[CONTRIBUTION FROM THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

Chemistry of Enolates. III. Cation and Solvent Effects in the Alkylation of Butyrophenone¹

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RECEIVED JUNE 1, 1959

The rates of alkylation of ethereal solutions of butyrophenone anion increase by more than three powers of ten as the accompanying cation is varied from lithium to potassium. Tetraalkylammonium salts are powerful catalysts. The reaction exhibits autocatalysis by the ketonic product. Ebullionietric studies of sodiobutyrophenone indicate an average association of three ion pairs in ether solution. Alkylation within a coördination complex is suggested by a reaction order greater than unity for alkyl halide, although no appreciable concentration of complex is evident from vapor pressure measurements of the system methyl bromide-ethereal sodiobutyrophenone.

The "carbanion" nature of metallic derivatives of organic compounds is frequently overemphasized in substitution and condensation mechanisms. Recently, Brändström3 has stressed the importance of chelation of anion and coördination of reagent with alkali metal in the alkylation and acylation of alcoholic solutions of malonic ester and related compounds. Similar coördination of reagents should be even more pronounced in the alkylation of enolates in less polar solvents. Although reasonable pseudo-first-order kinetics were observed throughout the first half-lives for the alkylations of a variety of phenyl alkyl ketones, increases in specific rates were observed during subsequent half-lives. These complications, as well as the results of ebulliometric measurements, suggested that the enolate was more complex than a single ion or ion pair.4

Variation of Cation.—In this study the rates of alkylation of ethereal solutions of lithio-, sodioand potassio-derivatives of butyrophenone are compared. Half-lives for thirteen alkylations are listed in Table I. The importance of the metallic cation

HALF-LIVES FOR ALKYLATIONS OF BUTYROPHENONE						
Enolate	Halide ^c	E^{0a}	$t^{1/2}$, sec. $\times 10^{-6}$			
K	EtBr	0.07	0.0045			
Na	EtBr	.09	0.39			
Li	EtBr	.07	31			
K	n-PrBr	.04	0.0096			
Na	<i>n</i> -PrBr	.09	.98			
K	<i>i</i> -PrBr	.05	.25			
Na	i-PrBr	. 09	~ 23			
Na	ΕtΙ	.08	0.031			
Li	ΕtΙ	.08	1.5			
Na	MeI	.10	0.00054			
Li	Mel	. 10	.035			
Na $(R_4N+ClO_4-)^b$	EtI	.08	.009			
Na $(R_4N^{-1}I^{-})^b$	EtI	.08	.013			

 a Initial molar concentration of enolate. b Tetra-n-butyl-ammonium salt, 0.3 g., added to 200 ml. of ethereal sodio-butyrophenone. c 1.72 M_{\odot}

in the transition state is evident from these data. For example, the rate of ethylation by ethyl

bromide increases more than 6000-fold as the metal

(1) The authors gratefully acknowledge support from the National Science Foundation (NSF-G4475) which made this work possible.

TABLE I

is varied from lithium to potassium. Alkylations of potassiobutyrophenone by iodides are too rapid for convenient measurement.

Attempts to prepare quaternary ammonium enolates have thus far been unsuccessful. However, the addition of a catalytic amount of tetra*n*-butylammonium perchlorate to a sodium enolate increases the rate of ethylation by a factor of three. That this effect is due to the cation is shown by similar catalysis by tetrabutylammonium iodide and no catalysis by sodium iodide.

These comparisons were made in terms of halflives taken from curves of enolate concentration *versus* time. Meaningful rate constants were not obtained in all cases.

Complexity of the Alkylation Reaction.—Although pseudo-first-order constants for alkylation by ethyl bromide deviate less than 5% from the mean during the first half-life,⁴ the constants for ethylations by ethyl iodide increase as much as 20% over this period. This increase is not due to a more rapid dialkylation to triethylacetophenone⁵ nor to concentration of the solution by loss of

TABLE II

		1.0000 11		
ETHYLAT	ION OF SOD	OBUTYROPHEN		
Run	Et1, M	Enolate, M	Ketone, ^a M	1nitial rate ^b
1	1.86	0.388	0.005	35.9
$\overline{2}$	1.86	.171	.003	20.8
3	1.86	.150		20.0
-1	1.86	. 120	.002	15.3
5	1.86	.080	.002	13.2
6	1.86	.050		8.1
7	0.506	.100		2.9
8	. 568	.100	.004	3.4
9	.845	.100	.004	5.1
10	. 994	.100		5.1
11	1.50	.100		10.1
1-6	1.86	$(-,100)^{c}$.002	$(14.2)^{\circ}$
12	2.01	.100		12.2
13	2.51	.100		21.2
14	1.86	$.176^{d}$.003	21.0
15	1.86	.110	. 50	100
16	1.86	.104	. 40 ^e	43.7
17	1.86	.108	$.50^{f}$	38.4

^{*a*} Free ketone present; butyrophenone unless otherwise stated. ^{*b*} Decrease in enolate concentration over the first 10–25% of the reaction in moles/1./sec. $\times 10^7$. ^{*c*} Initial rate at 0.100 *M* enolate taken from curve in Fig. 1. ^{*d*} Initially contained 13.1 g. of powdered sodium iodide. ^{*e*} Initial molar concentration of α -ethylbutyrophenone. ^{*f*} Hexamethylacetone.

(2) Taken in part from the M.S	thesis of W. L. Gumby, The Penn-
sylvania State University, August,	1959.
(3) A. Brändström, Arkiv Kemi,	6, 153 (1954); 7, 81 (1954).

(4) H. D. Zook and W. L. Rellahan, THIS JOURNAL, 79, 881 (1957).

(5) W. L. Rellahan and H. D. Zook, J. Org. Chem., 24, 709 (1959).

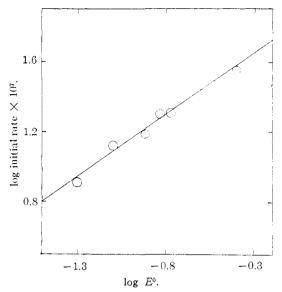


Fig. 1.-Ethylation of sodiobutyrophenoue; order in enolate.

ether. Evaporation of solvent during transfers is easily held to less than 3%.

At least two factors are responsible for the increase in specific rate. These factors have been separated by the method of initial rates in which the concentrations of the several reactants were varied independently.⁶ The results are presented in Table II.

The most obvious reason for the increase in specific rate is catalysis by products. In this case, one product, sodium iodide, begins to precipitate within the first 5% of the reaction. Kornblum recently described remarkable effects of surface catalysis in the alkylation of phenoxide ions.7 A comparison of runs 2 and 14 shows that a large amount of powdered sodium iodide, when rapidly stirred with the enolate, has no effect on the initial rate. However, the rate is tripled when the other product of the reaction, α -ethylbutyrophenone, is added in initial concentration of 0.40 \hat{M} (run 16). An even more effective catalyst is butyrophenone. Catalysis is not dependent upon the presence of α -hydrogen atoms in the ketone, for hexamethylacetone is almost equivalent to α -ethylbutyrophenone in activity.

Because the data for any single run did not conform to an expression for a first-order autocatalytic reaction, other factors contributing to the complexity were sought. For this work, enolate solutions which contained negligible amounts of free ketone were prepared. The maximum amounts of ketone listed in Table II were determined by infrared analysis of the enolate solutions. Runs 1-6 at constant concentration of alkyl halide were used to determine the order of the reaction in enolate. A plot of log dE/dt versus log E (Fig. 1) gives a slope of approximately 0.7. Although the precision is not as great as might be desired, the order in enolate is surely far from unity. The alkylations so far described in this and a former study⁴ were carried out in 10- to 25-fold excess of alkyl halide. In runs 7–13 the rates of ethylation of 0.1 M solutions of sodiobutyrophenone by excess ethyl iodide were measured at eight concentrations of ethyl iodide in the range 0.5– 2.5 M. The order in alkyl halide determined from the slope of a plot of log dE/dt versus log [Et I] (Fig. 2) is unity within experimental error at concentrations of halide less than 1 M, but increases to a value as great as 3/2 at higher halide concentrations.

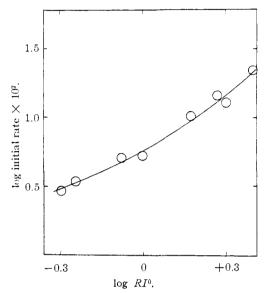


Fig. 2.—Ethylation of sodiobutyrophenoue; order in ethyl iodide.

Association of Sodiobutyrophenone.—Ebulliometric measurements on ethereal solutions of this enolate have been made over a range of concentration from 0.13 to 0.63 molal (Table III). The

TABLE III

Boiling Point Elevations and Aggregation Numbers of Sodiobutyrophenone Solutions

Enolate, molality	Free ketone molality	ΔT , °C.	α
0.630	0.008	0.421	3.0
.490	.029	. 363	2.8
.404	.004	.237	3.4
.397	.011	.273	2.9
.304	.005	. 196	3.1
.200	.010	.150	3.2
.152	.003	.105	2.9
. 134	.003	.084	3.2
		Average	3.1

solutions contained insignificant amounts of free butyrophenone (see Experimental). An average aggregation of three ion pairs is indicated by the boiling-point elevation.⁸ The constancy of the

(8) A value of two was reported earlier⁴ for a solution of enolate prepared from sodium triphenylmethide. It is now known that such solutions contain more than an equivalent amount of triphenylmethane, which, because of its relatively low molecular weight compared with that of the aggregated enolate, greatly reduces the precision of this determination.

⁽⁶⁾ A. A. Frost and R. G. Pearson, "Kinetics and Mechanism." John Wiley and Sons, 1nc., New York, N. Y., 1953, p. 44.

⁽⁷⁾ N. Kornblum and A. P. Lurie, Abstracts of Papers, 133rd Meeting of the American Chemical Society, San Francisco, Calif., April, 1958, p. 14-N.

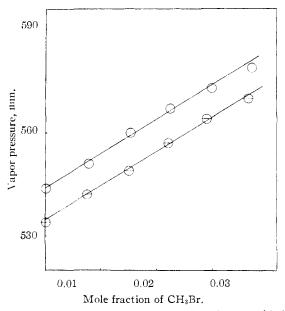


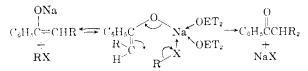
Fig. 3.—Vapor pressures of solutions of methyl bromide in ether, O, and in 0.42 M ethereal sodiobutyrophenone, \ominus .

aggregation number over the wide range of concentration suggests a trimeric species.

Discussion of Results.—Regardless of whether sodiobutyrophenone *in pure ether* exists as discrete trimers or as aggregates with this average association number, the reactivity of the enolate *in the alkylation solvent* containing excess alkyl halide increases with dilution. Initial specific rates calculated by the first-order law increase about 70% from run 1 to run 6. This effect is quite apart from the autocatalysis by product.

The comparison of three ketones which accelerate the reaction shows that the ability of the ketone to enolize is not a necessary condition for catalysis and that the catalytic influence is diminished by increased branching in the neighborhood of the carbonyl group.

These effects, which are functions of the solvent system, can be explained by changes in the reactivity of the sodium enolate through coördination with the alkyl halide or with the carbonyl group of the ketonic product. The alkylation could occur within the coördination complex as proposed by Brändström for the alkylation and acylation of β -dicarbonyl compounds.³



A six-centered reaction within a coördination complex would explain orders of reaction greater than unity in alkyl halide. Higher orders would be expected if more than one halide molecule were coördinated to sodium in the transition state. The absence of enol ethers in the product from the alkylation of sodiobutyrophenone is in line with this mechanism. No trace of enol ether could be detected by infrared analysis, thus confirming the chemical evidence reported previously. When steric or other special effects interfere with a similar transition state in the chelated enolates of β -dicarbonyl compounds, O - alkyl products are formed.³ The six-centered transition state is analogous to that required to explain the kinetics and abnormal products formed in the reactions of other organometallic compounds with ketones and acyl halides.⁹ A similar mechanism recently has been proposed for the acylation of simple enolates.¹⁰

The concentration of a coördination complex in the alkylation reaction cannot be large. Evidence for this fact has been obtained from vaporpressure measurements of the system methyl bromide-ethereal sodiobutyrophenone. The increase in vapor pressure of a 0.42~M solution of enolate. as methyl bromide was added, was the same as that obtained when the bromide was added to pure ether (Fig. 3). The final concentrations represented approximately stoichiometric amounts of reactants, and the amount of alkylation in the time of mixing was negligible.

Solvated complexes of alkali-metal enolates of β -dicarbonyl compounds have been isolated.¹¹ Added stability due to chelation is present in these compounds, and for at least one such complex,¹² formation constants decrease from lithium to cesium, an order opposite to that found for the relative rates of alkylation in this study.

The large variation in the rate of alkylation with change of cation does not demand reaction within a coördination complex but offers convincing evidence that free enolate ions are not involved in the rate-determining step.

Experimental

Preparation of Enolates.—The ketones used in this study have been described previously.^{4,13} Metallic enolates are extremely hygroscopic and react rapidly with oxygen. All apparatus was dried overnight at 110° or rinsed well with dry ether and flushed with nitrogen. Solutions were transferred by siphoning and stored under positive nitrogen pressure. Ethyl ether was distilled from lithium aluminum hydride into 3-1. storage bottles fitted with siphons to make possible all transfers in nitrogen atmosphere.

Sodiobutyrophenone was best prepared from the ketone and excess sodium hydride. In a typical preparation, the mineral oil was washed from 61.2 g. of a 51.1% hydride dispersion (Metal Hydrides, Inc.) with five 75-ml. portions of dry ether, each filtered by uitrogen pressure through a sintered disk. The fourth and fifth washes contained 0.8 and 0.4 g. of oil, respectively. The sodium hydride was stirred and refluxed for five days with 59.3 g., 0.400 mole, of butyrophenone in 200 ml. of dry ether. The mixture was then diluted with ether, and stirring and refluxing were continued for six days. The infrared absorbance of the pale yellow solution at 5.89 μ in a 0.160-mm. cell was 0.036, which corresponds to a maximum concentration of 0.006 M in free butyrophenone. The enolate concentration was 0.42 M, determined by the titration of a 25.00-ml. aliquot with standard acid.

Lithiobutyrophenone was made in a similar manner from lithium hydride (Maywood Chemical Co.) pulverized in a nitrogen atmosphere.

Potassiobutyrophenone was prepared by the addition of 22.2 g. of ketone in 2 l. of dry ether to a solution of potassium amide freshly prepared from 15 g. of the metal in liquid

⁽⁹⁾ C. G. Swain and L. Kent, THIS JOURNAL, 72, 518 (1950); H. S. Mosher and E. LaCombe, *ibid.*, 72, 3994, 4991 (1950).

 ⁽¹⁰⁾ D. G. Hill, J. Burkus and C. R. Hauser, *ibid.*, **81**, 602 (1959).
 (11) N. V. Sidgwick and F. M. Brewer, J. Chem. Soc., 2379 (1925).

⁽¹²⁾ W. C. Fernelius and L. G. Van Uitert, Acta Chem. Scand., 8, 1726 (1954).

⁽¹³⁾ H. D. Zook, W. S. Smith and J. L. Greene, *ibid.*, 79, 4436 (1957).

ammonia. Ammonia was distilled, and the mixture was refluxed for three days, filtered and refluxed for another three days under a column to remove last traces of ammonia.

Alkylation Studies.—The apparatus and procedure for the kinetic studies have been described.⁴ All reactions were carried out at $30.00 \pm 0.02^\circ$. Nitrogen gas for the sampling operation was bubbled through ethereal sodium triphenylmethide solution to remove traces of oxygen and water vapor and to saturate the gas with ether vapor. At all other times the system was closed and contained a small positive pressure. Evaporation throughout an entire run amounted to less than 3%, most of which occurred during the initial addition of the enolate solution to the nitrogen-filled flask. In order to eliminate this error, as well as any error due to possible non-additivity of volumes of halide and enolate solutions, a "zero-time" aliquot was titrated soon after mixing. The results of thirty alkylations are listed in Tables I and II.

Vapor Pressure of Methyl Bromide-Enolate System.—A 55-nl. flask immersed in a constant-temperature bath at $25.30 \pm 0.05^{\circ}$ was attached to a manometer, gas buret and vacuum line. The flask was filled with anhydrous ether freshly distilled from lithium aluminum hydride. The system was evacuated intermittently until a constant vapor pressure of 545 mm. was obtained. The vapor pressure of ethyl ether at 25.3° is 544 mm.¹⁴ The volume of liquid at this time was 52 ml. Five portions of about 100 ml. each of methyl bromide (Dow Chemical Co., purified by isothermal distillation) were accurately measured and added through a capillary at the bottom of the flask. After each addition, air pressure was applied to the open end of the manometer in order to fill the other leg with mercury and thereby force the vapor back into the flask. After circulating the mercury in this way several times, a constant value of the vapor pressure sure was obtained. The vapor pressures are plotted against nucle fraction of methyl bromide in Fig. 3.

The procedule was repeated with a $0.42 \ M$ solution of sodiobutyrophenone. The five portions of methyl bromide were added over a period of one hour. The slope of the vapor

(14) "International Critical Tables," Vol. 3, McGraw-Hill Book Co., Inc., New York, N. Y., 1928, p. 19.

pressure curve was the same as that for the system ethermethyl bromide. The amount of alkylation in this time is negligible. A titration after 17 hours indicated that the reaction was then only 48% complete.

Example 1 The nonly 48% complete. **Ebulliometric Studies.**—A differential ebulliometer of the type described by Swietoslawski and Anderson¹⁶ was employed. The exit led to a 2-ml. receiver and thence through Drierite to a T-tube over which was passed a very slow stream of nitrogen. Temperatures were measured to 0.001° with micro-Beckmann the mometers. In order to obtain constant reproducible temperature differences, it was necessary to drain the water from the condenser for several minutes and distil up to 2 ml. of ether.

The enolate solutions were freshly prepared in 2-3-liter batches and forced by nitrogen pressure directly from the sodium hydride into the boiler. The apparatus was flushed several times with the solution and filled to a 40.0-ml. calibration mark. After the boiling point determination, a 25.0ml. aliquot was drained into a volumetric flask, weighed and titrated. The remainder of the solution was transferred to a 0.16-mm, infrared cell for estimation of ketone at 5.88μ . The results for eight separate preparations are listed in Table III. The concentrations of free ketone represent maximum amounts that could be present. They are calculated on the unlikely assumptions that the pure enolate has no absorption in the carbonyl region and that no moisture was adsorbed on the surfaces of the infrared cell. The aggregation numbers listed in Table III have been calculated without correction for free ketone. When corrections are applied, the average aggregation number is 3.35, an increase of about 8%

The molal boiling point constant for ethyl ether in the instrument used, 2.00, was determined by measuring boiling point elevations of 0.1-0.4 molal solutions of triphenylmethane, m.p. 92-93°.

(15) A. Weissberger, "Physical Methods of Organic Chemistry," Vol. 1, 2nd Ed., 1nterscience Publishers, 1nc., New York, N. Y., 1949, p. 121.

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Studies of the Mechanisms of the Reactions of Benzoyl Peroxide with Secondary Amines and Phenols

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Received July 23, 1959

The reactions of dibenzylamine, diphenylamine and p-cresol with benzoyl peroxide, labeled with oxygen-18 in the carbonyl positions, have been studied. Dibenzylamine reacts by nucleophilic displacement on an oxygen of the peroxide link to give ultimately benzoic acid and O-benzoyl-N,N-dibenzylhydroxylamine which contains all of the excess oxygen-18 in the carbonyl oxygen. Diphenylamine reacts by the same process to give O-benzoyl-N,N-diphenylhydroxylamine which is unstable under these conditions and rearranges to give N-phenyl-N-o-hydroxyphenylbenzamide. The amide contains 55% of the excess oxygen-18 in the carbonyl group and 45% in the phenolic hydroxyl group. Similarly p-cresol reacts to give 2-hydroxy-4-methylphenyl benzoate which contains 87% of the excess oxygen-18 in the carbonyl group and 13% in the phenolic hydroxyl group. Mechanisms for these reactions are proposed and discussed.

Amine Reactions.—The reactions of amines with peroxides, in particular benzoyl peroxide, have been studied by a large number of investigators.¹

The reaction of tertiary amines with diacyl peroxides is thought to proceed by an initial polar displacement, as shown below, to give I which then decomposes by a radical path into products.²

$$R_{3}N + (RCO_{2})_{2} \longrightarrow R_{3}^{+}N - O - CR + RCO_{2}^{-} \longrightarrow Products$$
I

Secondary aliphatic amines react quite simply with benzoyl peroxide to give N,N-dialkyl-O-benzoylhydroxylamines and benzoic acid. There has

(2) W. B. Geiger, J. Org. Chem., 23, 298 (1958), has prepared N-acetoxytrimethylammonium bromide by treatment of trimethylamine with acetyl peroxide and then with concentrated hydrobromic acid. Thus it has been demonstrated that 1 is formed by the initial reaction of a tertiary amine with an acyl peroxide. D. Buckley, S. Dunstan and H. B. Henbest, J. Chem. Soc., 4901 (1957), also have suggested this mechanism for these reactions and have spectral evidence for the

$$N(CH_2CH_2)_3^{\dagger}N - O - C - C_6H_5$$

ion obtained from the reaction of triethylenediamine with benzoyl peroxide.

⁽¹⁾ C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 590-595.