The enol content of the equilibrium mixture for each member of the diketone series was estimated by assuming that the absorbance of the 2500–2800 Å. band is entirely due to the keto form, and that the 3000–3150 Å. band is entirely due to enol form. This assumption gives crude results, but permits an estimate of enol content in those cases in which only one pure tautomer is available. The enol content obtained by this method is listed in Table IV. The order of increasing enol content in 95% ethanol by the spectroscopic method agrees well with the order of increasing enol content found in methanol by bromine titration[2] (Table I).

Experimental

Materials.—The compounds studied were analytical samples as reported in the previous article,[2] or were prepared and purified according to literature methods as indicated in the tables in which the data appear. The solvents used were 95% ethanol (Commercial Solvents) for ultraviolet spectra and carbon tetrachloride (Brothers Chemical Co.) for infrared spectra and were used without further purification.

Measurement of Spectra.—The ultraviolet spectra were determined using a Cary recording spectrophotometer, model 11. Procedure used was according to the manufacturer's instructions. Matched quartz cells were used. The slit control was set at 10 and the fast scanning speed was used. The spectrophotometer was housed in a constant temperature room at 28°. The concentration employed was 10^{-4} molar in all cases. The solutions were freshly prepared and, for equilibrium data, were stored in the dark. Data obtained are listed in Tables III and IV.

The infrared spectra were measured using a Perkin–Elmer model 21 double-beam recording spectrophotometer, with a sodium chloride prism. The control settings were maintained constant at: resolution, 926; response, 1; gain, 5; speed, 4; suppression, 4. The concentration used was 10 mg./ml. Matched 1-mm. cells were used in standard double beam operation. Data obtained are listed in Tables II and III.

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[CONTRIBUTION FROM THE MALLINCKRODT LABORATORIES OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

Reactivity of Thiobenzophenone with Phenylhydrazine

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Thiobenzophenone reacts with phenylhydrazine and with semicarbazide at *p*H 4 about ten times as rapidly as does benzophenone. However, since the reaction of the thio compound is catalyzed by bases, whereas the reaction for the ketone is catalyzed only by acids, the rates differ, at *p*H 6, by a factor of around 2000, and the difference becomes much larger in alkaline solution. Two mechanisms for the processes are discussed.

Thiobenzophenone is reduced non-enzymatically by DPNH (*i.e.*, diphosphopyridine nucleotide) and by N-benzyl dihydronicotinamide to benzhydryl thiol.[1] Since the corresponding reaction of benzophenone has not been observed, the thiocarbonyl group appears, in this particular oxidation–reduction system, very much more reactive than the carbonyl group. The present research was undertaken in the attempt to evaluate the general reactivity of thiobenzophenone. Two reactions were studied: the reduction of the thioketone with sodium borohydride,[2] and the reaction of the thioketone with carbonyl reagents. The first of these processes is, presumably, a hydride ion transfer reaction. The second reaction is a complex one, where two separate steps are involved; the addition of the reagent to the carbon–sulfur double bond, and subsequent loss of hydrogen sulfide. Each of these reactions may in principle be catalyzed by acid or base, and the acidities and basicities of the reactants will influence the outcome of the reactions. Although in such a complex system the analogy with the reduction by the dihydropyridines is tenuous, the high reactivity of the thioketone, relative to that of the ketone, was here observed. The experiments are described below.

Experimental

Materials.—Benzophenone, recrystallized from ligroin, melted at 47.5–48.5°. Thiobenzophenone was prepared by the method of Staudinger and Freudenberger.[1,3] The compound, on recrystallization from ligroin under nitrogen, was obtained as blue crystals. The product was sealed in 50-mg. quantities in nitrogen-filled ampoules, and stored in a refrigerator prior to use; the compound assayed 95% or better on the basis of its absorption[1] at 600 mμ. Phenylhydrazine hydrochloride, recrystallized from 95% ethanol, melted at 244°; semicarbazide hydrochloride, recrystallized from ethanol–water, melted at 172°. Phenylhydrazinium *p*-toluenesulfonate, prepared from the crude base and acid in ethanol, and recrystallized from 95% ethanol, melted at 185–187°. *Anal.* Calcd. for $C_{13}H_{16}N_2SO_3$: C, 55.69; H, 5.76; N, 9.99. Found: C, 55.41; H, 5.78; N, 9.85.

Tris (*i.e.*, trishydroxymethylaminomethane), obtained from Sigma Chemical Co., melted at 171°; after recrystallization from ethanol–water it melted at 172°; no difference in the kinetic results from the two kinds of material was noted. *p*-Toluenesulfonic acid monohydrate, after recrystallization from aqueous hydrochloric acid, melted at 103–104° and had a neutralization equivalent of 188. Crude sodium *p*-toluenesulfonate was recrystallized three times from water; the final product was free of chloride ion. Salicylic acid melted at 158–159°, benzoic acid at 122°, *o*-chlorobenzoic acid at 140°, *p*-chloroaniline at 70–71°. *o*-Chloroaniline boiled at 109° (35 mm.), benzylamine at 81–84° (35 mm.), pyridine (dried over barium oxide) at 113° at atmospheric pressure, ethanolamine at 165–166° at atmospheric pressure, $n^{25}D$ 1.4533. The solvent was prepared by mixing four parts by volume of absolute ethanol (Gold Shield) to one part of distilled water; it is described hereafter as "80%" ethanol.

Products.—Approximately 0.7 g. of crude thiobenzophenone was allowed to react at room temperature overnight with 3 g. of phenylhydrazinium *p*-toluenesulfonate in 80% ethanol at *p*H 5–6 under nitrogen. After the solution was cooled in an ice-bath, 0.8 g. of benzophenone phenylhydrazone, m.p. 138–139°, was obtained; yield 83%.

***p*H Measurements.**—The "*p*H" was measured in 80% ethanol at an ionic strength of 0.2 with a Beckman model

(1) R. H. Abeles, R. F. Hutton and F. H. Westheimer, THIS JOURNAL, **79**, 712 (1957).

(2) J. C. Powers, Thesis, Harvard University, 1958.

(3) H. Staudinger and H. Freudenberger, *Ber.*, **61**, 1576 (1928).

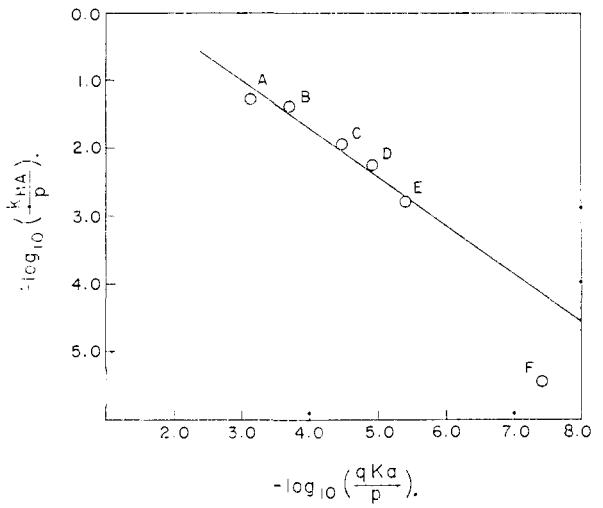


Fig. 1.—General acid catalysis in the formation of benzophenone phenylhydrazone. The logarithm of the rate constant for any acid is plotted against the logarithm of the corresponding ionization constant; each constant is corrected by the statistical favors shown in Table I: *p*-chloroanilinium ion, A; salicylic acid, B; phenylhydrazinium ion, C; *o*-chlorobenzoic acid, D; benzoic acid, E; and "Tris" cation, F.

G *p*H meter, connected through a 0.1 *M* potassium chloride agar–agar bridge to a saturated aqueous calomel cell. A solution of 0.001 *M* hydrochloric acid and 0.2 *M* sodium *p*-toluenesulfonate in 80% ethanol was arbitrarily defined as a "*p*H" of 3.00; all measurements were referred to this standard on the assumption that the glass and liquid junctions remained constant throughout the work.

Kinetic Method.—The formation of benzophenone phenylhydrazone was followed by measuring the optical density of the solutions in a Beckman model DU spectrophotometer at 342 mμ. At this wave length, phenylhydrazine does not absorb appreciably, but the extinction coefficient for the phenylhydrazone (about 2×10^4) is at a maximum.

The rates were determined by introducing into a 25-ml. volumetric flask 10 ml. of a 0.2 *M* solution of phenylhydrazinium tosylate, 5 ml. of buffer solution and 4 ml. of sodium hydroxide solution. The flask was flushed with nitrogen, closed with a rubber stopple, and thermostated at 50°. To initiate the reaction, 1 ml. of a 0.04 *M* solution of benzophenone was injected with a syringe through the rubber stopple. The sodium hydroxide solution was used to neutralize part of the phenylhydrazinium ion. Its concentration was adjusted so that the resulting phenylhydrazine–phenylhydrazinium ion buffer had (at least approximately) the same "*p*H" as that of the auxiliary buffer. Aliquots were withdrawn with a 2-ml. nitrogen-filled syringe, and the contents flushed into 90 ml. of ethanol–water; the solution was then made up to 100 cc. and analyzed spectrophotometrically. A slight yellow color, which occasionally developed during the "runs," did not interfere with the analysis. Since the phenylhydrazine was present in large excess, first-order constants were calculated from the data; they gave good kinetics to two half-lives.

In the most acidic buffer solutions, the reaction did not go to completion. The same equilibrium point was achieved from the reactants or from the products; the rate constants were obtained from the equation for a reversible first-order process.

Kinetic Method—Thiobenzophenone.—The rates were determined by observing the disappearance of the band (responsible for the blue color) at 600 mμ. For each experiment, all the components except thiobenzophenone were pipetted into the spectrophotometer cell, the system thoroughly flushed with nitrogen, and sealed with a size A rubber stopple. The cell and its contents (total volume, 3 ml.) were thermostated for 30 minutes and at time zero a 1-ml. sample of a solution of thiobenzophenone (also at the temperature of the thermostat) was injected through the stopple. The reactions went to completion, and the absence of reaction of thiobenzophenone with the buffers was established by suitable controls. Again, since the concentration of phenylhydrazine greatly exceeded that of the thioketone, each "run" was essentially first order.

To determine the effect of any specific buffer upon the reaction, a series of experiments was conducted in which the concentration of the buffer was varied at constant buffer ratio and at constant ionic strength; the series was then repeated at different buffer ratio. In this way, the catalytic constants for both the acid component and the basic component of the buffer could be individually evaluated.

Results

Benzophenone.—The rate constants for the reaction of benzophenone with phenylhydrazine are given in Table I.

TABLE I

PHENYLHYDRAZONE FORMATION FROM BENZOPHENONE AT 50° IN "80%" ETHANOL[a]

Compound	*p*H	"pK_a"	$10^2 k_{HA}$, in l.²/mi.² sec.	*p*/*q*
Tris	6.94	6.94	0.00124	3
Benzoic acid	5.99	5.69	.194	
Benzoic acid	5.69	5.69	.164	1/2
Benzoic acid	5.39	5.69	.141	
o-Chlorobenzoic acid	4.74	4.74	1.12	1/2
Phenylhydrazinium ion	4.74	4.43	1.64	3
Salicylic acid	3.98	3.98	4.20	1/2
p-Chloroanilinium ion	2.64	2.64	16.1	3
o-Chloroanilinium ion	1.41	1.41	....	

[a] The rate of reaction is calculated on the basis of the equation $v = k_2(\text{ketone})(\text{phenylhydrazine}) = k_2'(\text{ketone})\cdot(\text{total phenylhydrazine} + \text{phenylhydrazinium ion})$.

The observed rate constant k_2' falls off in acid solution as the fraction of phenylhydrazine present as the free base diminishes. The value of k_2 for each experiment can be calculated from the pK of phenylhydrazine, the *p*H of the buffer and the observed value of k'_2; $k_2' = k_2/[1 + (H^+)/K_{HA}]$. Plots of k_2 against buffer concentration at constant buffer ratio yield straight lines of slope k_{HA}; at least four, and usually six, points were determined for each catalytic constant. Thus, although the actual rates fall in acid solution, the catalytic constants associated with the individual acids increase with increasing values of the ionization constant, K_{HA}. The Brönsted[4] plot of the data in Table I is presented in Fig. 1, using the ratio of statistical factors, *p*/*q*, recorded in the last column of Table I. The behavior of *o*-chloroanilinium ion was exceptional; for this compound, general acid catalysis was not observed. The plot for the other acids leads to a Brönsted exponent of 0.60.

Thiobenzophenone.—The data for the reaction of thiobenzophenone with phenylhydrazine are presented in Table II; the "pK_a" values were redetermined at 30°. The rates also are computed for the reaction of free phenylhydrazine with the thioketone. The observed rate constants k_2' fall off in acid solution because the concentration of phenylhydrazine is diminished in acid; the constants k_2 (which are computed on the basis of the assumption that only free, unprotonated phenyl-

(4) J. N. Brönsted and K. J. Pedersen, *Z. physik. Chem.*, **108**, 185 (1924); J. N. Brönsted and E. A. Guggenheim, THIS JOURNAL, **49**, 2554 (1927).

hydrazine can react) increase in acid solution. But the constants k_2 also increase in basic solution; the minimum is around a "pH" of 4.5. The reaction of phenylhydrazine with thiobenzophenone, in sharp contrast with the reaction with benzophenone, is catalyzed by bases as well as by acids. The difference in reactivity between ketone and thioketone rests primarily upon this fact.

TABLE II

PHENYLHYDRAZONE FORMATION FROM THIOBENZOPHENONE AT 30° IN "80%" ETHANOL

Compound	"pK_a"	"pH"	k_{HA}(l.²/ m.² sec.)	k_B(l.²/ m.² min.)
Tris	7.40	7.40		0.48
Benzoic acid	5.70	5.40, 4.69	0.40	.46
Phenylhydrazine	4.73	3.52, 4.69	.25	.64
o-Chlorobenzoic acid	4.69	4.69, 4.99	.24	.32
Salicylic acid	4.01	4.01, 4.31	.20	.43
Pyridine	3.52	3.52, 3.82	1.5	.15
p-Chloroaniline	2.82	2.82	3.3	

The two rate constants k_{HA} and k_B are obtained as the result of a complex calculation and a correction for the fraction of phenylhydrazine ionized, and cannot be precise. The rate ascribed to each buffer is obtained by plotting k_2' against the buffer concentration at two or more different values of the "pH"; the slopes of these lines must then be resolved into a combination of k_{HA} and k_B. In general, the more basic compounds show the higher catalytic constants for base catalysis, and the more acid ones the higher constants for acid catalysis. The reaction of phenylhydrazine with benzophenone has been shown to be first order in ketone over a hundred-fold range in concentration, first order in phenylhydrazine over a five-fold range in concentration. The reaction with thiobenzophenone has been shown to be first order in phenylhydrazine over a five-fold range in concentration, and first order in thioketone over a two-fold range in concentration.

The rate constant, calculated for zero buffer concentration, and computed on the basis of the stoichiometric concentration of phenylhydrazine is called k_0'; it shows the rate which would obtain in the presence of phenylhydrazine, the ketone or thioketone, and H^+ and OH^- ions. The data, because of the extrapolations, are only approximate; they are presented in Fig. 2. The curve for the reaction with benzophenone is the bell-shaped curve, obtained by many previous investigators,[5] for reactions of carbonyl compounds with phenylhydrazine and semicarbazide. By contrast, the rate for the reaction of phenylhydrazine with thiobenzophenone drops in acid solution; here the concentration of free (unprotonated) phenylhydrazine is low, and the catalysis by acids is (relatively) unimportant. The rates rise strongly in alkaline solutions, where the phenylhydrazine is largely in the form of the free base, and where base catalysis is prominent. Thus the ratio of the rates of reaction of thiobenzophenone to benzophenone, estimated for 30°, varies from about 10 at a pH of 4.5

(5) J. B. Conant and P. D. Bartlett, THIS JOURNAL, **54**, 2881 (1932); *cf.* L. P. Hammett, "Physical-Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 330–332; E. B. Barrett and A. L. Lapworth, *J. Chem. Soc.*, **93**, 85 (1908).

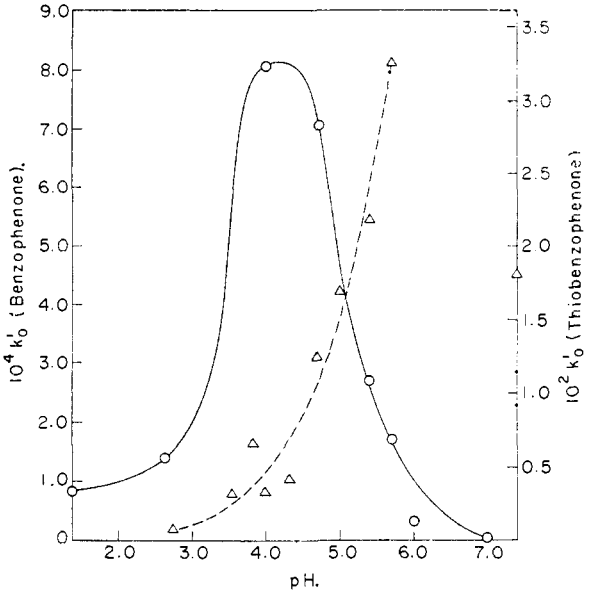


Fig. 2.—Rate constants for the formation of benzophenone phenylhydrazone from benzophenone and from thiobenzophenone. The rate constants extrapolated to zero buffer concentration are plotted as a function of pH. The data for benzophenone (circles, solid-line, left-hand scale) are for 50°; those for thiobenzophenone (triangles, dotted-line, right-hand scale) are at 30°.

to a value at pH 6 of 2000, and to much higher values in more alkaline solutions. (In Fig. 2, the curve for benzophenone refers to rate constants at 50°; that for thiobenzophenone to rate constants at 30°. Note also that the scales for the two rate constants are different.)

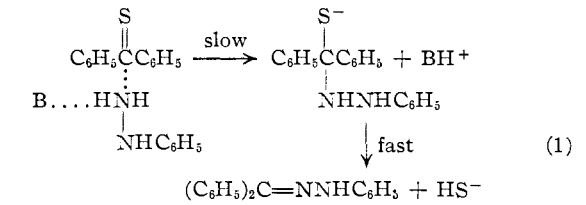
Discussion

Although the variations in rate with pH show that the mechanism for the reaction of thiobenzophenone with phenylhydrazine must differ substantially from that for benzophenone, the precise mechanisms cannot yet be specified. In a brilliant paper, Jencks[6] has discovered that in neutral solution the reaction of pyruvic acid and other ketones with semicarbazide or hydroxylamine proceeds very rapidly to an adduct, which then, in the rate-controlling step, is dehydrated to the semicarbazone or oxime. The rapid first step has a favorable equilibrium constant for pyruvic acid, and a measurable but rather unfavorable one for acetone. Jencks further suggested that the shape of the pH-rate profile for phenylhydrazone and semicarbazone formation may result from a change in the rate-controlling step of the reaction. He postulates that, in relatively basic solutions, the slow step of the process is the dehydration of the carbinolamine intermediate (see eq. 2 below), whereas in strongly acidic solutions its formation (see eq. 1 below) becomes rate limiting. This explanation may very well apply to the pH–rate profile for the reaction of phenylhydrazine with benzophenone.

The mechanism for the formation of carbonyl derivatives of ketones has been previously discussed in detail.[6] The novel feature brought out in this work is the base catalysis for the formation of de-

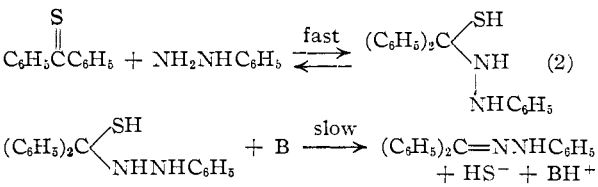
(6) W. P. Jencks, THIS JOURNAL, **81**, 475 (1959).

rivatives from thiobenzophenone. This could occur in either of the necessary steps; the equations are



(1)

or



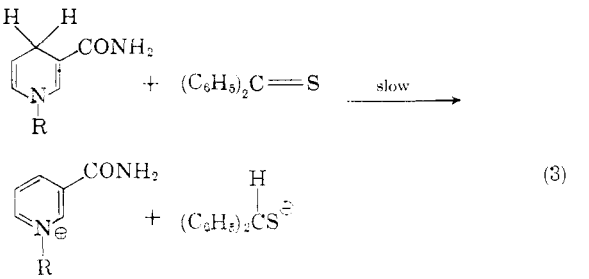
(2)

The usual methods of kinetic analysis (solvent effects, isotope effects) cannot easily distinguish between these possibilities. In either instance, the greater ability of sulfur, relative to oxygen, to hold a negative charge will account for the base catalysis in the formation of a derivative from the thioketone, in contrast to one from the ketone. If scheme 2 is correct, then the fact that HS^-, relative to $\bar{O}H$, is a better "leaving group" can explain why base catalysis is successful here. Alternatively, if scheme 1 is correct, the rate-determining step can proceed readily because the mercaptide ion is comparatively stable. With the oxygen ketone, the corresponding alcoholate ion is less stable, and must be protonated for effective reaction. Mercaptans are stronger acids than alcohols, H_2S a stronger acid than water, and these facts are then related to the observation that phenylhydrazone formation from thioketones shows general base catalysis and proceeds rapidly in neutral and slightly alkaline solutions. Incidentally, oxime formation shows base catalysis[7] with ordinary ketones, and base catalysis of semicarbazone formation has been demonstrated[8] in some special cases.

Some question then arises whether the phenomena here noted are related to the rapid reduction, in neutral solution, of thiobenzophenone by derivatives of 1,4-dihydropyridines.[1]

(7) A. Ölander, *Z. physik. Chem.*, **129**, 1 (1927).

(8) B. M. Anderson and W. P. Jencks, THIS JOURNAL, **82**, 1773 (1960).



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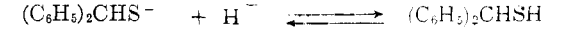

The reactions in question are not necessarily comparable. If, with benzophenone as with pyruvic acid, the formation of an adduct to the carbonyl group is rapid and the rate-controlling step is the loss of water or H_2S, then the analogy may seem a bit forced. The analogy will also fail if the reaction between thiobenzophenone and 1-benzyl-1,4-dihydronicotinamide should eventually prove to be a free-radical process; the available evidence[1] suggests that such is not the fact. But a possibility exists that the reactions are nevertheless fundamentally similar. One cannot examine the rate of the acid-catalyzed reactions of 1,4-dihydropyridines with ketones because the heterocycles, like DPNH itself, are sensitive to acid, and decompose irreversibly in solutions of $pH < 7$. The reaction of the thioketone (eq. 3) in alkaline solution will lead to the formation of a mercaptide ion. Here the greater stability of the mercaptide ion, relative to that of an alkoxide ion, may be one of the fundamental causes of the rapid reaction of the thioketone relative to that of the oxygen ketone. A second reason (which would of course apply to any reaction of thiobenzophenone regardless of mechanism) is the much higher energy of the starting material, *i.e.*, the much lower stability of the C=S bond as contrasted to the C=O bond. This second argument, however, appears relatively unconvincing, since sodium borohydride in "80%" alcohol reduces thiobenzophenone only about ten times as fast as it reduces benzophenone.[2]

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