is 18.8 ± 0.2 with a maximum deviation of 0.6 kcal mol^{-1}. Clearly within experimental error $\Delta H^{\pm}$ is the same for all esters investigated. Inspection of the values of $T\Delta S^{\pm}$ in Table III reveals that the largest value of $\Delta(T\Delta S^{\pm})$ is 3.2 kcal mol^{-1} which compares favorably to the largest value of $\Delta\Delta F^{\pm}$ of 3.0 kcal mol^{-1} (at 25° $\Delta F^{\pm}$ = 20.3 kcal mol^{-1} for R, R′ = Ph, Ph; Me, *i*-Pr; and Ph, Et and $\Delta F^{\pm}$ = 23.3 kcal mol^{-1} for R = R′ = H). These considerations lead to the conclusion that changes in $\Delta F^{\pm}$ are, within experimental error, primarily attributed to steric effects on $T\Delta S^{\pm}$. The relative constancy of the values of $\Delta H^{\pm}$ compared to the steric dependence of $T\Delta S^{\pm}$ is as anticipated if one assumes that the former reflects potential energy and the latter kinetic energy parameters.[13]

(13) This is a certain oversimplification since $\Delta H^{\pm}$ possesses both potential and kinetic energy terms, whereas $\Delta S^{\pm}$ is composed of only kinetic energy terms. See R. W. Taft, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp 556–675.

A comparison of the values of $T\Delta S^{\pm}$ for the hydrolysis of the 11 mono-*p*-bromophenyl glutarate esters (Table III) to the values established for carboxyl general base catalyzed reactions reveals that the former are greater by ~5 kcal mol^{-1}. The smaller values of $T\Delta S^{\pm}$ for the general base mechanisms are as expected for the inclusion of water molecules in the transition state. No evidence exists, therefore, that general base catalysis is an important mechanism for the hydrolysis of phenyl glutarates. It should be noted that care should be taken in assigning mechanisms on the basis of $T\Delta S^{\pm}$ values alone since it is an established fact that these values are not only a function of steric effects but are markedly dependent on the electronic nature of the leaving phenolate anion.[5,11] In this study the leaving group has been held constant.

Acknowledgment. This work was supported by a grant from the National Institutes of Health.

Carbonyl Participation in the Solvolysis of Ketone Derivatives. The Observation and Isolation of Intermediates[1]

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Abstract: The solvolyses of γ- and δ-keto-*p*-bromobenzenesulfonates in formic or trifluoroacetic acid proceed with participation of the carbonyl through intermediates which have been directly observed by nmr. The rates of formation of these intermediate oxonium ions (**1** and **13**) have been measured for 4-(*p*-bromobenzenesulfonoxy)-butyrophenone (1.9×10^{-2} sec^{-1}, 30°) and 5-(*p*-bromobenzenesulfonoxy)valerophenone (4.9×10^{-4} sec^{-1}, 30°). The hexachloroantimonate salt of **1** has been isolated and found to be stable to 120°. The relative shifts in the nmr spectra of these intermediate ions compared to model compounds indicate that most of the positive charge resides on oxygen. Intermediates have not been observed for β- or ε-keto-*p*-bromobenzenesulfonates.

There has been much concern in the recent literature about the intramolecular effect of nonbonding and π-bonding electron pairs on the formation of carbonium ions. Examples of this effect include the participation of olefinic bonds[2] and of carbonyl oxygen[3-5] in solvolytic reactions of halides and sulfonates. The evidence for participation commonly includes an acceleration in the solvolysis rate, when compared to a similar system where such participation cannot occur, and the observation of rearranged products which would result from the interaction of the neighboring group with the potential charge center. For example, the solvolyses of several halo ketones have been shown to proceed faster than the normal alkyl halides,[3,4] even though the carbonyl group would be expected to inductively retard the reaction. In addition, in the same systems, rearranged products which could arise from participation have been observed.[4] The results of these studies, by Oae[3] and by Pasto and Serve,[4] are summarized in Table I.

Table I. Relative Rates of Solvolysis of Halo Ketones

	Relative rate	
	Cl[a]	Br[b]
n-Butyl halide	1.00	1.00
Phenacyl halide	1.3	0.055
3-Halopropiophenone	7.9	0.31
4-Halobutyrophenone	759.0	71.1
5-Halovalerophenone	21.3	
6-Halocapriophenone	2.7	

[a] The reaction of chloro ketones with silver perchlorate in 80% aqueous ethanol at 56.2°.[4] [b] The reaction of bromo ketones with mercuric nitrate in weakly acidic dioxane at 40.05°.[3]

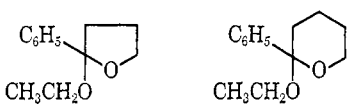
The most striking facet of these data is that the 4-halobutyrophenones are by far the most reactive of both series. Both research groups suggested that there is a participation of the carbonyl oxygen which assists

(1) Parts of this work were published as a preliminary communication: H. R. Ward and P. D. Sherman, Jr., *J. Am. Chem. Soc.*, **89**, 4222 (1967).
(2) See P. D. Bartlett, S. Bank, R. J. Cranford, and G. H. Schmid, *ibid.*, **87**, 1288 (1965).
(3) S. Oae, *ibid.*, **78**, 4030 (1956).
(4) D. J. Pasto and M. P. Serve, *ibid.*, **87**, 1515 (1965).
(5) O. K. J. Kovacs, G. Schneider, L. K. Lang, and J. Apjok, *Tetrahedron*, **23**, 4186 (1967).

the solvolysis, forming an intermediate of the following type.[3,4]

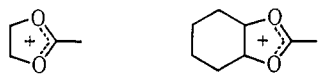
1a 1b

For the homologous ketones, intermediates of the same sort, but of lower stability, were proposed to explain their slightly accelerated rates. Support for such intermediates in the ethanolysis of chloro ketones was provided by the isolation of products which would result from the attack of the solvent at the 2 carbon of the intermediate, to give compounds **2** and **3**.



2 3

Neighboring group assistance has been shown to occur with the carbonyl oxygen of esters as well.[5-7] In two cases an intermediate acetoxonium ion actually was isolated. The ethyleneacetoxonium salt **4** was isolated by Meerwein as the tetrafluoroborate.[6] Later



4 5

Winstein and his coworkers[7] isolated the cyclohexeneacetoxonium tetrafluoroborate salt **5**. The cation **5** had been postulated as an intermediate in the solvolysis of *trans*-2-acetoxycyclohexyl bromide in order to explain the unusual retention of configuration which was observed. The isolation of **5** provided final proof of its intermediacy in the reaction scheme.[7]

This paper will serve to describe the observation and isolation of intermediates in the solvolysis of ketosulfonate esters in strongly acidic solvents.

Results and Discussion

During the course of the investigation of the formolysis of 4-(*p*-bromobenzenesulfonoxy)-1-phenylbutyne (**6**), several peaks were observed in the nmr spectrum of the reaction solution which initially could not be explained.[8] The peaks were related by nmr decoupling and integration of the peak areas and had the following chemical shifts: τ 4.29 (triplet), 5.78 (triplet), and 7.25 (pentuplet), all of equal areas.[9] The peaks appeared to be the absorption spectrum of a species **8** which was formed from the enol esters **7** of the butyne, for they increased with the decrease of the enol ester absorption. In the absence of pyridine or sodium formate buffer and with added strong acid, such as benzenesulfonic acid, the species **8** could be formed to the extent of about 50% of **6**. The addition of pyridine to this solution caused an immediate disappearance of **8** and the formation of peaks corresponding to 4-formoxybutyrophenone (**9**).

(6) H. Meerwein, V. Hederick, H. Morschel, and K. Wunderlich, *Ann.*, **635**, 1 (1960).

(7) C. B. Anderson, E. C. Friedrich, and S. Winstein, *Tetrahedron Letters*, 2037 (1963).

(8) H. R. Ward and P. D. Sherman, Jr., *J. Am. Chem. Soc.*, **89**, 1962 (1967).

(9) Only the aliphatic portion of the molecule is represented here. The absorption of the aromatic protons is obscured by the solvent absorption.

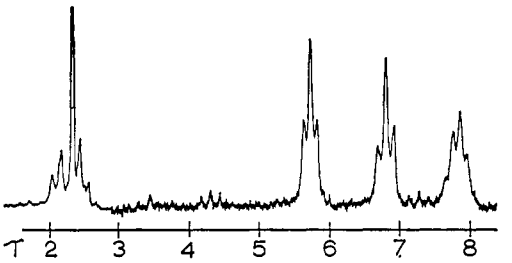
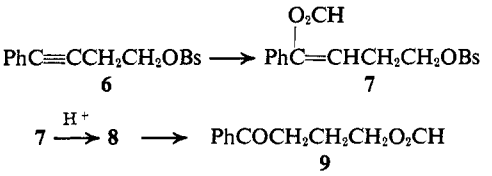


Figure 1. The nmr spectrum of **10** dissolved in trifluoroacetic acid at −10°.

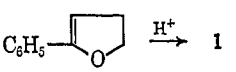
To test the source of the downfield absorption (τ 4.29) of **8**, the solvolysis was performed in deuterioformic acid (both d_1 and d_2). As expected the absorption of the α protons of **9** did not appear and the multiplet at



τ 7.85 became a slightly broadened triplet. The protons on the 4 carbon remained unchanged. In the spectrum of **8**, however, the low-field triplet at τ 4.29 remained unchanged while the pentuplet at τ 7.25 became a broadened triplet. It was the triplet at τ 5.78 which disappeared. This demands that the low-field absorption in **8** must be assigned to the protons on the 4 carbon.

Because the formation of enol esters in this system was established, and because conversion of enol esters to the corresponding ketones is a known reaction,[10] 4-(*p*-bromobenzenesulfonoxy)butyrophenone (**10**) was synthesized and subjected to the conditions of formolysis. Based on the nmr spectrum, **8** was formed to the extent of 85%. When **10** was dissolved in trifluoroacetic acid at about −10°, the spectrum of the *p*-bromobenzenesulfonate was observed (Figure 1). However, on standing at the same temperature for 3 hr, **8** was completely formed.[11] A spectrum taken immediately after solution of **10** in trifluoroacetic acid at room temperature shows a quantitative formation of **8** (Figure 2). The remarkable nmr downfield shifts of the absorption of the protons on the 4 carbon of **8** coupled with the literature hypothesis of a cyclic intermediate in the solvolysis of keto halides[3,4] led to the assignment of **1** as the structure of the species **8**.

The cyclic nature of the intermediate was confirmed by solvolyzing a compound which already contained the furan-like ring. 2-Phenyl-4,5-dihydrofuran (**11**) was synthesized and dissolved in trifluoroacetic acid. The ring was expected to protonate at the 3 carbon giving **1** directly, and, in fact, **1** was formed in about 50% conversion.



11

(10) P. E. Peterson and J. E. Duddey, *J. Am. Chem. Soc.*, **88**, 4990 (1966).

(11) The measurement of the temperature in the nmr probe is quite crude. As a consequence, the value for the rate of formation of **8** as reported earlier[1] is in error.

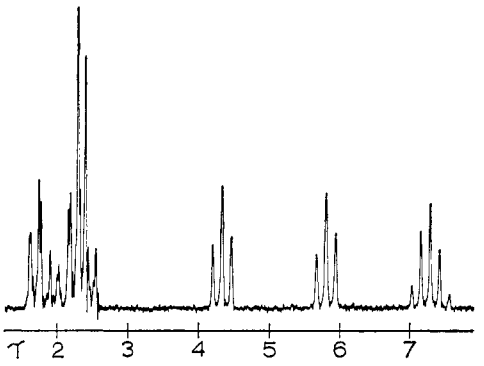


Figure 2. The nmr spectrum of the intermediate oxonium ion **8** formed from 4-(*p*-bromobenzenesulfonoxy)butyrophenone dissolved in trifluoroacetic acid at *ca.* 40°.

The chemical shifts of the various methylene absorptions of **1** should provide an approximate measure of the electron density on that methylene, if an appropriate model can be found for comparison. The shifts, relative to the starting material, are the greatest for the proton absorption of the 4 carbon, 1.6 ppm. The 2-carbon proton absorption is shifted by only 1.0 ppm. A better model for the 4-carbon protons may be tetrahydrofuran or 2-phenyl-4,5-dihydrofuran, which have chemical shifts of τ 6.40 and 6.2, respectively. The shifts of the intermediate **1** relative to these compounds are 1.9 and 2.1 ppm, a more pronounced deshielding effect. The deshielding effect of the positive charge is thus greatest for the protons on the carbon bonded to oxygen of the intermediate indicating greater charge density there than at the 1 carbon of the two resonance forms, **1a** and **1b**. A similar conclusion was reached by Olah in the examination of the protonation of aliphatic ketones.[12] There is also a substantial shift of the aromatic proton absorption of **1**. Part of the absorption occurs as low as τ 1.55, a minimum shift of 0.35 ppm from the starting ketone **10**, indicating some delocalization of the charge into the ring.

Other Systems. The observation of an oxonium ion intermediate in the butyrophenone solvolysis encouraged a search for similar intermediates in the solvolysis of homologous ketones. The criterion used for the presence of an oxonium ion was the appearance of a peak in the nmr spectrum of the solvolysis reaction mixture corresponding to protons on carbon next to a positive charge. The chemical shift of such protons is expected to be in the vicinity of τ 4.3, as observed with the butyrophenone intermediate.

A series of homologous ketosulfonate esters **12** were prepared and subjected to the trifluoroacetolysis. Phenacyl bromide was exposed to the same solvolysis

$$\mathrm{RCO(CH_2)_nOBs}$$
12a, R = C_6H_5, n = 2, 4, 5
b, R = CH_3, n = 3

conditions, but no reaction was observed. The phenyl ketones **12a** (n = 2 and 5) solvolyzed to form the corresponding trifluoroacetates with no observable intermediate formation. However, 5-(*p*-bromobenzenesulfonoxy)valerophenone (**12a**) (n = 4) and 5-(*p*-bromobenzenesulfonoxy)-2-pentanone (**12b**) (n = 3) both produced intermediates in high yield, **13** and **14** (Figures 3 and 4). These intermediates, although formed extensively, decomposed to give trifluoroacetates quite rapidly, in contrast to the extremely stable **1**. The absence of the spectrum of an intermediate from the other ketones does not preclude the existence of one, but merely indicates that if it is formed, its formation is at a slower rate than its decomposition to the trifluoroacetates.

(12) G. A. Olah, M. Calin, and D. H. O'Brien, *J. Am. Chem. Soc.*, **89**, 3586 (1967).

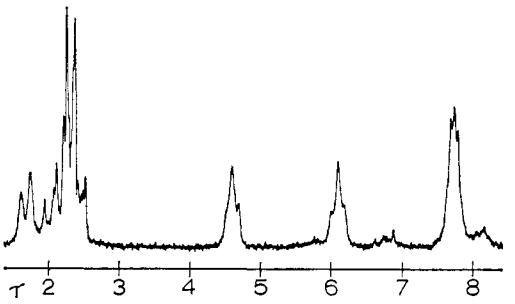


Figure 3. The nmr spectrum of the intermediate oxonium ion **13** formed from 5-(*p*-bromobenzenesulfonoxy)valerophenone dissolved in trifluoroacetic acid at *ca.* 40°.

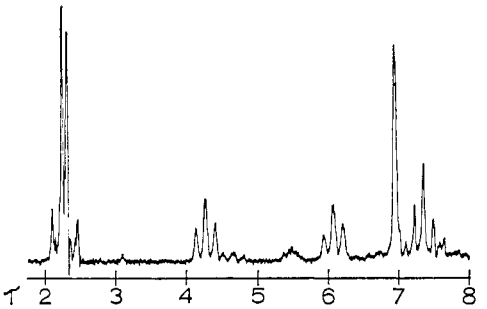
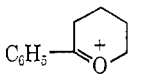
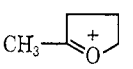


Figure 4. The nmr spectrum of the intermediate oxonium ion **14** formed from 5-(*p*-bromobenzenesulfonoxy)-2-pentanone dissolved in trifluoroacetic acid at *ca.* 40°.



13



14

Isolation. The relatively high stabilities of the oxonium ions in trifluoroacetic acid prompted an attempt at the isolation of their salts. The most convenient method was that reported recently by Breslow.[13] When 4-chlorobutyrophenone was treated with an equivalent amount of antimony pentachloride in methylene chloride, white plates crystallized from the solution. 2-Phenyl-1-oxonia-1-cyclopentene hexachloroantimonate (**15**) was easily collected and was found to be exceptionally stable. The salt decomposed at 120–123° when heated in a capillary and decomposed only slowly upon exposure to the atmosphere. The analysis of the salt, as filtered from the reaction mixture with no further purification, corresponded quite closely to the calculated values. The nmr spectrum in sulfur dioxide or acetonitrile had the characteristic chemical shifts of the cation **1** observed in strong acids. The infrared spectrum of the salt in a potassium bromide pellet showed no carbonyl absorption around 1700 cm^{-1}. The ultraviolet spectrum of the salt was obtained in acetonitrile and trifluoroacetic acid solvents. In acetonitrile, two broad absorptions were

(13) R. Breslow, J. T. Groves, and G. Ryan, *ibid.*, **89**, 5048 (1967).

observed at 239 (ϵ 9100) and 272 mμ (ϵ 13,400). In trifluoroacetic acid, the long-wavelength band was shifted to 292 mμ; the short-wavelength band was obscured by solvent absorption.

The reaction of 5-chloro-2-pentanone with antimony pentachloride in methylene chloride resulted in a solution of the corresponding salt (indicated by the nmr spectrum) which crystallized only after cooling to less than 0°. The solution was unstable, darkening when stored at 0°. The crystals could be collected, but decomposed when exposed to the atmosphere for a short period of time. An approximate decomposition point of 110–120° could be obtained when the crystals were heated in a capillary.

Treatment of a methylene chloride solution of 5-chlorovalerophenone with antimony pentachloride led to crystallization of a salt at 0°. The resulting crystals had a poorly defined decomposition point at about 90°. When placed on a filter paper, they rapidly decomposed to a red material.

When the hexachloroantimonate salt **15** from 4-chlorobutyrophenone was treated with methanol or methanolic methoxide, an adduct **16** was formed very rapidly. The nmr and infrared spectra of the adduct corresponded to 2-methoxy-2-phenyltetrahydrofuran. This adduct rearranged under acidic conditions to give a compound containing a carbonyl adjacent to the aromatic ring, as indicated by the characteristic splitting of the aromatic protons in the nmr spectrum and a band at 1700 cm^{-1} in the infrared. This compound is presumed to be 4-methoxybutyrophenone.

Kinetics. Relatively few reactions provide the opportunity to study the kinetics of formation and decomposition of an intermediate and thereby to obtain a detailed reaction coordinate diagram for the entire reaction. The solvolysis of the ketosulfonate esters seemed to be a reaction where this could be done. The butyro- and valerophenone derivatives formed intermediates in trifluoroacetic acid at rates which could be measured by standard techniques. The valerophenone intermediate decomposed at a slower, but an easily measured, rate. The butyrophenone intermediate, however, appeared to react too slowly for convenient rate measurement.

The intermediates have a characteristic ultraviolet absorption at 292 and 298 mμ for the five- and six-membered rings, respectively. There appeared to be no important side reactions because of the clean nmr spectra and because each reaction had a sharp isosbestic point in the ultraviolet spectra. The rates of formation of the intermediate ions were obtained at several temperatures by observing the increase in the ultraviolet absorption of the intermediates as a function of time, and the activation parameters were calculated (Table II).

Table II. Activation Parameters for the Trifluoroacetolysis of Keto-*p*-bromobenzenesulfonates

Ketone	$k \times 10^3$, sec^{-1} [a]	E_a, kcal/mol	$\Delta S^{\ddagger}$, eu[a]
4-(*p*-Bromobenzenesulfonoxy)-butyrophenone	19.2	17.4	−11.0
5-(*p*-Bromobenzenesulfonoxy)-valerophenone	0.49	17.8	−17.0

[a] Extrapolated values at 30°.

The activation parameters can be compared to those obtained in the chloro ketone solvolysis where the rate enhancement of the butyrophenone relative to the valerophenone was 36.[4] In the present work, the rate of formation of the intermediate from 4-(*p*-bromobenzenesulfonoxy)butyrophenone (**10**) was 39 times faster than the rate of formation of the intermediate from 5-(*p*-bromobenzenesulfonoxy)valerophenone (**12a**) (n = 4). The other parameters were of similar direction and magnitude. Pasto and Serve explained the rate and entropy differences on the basis of a rate-limiting formation of cyclic cationic intermediates,[4] and the agreement of the rate ratios obtained in the two systems fully supports their explanation.

Several attempts at obtaining reproducible rates for the decomposition of the six-membered oxonium ion **13** proved unsuccessful. The inconsistent results were apparently due to the slow attainment of an equilibrium between **13** and the ketotrifluoroacetate. To check this possibility, the ketotrifluoroacetate was synthesized by dissolving the alcohol in trifluoroacetic anhydride in an nmr tube. The resulting spectrum showed quantitative formation of 5-trifluoroacetoxyvalerophenone. When a small amount of water was added to the solution to hydrolyze the anhydride to the acid, there was a slow reaction to form the low-field triplet in the nmr spectrum, indicative of the cationic intermediate **13**. Repeating the reactions to form 4-trifluoroacetoxybutyrophenone and adding water to the solution produced the characteristic low-field triplet of **1** in the nmr spectrum. The position of equilibrium is very much dependent on the acidity of the solvent, for addition of strong acid, such as benzenesulfonic, perchloric, or fluoroboric acids, to the equilibrium mixtures of either reaction causes a shift toward the respective cations. In the ketosulfonate ester solvolysis, the ionization to produce the intermediate also produces *p*-bromobenzenesulfonic acid, a strong acid. The addition of sodium trifluoroacetate to this solution reduces the acidity, but apparently not sufficiently to allow complete reaction to the final trifluoroacetates.

The trifluoroacetate nucleophile would be expected to add to the 2 carbon of the intermediates to give 2-trifluoroacetoxyfuran (or -pyran) derivatives. Since these compounds were not observed in the nmr spectrum of the solvolysis reaction solution, they must reionize to the intermediate, giving an equilibrium and eventually forming the more stable substituted phenyl ketone.

The existence of an equilibrium in the reaction implies that any substituted butyrophenone with a reasonable leaving group will also give the intermediate cation. When 4-hydroxybutyrophenone (**17**) was dissolved in trifluoroacetic acid, the intermediate **1** was formed in about 75% conversion, and reached equilibrium (25% intermediate) with the ketotrifluoroacetate after heating for 12 hr at 81°.

Experimental Section

General. Melting points were determined using a Mel-Temp block and are uncorrected. Infrared spectra were recorded from samples in carbon tetrachloride solution with a Perkin-Elmer Model 337 or Model 257 grating infrared spectrophotometer. The nmr spectra were recorded on a Varian Model A-60-A spectrometer[14]

(14) These instruments were purchased with funds supplied by the National Science Foundation.

using tetramethylsilane or sodium 3-(trimethylsilyl)-1-propanesulfonate, τ 10.00, as an internal standard. Mass spectra were recorded on a Hitachi-Perkin-Elmer Model RMU-6D mass spectrometer.[14] The analyses were performed by Geller Laboratories, Saddle River, N. J.

Solvolysis Reactions. The solvolysis reactions were performed in anhydrous formic acid which had been distilled into the reaction mixture through a 70-cm column packed with glass helices, bp 101.1°, or trifluoroacetic acid[15] which was used as supplied by Aldrich Chemical Company. The reactions were carried out using approximately 100 mg of starting material and 0.3–0.5 ml of solvent in an nmr tube. The tubes were sealed with a pressure sealing cap and spectra taken.

Trifluoroacetolysis of 4-(*p*-Bromobenzenesulfonoxy)butyrophenone (10). Addition of 0.2 ml of trifluoroacetic acid to 0.1 g of 4-(*p*-bromobenzenesulfonoxy)butyrophenone produced a solution whose spectrum showed quantitative formation of the intermediate **1**; nmr, τ 1.5–2.5 (m, nine protons),[16] 4.29 (t, two protons), 5.78 (t, two protons), and 7.25 (p, two protons) (Figure 2).

Trifluoroacetolysis of 5-(*p*-Bromobenzenesulfonoxy)-2-pentanone (12b, n = 3). Addition of 0.3 ml of trifluoroacetic acid to 0.1 g of 5-(*p*-bromobenzenesulfonoxy)-2-pentanone produced a solution whose spectrum showed the initial *p*-bromobenzenesulfonate which slowly ionized to the intermediate **14**; nmr, τ 2.26 (q, four protons),[16] 4.30 (t, two protons), 6.10 (t, two protons), 6.93 (s, three protons) and 7.38 (p, two protons) (Figure 4).

Trifluoroacetolysis of 5-(*p*-Bromobenzenesulfonoxy)valerophenone (12a, n = 4). The addition of 0.2 ml of trifluoroacetic acid to 0.1 g of 5-(*p*-bromobenzenesulfonoxy)valerophenone produced a solution whose spectrum showed the initial *p*-bromobenzenesulfonate which ionized slowly to the intermediate **13**; nmr, τ 1.6–2.6 (m, nine protons),[16] 4.6 (broad t, two protons), 6.1 (broad t, two protons), and 7.8 (broad m, four protons) (Figure 3).

Kinetics. The kinetic data were obtained through the use of a Hitachi-Perkin-Elmer ultraviolet spectrophotometer, Model 139. The peak maxima were first located by the use of a Cary 14 recording spectrophotometer. It was determined that the solid ketosulfonates were most easily handled in solution, so that an inert solvent was required. Chloroform appeared to be the best solvent.[17] A known amount of the ketosulfonate was dissolved in chloroform and a small amount of this solution, usually about 5 μl, was added to temperature-equilibrated solutions of sodium trifluoroacetate (1.2×10^{-2} *M*) in trifluoroacetic acid. The concentration of the ketosulfonate was usually on the order of 5×10^{-5} *M*. The spectrophotometer set at the appropriate wavelength (292 mμ for 4-(*p*-bromobenzenesulfonoxy)butyrophenone, 298 mμ for 5-(*p*-bromobenzenesulfonoxy)valerophenone) was connected to a recorder which plotted the absorbance as a function of time. On the same chart the temperature in the cell compartment was recorded through the use of an iron–constantan thermocouple, referenced to 0° (ice–water). The temperature variation was less than ±0.1°.

The rate constants were calculated assuming pseudo-first-order rate laws and plotting the log of absorbance at infinity (highest value) minus the absorbance at any time *vs.* that time. The plot usually resulted in a straight line through two half-lives. The first-order character of the reaction was not rigorously demonstrated, but is supported by the fact that the crude kinetic measurements by nmr at concentrations of 1 *M* gave approximately the same rate.

3-Hydroxypropiophenone.[4] The following procedure for the synthesis of the keto alcohols was used in all similar preparations and will be presented for this preparation alone.

To 30.0 g (0.156 mol) of ethyl benzoylacetate in 150 ml of benzene was added 30.0 ml of ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid (<0.5 g). The reaction mixture was refluxed overnight, using a Dean–Stark trap to remove water. After the addition of potassium carbonate and water, the layers were separated, and the benzene layer was washed with sodium bicarbonate solution and dried over magnesium sulfate. The benzene was removed to give 33.2 g of the ketal. The ketal was dissolved in a solution of methoxide prepared from 4.0 g (0.174 mol) of sodium in 150 ml of methanol, and stirred under nitrogen overnight. Evaporation of the solvent, extraction of an ether solution of the residue with sodium bicarbonate solution, drying the solution, and evaporating the ether gave a pale yellow oil, the ketal ester, which was used directly in the next step of the sequence.

To a suspension of 2.13 g (0.056 mol) of lithium aluminum hydride in dry ether was added slowly 10.0 g of the ketal ester in ether solution (25%). The mixture was refluxed for 1 hr, then 50 ml of (1:1) acetone–hydrochloric acid (6 *N*) solution was slowly added to decompose the complex. After the completion of the addition, 25 ml of 6 *N* hydrochloric acid was added and the mixture stirred overnight. The volatiles were removed by evaporation, and the residue was extracted with ether twice. The ether layer was washed with dilute hydrochloric acid, three times with sodium bicarbonate solution, and once with sodium chloride solution. The solution was dried and the ether removed, giving 5.09 g (0.038 mol, 79%) of 3-hydroxypropiophenone. This material was used directly for the preparation of the *p*-bromobenzenesulfonate ester.

4-Hydroxybutyrophenone (17) was prepared from 30.0 g (0.17 mol) of 3-benzoylpropionic acid in an over-all yield of 55%. The white solid was recrystallized from carbon tetrachloride to mp 32.0–32.2° (lit.[4] 32–33°); ir, 3460 cm^{-1} (OH), 1690 cm^{-1} (C=O); mass spectrum, *m/e* (relative intensity) 164 (4), 146 (45), 115 (19), 105 (100), and 77 (48).

5-Hydroxyvalerophenone was prepared from 15.8 g (0.082 mol) of 4-benzoylbutyric acid in 50% over-all yield. The keto alcohol was not purified, but used directly in the preparation of *p*-bromobenzenesulfonate ester.

6-Hydroxycapriophenone was prepared from 10.0 g (0.048 mol) of 5-benzoylvaleric acid in 54% over-all yield. The keto alcohol was not purified but used directly in the preparation of the *p*-bromobenzenesulfonate ester.

3-(*p*-Bromobenzenesulfonoxy)propiophenone (12a, n = 2). The keto-*p*-bromobenzenesulfonates were all prepared by a preparation[18] similar to that described for 3-(*p*-bromobenzenesulfonoxy)-propiophenone.

To 3.0 g (0.02 mol) of 3-hydroxypropiophenone in 15 ml of pyridine, cooled to 0°, was added 5.10 g (0.02 mol) of *p*-bromobenzenesulfonyl chloride. The solution was kept cold for 1 hr, then warmed to room temperature for 1 hr. The solution was taken up in ether, washed once with water, three times with 1 *N* hydrochloric acid, once with saturated sodium bicarbonate solution, and with sodium chloride solution. The ether solution was dried and the ether evaporated, giving 0.2 g (2.7%) of 3-(*p*-bromobenzenesulfonoxy)-propiophenone which was recrystallized from carbon tetrachloride, mp 86°; nmr, τ 2.3 (m), 5.34 (t), and 6.48 (t).

4-(*p*-Bromobenzenesulfonoxy)butyrophenone (10) was prepared from 3.0 g (0.018 mol) of 4-hydroxybutyrophenone and 4.5 g (0.018 mol) of *p*-bromobenzenesulfonyl chloride in pyridine. The white crystals (2.36 g) were obtained in 34% yield, mp 83.4–84° dec; ir, 1699 cm^{-1} (C=O); nmr ($CDCl_3$), τ 2.0–2.7 (m, nine protons), 5.78 (t, two protons), 6.95 (t, two protons), and 7.86 (p, two protons).

Anal. Calcd for $C_{16}H_{15}BrO_4S$: C, 50.16; H, 3.95. Found: C, 50.04; H, 3.95.

5-(*p*-Bromobenzenesulfonoxy)-2-pentanone (12b, n = 3) was prepared from 10.2 g (0.1 mol) of 5-hydroxy-2-pentanone (Aldrich) and 25.5 g (0.1 mol) of *p*-bromobenzenesulfonyl chloride. The white solid was obtained in 11% yield (3.5 g), mp 37.8–38°; nmr, τ 2.28 (s, four protons), 5.95 (t, two protons), 7.51 (t, two protons), 7.95 (s, three protons), and 8.00 (p, two protons).

5-(*p*-Bromobenzenesulfonoxy)valerophenone (12a, n = 4) was prepared from 2.0 g (0.011 mol) of 5-hydroxyvalerophenone and 2.85 g (0.011 mol) of *p*-bromobenzenesulfonyl chloride in pyridine. The white solid (1.27 g) was obtained in 29% yield, mp 69–70°; nmr, τ 2.3 (m, nine protons), 5.95 (t, two protons), 7.13 (t, two protons), and 8.28 (m, four protons).

Anal. Calcd for $C_{17}H_{17}BrO_4S$: C, 51.39; H, 4.31. Found: C, 51.36; H, 4.27.

6-(*p*-Bromobenzenesulfonoxy)capriophenone (12a, n = 5) was prepared from 2.8 g (0.015 mol) of 6-hydroxycapriophenone and 3.7 g (0.015 mol) of *p*-bromobenzenesulfonyl chloride in pyridine and gave 2.8 g (47%) of a white solid, mp 93–93.5°; nmr, τ 1.8–2.8 (m, nine protons), 5.90 (t, two protons), 7.06 (t, two protons), and 8.40 (m, six protons).

Anal. Calcd for $C_{18}H_{19}BrO_4S$: C, 52.56; H, 4.66. Found: C, 52.60; H, 4.67.

(15) Distillation (bp 72.5°) of this solvent appeared to have no effect on the reactions.

(16) The aromatic proton absorption includes the protons from the *p*-bromobenzenesulfonate leaving group which may or may not be directly involved as the counterion in the intermediate.

(17) With the butyrophenone, decomposition took place, but was only important after storage at 0° for more than 5 hr.

(18) J. D. Roberts and K. L. Servis, *J. Am. Chem. Soc.*, **87**, 1331 (1965).

2-Phenyl-4,5-dihydrofuran (11) was formed by heating 4-hydroxybutyrophenone at reduced pressure. The material collected, bp 65° (0.07 mm), did not contain the alcohol function, but did contain a band in the ir corresponding to the vinyl ether of a dihydrofuran (1690 cm^{-1}); nmr, τ 2.3–3.0 (m, five protons), 4.8 (t, J = 3 Hz, one proton), 5.6 (t, J = 9.5 Hz, two protons), and 7.3 (t of d, J = 3, 9 Hz, two protons); mass spectrum, *m/e* (relative intensity) 146 (85), (17), 115 (34), 105 (100), and 77 (54).

4-Chlorobutyrophenone. The chloro ketones were all prepared in a manner similar to that described for this ketone.[4] The ketal of methyl benzoylpropionate (2.8 g, 0.0118 mol) in 25 ml of diethyl ether was added slowly to 0.5 g (0.013 mol) of lithium aluminum hydride in ether solution. This was stirred overnight at room temperature. The solution was hydrolyzed with water, the layers were separated, the ether layer was washed with dilute hydrochloric acid, and the ether removed under vacuum. The crude ketal alcohol was heated for 3 hr with concentrated hydrochloric acid at 60°. The mixture was cooled and extracted with ether. The ether layer was washed with water and sodium bicarbonate solution. After drying with magnesium sulfate and evaporating the ether, 1.45 g of pale yellow oil, 4-chlorobutyrophenone (67%), was obtained. The structure was confirmed by the nmr and infrared spectra: ir, 1685 cm^{-1}; nmr, τ 2.1, 2.5 (m, five protons), 6.37 (t, two protons), 6.89 (t, two protons), and 7.83 (p, two protons).

5-Chloro-2-pentanone was prepared from 5.0 g (0.05 mol) of 5-hydroxy-2-pentanone and 30 ml of concentrated hydrochloric acid. The keto chloride (4.3 g, 69%) was distilled, bp 71° (30 mm) (lit.[19] 76° (34 mm); nmr, τ 6.45 (t, two protons), 7.40 (t, two protons), 7.88 (s, three protons), and 8.02 (p, two protons).

5-Chlorovalerophenone was prepared from 3.0 g (0.012 mol) of the ketal of 5-hydroxyvalerophenone and 30 ml of concentrated hydrochloric acid. The keto chloride (1.19 g) was obtained in 50% yield, mp 48.5–49° (lit.[4] 49–50°); nmr, τ 1.92–2.8 (m, five protons), 6.49 (t, two protons), 7.08 (t, two protons), and 8.2 (m, four protons).

(19) "Handbook of Chemistry and Physics," College Edition, No. 46, The Chemical Rubber Co., Cleveland, Ohio, 1965–1966, p C 458.

2-Phenyl-1-oxonia-1-cyclopentene Hexachloroantimonate (15). The organohexachloroantimonate salts were all prepared in a similar manner.[18]

To 0.18 g (0.001 mol) of 4-chlorobutyrophenone in 2.5 ml of methylene chloride was added 0.3 g (0.001 mol) of antimony pentachloride. The white crystals which formed were filtered and washed with small amounts of cold methylene chloride. The salt (0.31 g) was obtained in 65% yield, mp 120–123° dec; ir bands at 1595, 1510, 1440, 1390, and 1270 cm^{-1}; no carbonyl absorption; nmr (CH_3CN), τ 1.9 (m), 4.42 (t, J = 8 Hz), 5.88 (t, J = 8 Hz), and 7.40 (p, J = 8 Hz).

Anal. Calcd for $C_{10}H_{11}Cl_6OSb$: C, 24.93; H, 2.30; Cl, 44.16. Found: C, 25.38; H, 2.27; Cl, 43.09.

2-Phenyl-1-oxonia-1-cyclohexene hexachloroantimonate was prepared from 0.20 g (0.001 mol) of 5-chlorovalerophenone and 0.3 g (0.001 mol) of antimony pentachloride. Cooling of this solution overnight gave crystals which could not be easily isolated, and decomposed when heated above 110°. The isolated crystals decomposed rapidly on exposure to the atmosphere.

2-Methyl-1-oxonia-1-cyclopentene hexachloroantimonate was prepared from 0.24 g (0.002 mol) of 5-chloro-2-pentanone and 0.60 g (0.002 mol) of antimony pentachloride. Prolonged cooling of this solution at 0° gave white crystals which decomposed rapidly when exposed to the atmosphere and decomposed about 90° when heated in a capillary. The nmr spectrum of the methylene chloride solution showed the characteristic low-field triplet of the cations at τ 4.23.

Methanolysis of the Hexachloroantimonate Salt of 1. To 0.1 g of 2-phenyl-1-oxonia-1-cyclopentene hexachloroantimonate was added 0.2 ml of methanol containing 1 equiv of methoxide. The nmr spectrum contained peaks at τ 2.4–2.9 (m, five protons), 5.96 (complex triplet, two protons), and 7.6–8.4 (m, four protons) consistent with 2-methoxy-2-phenyltetrahydrofuran. The infrared spectrum showed the absence of a carbonyl; mass spectrum, *m/e* (relative intensity) 146 (69), 117 (16), 115 (27), 105 (100), and 77 (39).

Performing the same reaction but with the absence of methoxide and observing the nmr showed initial formation of the adduct as above, followed by rearrangement of this to a compound consistent with 4-methoxybutyrophenone; nmr, split aromatic proton absorption, τ 2.0 (*ortho*) and 2.5 (*meta* and *para*); ir, 1700 cm^{-1} (ArC=O).

Intramolecular Catalysis in the Reactions of Nucleophilic Reagents with Aspirin[1]

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Abstract: The rates of reactions of aspirin and some related phenyl esters with a series of nucleophilic reagents have been measured in order to determine the nature of catalysis by the *o*-carboxyl group in kinetically unambiguous reactions. The reactions of aspirin with the weakly basic amines nicotinamide, semicarbazide, and methoxyamine occur predominantly with the acidic, uncharged species of aspirin and exhibit rate accelerations of up to 150-fold which are ascribed to intramolecular general acid catalysis. The reactions of aspirin anion with water, semicarbazide, and methoxyamine (but not nicotinamide) exhibit rate accelerations of a similar or slightly smaller magnitude which are ascribed to general base catalysis by the *o*-carboxylate anion. Estimates have been made of the polar, steric, and electrostatic effects of *p*-COO^-, *o*-CO_2CH_3, and *o*-COO^- groups on nucleophilic reactions of substituted phenyl acetates; the value of σ for *p*-COO^-, based on the reaction with the uncharged piperidine molecule, is 0.46. These results, the failure to observe a comparable rate acceleration with more strongly basic nucleophiles, kinetic arguments, and the failure to trap an anhydride intermediate in the presence of dilute hydroxylamine rule out several alternative mechanisms for intramolecular catalysis.

It has been generally believed that the hydrolysis of aspirin monoanion,[3] a classical example of intramolecular catalysis, proceeds by a rate-determining intramolecular attack of carboxylate ion to give the

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(3) L. J. Edwards, *Trans. Faraday Soc.*, **46**, 723 (1950); **48**, 696 (1952).