl-2-ethoxytetrahydropyran. 2-Phenyl-2-ethoxytetrahydropyran was purified by molecular distillation, $n^{23}D$ 1.4728. The infrared spectrum was transparent in the 2–3- and 5–6-μ regions. The n.m.r. spectrum indicated the presence of an ethoxyl group with a triplet at τ 8.86 and multiplet at 6.30.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.66; H, 8.91.

2-Methyl-6-hydroxy-3-hexanone. A mixture of dimethyl-2-tetrahydrofuranylcarbinol (5 g., 0.0385 mole) and 20% sulfuric acid (30 ml.) were heated at 65° for 7 hr. The mixture was saturated with sodium sulfate and extracted with ether. The extract was dried over potassium carbonate and the solvent was removed under reduced pressure. Distillation of the residue gave 3.5 g. (70%) of methyl-6-hydroxy-3-hexanone, b.p. 82° at 2.4 mm. with $n^{20}D$ 1.4419. The infrared spectrum displayed peaks at 2.80 and 5.83 μ.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.57; H, 10.84. Found: C, 64.81; H, 10.88.

2-Methyl-6-ethoxy-3-hexanone. 2-Methyl-6-hydroxy-3-hexanone (1.0 g., 0.0087 mole) was dissolved in 40 ml. of absolute ethanol. Sulfuric acid (10 ml.) was added and the reaction mixture was heated at 60° for 13 hr. The reaction mixture was poured into 50 ml. of water and extracted with ether. The extract was washed with 10% sodium bicarbonate and dried over magnesium sulfate. The ether was removed by distillation and the residue was distilled giving 1.43 g. (79%) of 2-methyl-6-ethoxy-3-hexanone with b.p. 68° at 4.3 mm., $n^{25}D$ 1.4162. The infrared spectrum showed strong bands at 5.79 and 9.00 μ. The n.m.r. showed, in part, the presence of an ethoxy group with triplet at τ 8.79 and a quartet at 6.56.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.62; H, 11.18. Found: C, 66.59; H, 11.09.

Procedure for Measurement of the Reaction Rates. Standard solutions of the chloro ketone (0.0025 mole in 50 ml.) and silver perchlorate (0.0057 mole in 25 ml.) in 80% by volume ethanol were prepared. Aliquots of the chloro ketone solution (5 ml.) and silver perchlorate solution (2.5 ml.) were placed in an ampoule. The ampoule was sealed, wrapped in aluminum foil, and placed in a constant-temperature bath. Ampoules were periodically removed and their contents were emptied into a beaker containing 25 ml. of benzene. The ampoule was washed several times, the washings being added to the beaker. The amount of free perchloric acid present was titrated with standard sodium hydroxide using a Beckman Model 42 glass electrode, standard Beckman calomel, and Model G pH meter.

Acknowledgment. The authors wish to acknowledge the National Science Foundation for financial support of this work (Grant G-24084).

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