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Kinetics of Thiosemicarbazone Formation of Some Alkylbutyrophenones

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The energies and entropies of activation have been determined for the thiosemicarbazone formation of butyrophenone and three alkylbutyrophenones in anhydrous methanol with a pyridine–pyridine hydrochloride buffer. The data show that the "*ortho*-effect" of a methyl group which slows the reaction by a factor of 20 is primarily a result of an increased E_a and not a change in ΔS^*. A comparison of the values for 2,5-dimethylbutyrophenone and 2-methyl-5-isopropylbutyrophenone indicates that the *m*-isopropyl group causes a marked lowering of E_a and increases in negative value of ΔS^* over the *m*-methyl group. This effect is attributed to steric requirements of the isopropyl group.

Recent contributors[2] to the study of semicarbazone and oxime formation have dealt with *p*- and *m*-substituted aldehydes and ketones and have discussed the variations of rates and energies of activation in terms of the polar effects of the substituent. The carbonyl reaction is, however, strongly dependent on the steric requirements of the ketone, as well.[3] The energies and entropies of activation calculated from rate constants reported by Lester and co-workers for the hydroxylamine reaction with *o*-alkylphenyl ketones[4] show rather marked and somewhat unexpected differences among the four series of ketones studied. Notable among these values is the large difference in entropy of activation between 2-methylbutyrophenone and 2-methyl-5-isopropylbutyrophenone. Since it was considered very likely that for these closely related aromatic ketones the effects of substituents would be very similar on the hydroxylamine and thiosemicarbazide reactions, it seemed possible that confirmation of such a value could be obtained through a study of thiosemicarbazone formation under similar conditions. There was, however, the possibility that no such correlation would be found, since Fitzpatrick and Gettler[5] in their study of oxime formation found a distinct lack of correlation in the differences in ΔH^* with those obtained by Price and Hammett[3] for semicarbazones; there was also no similarity in the order of $\Delta\Delta S^*$. A study of the thiosemicarbazide reaction with the *o*-substituted ketones was undertaken to learn whether such a correlation exists and to obtain the energy and entropy of activation values.

Results and Discussion

The rates of formation of butyrophenone semicarbazone and the thiosemicarbazones of butyrophenone and three alkylbutyrophenones were determined in anhydrous methanol with a pyridine–pyridine hydrochloride buffer; the apparent *p*H of the reaction solution was 3.5. It proved to be more convenient to study the thiosemicarbazones rather than the semicarbazones, since the former absorb more strongly in the ultraviolet and have maxima at longer wave lengths; the reaction was followed by the increase in absorption by the product. The assumption has been made that the kinetics of the semicarbazide reaction would also apply for thiosemicarbazide. This assumption seems justified by the constancy of the pseudo-second-order rate constants obtained. It is not known whether the measurements apply to the rate of attack of the nitrogen base on the carbonyl group or to a pre-equilibrium formation of an addition compound followed by a rate-limiting dehydration as discussed by Anderson and Jencks.[2c]

The rate constants obtained at 25 and 39° and the calculated energies and entropies of activation

TABLE I

DATA FOR REACTIONS OF KETONES WITH THIOSEMICARBAZIDE, SEMICARBAZIDE AND HYDROXYLAMINE IN ANHYDROUS METHANOL

	10^4k_{25}[a]	10^4k_{39}[a]	E_a[a]	ΔS^*[a,f]
Thiosemicarbazone				
Butyrophenone	35.6	64.6	7.9	−45.2
2-Methyl-	1.40	2.85	9.4	−46.5
2,5-Dimethyl-	1.50	3.20	10.1	−44.3
2-Methyl-5-isopropyl-	1.45	2.50	7.2	−53.9
Semicarbazone				
Butyrophenone	268	398[b]	7.7	−41.9
Oxime				
Butyrophenone[c]		215[d]	13.3	−30
2,5-Dimethyl-[c]		12.0[d]	13.8	−30
2-Methyl-5-isopropyl-[e]		8.91[d]	10.6	−40

[a] Units: k, l. mole^{-1} sec.$^{-1}$; E_a, kcal. mole^{-1}, ΔS^*, cal. deg.$^{-1}$ mole^{-1}. [b] At 35°. [c] Calculated from rate constants given in ref. 4a. [d] At 40°. [e] Ref. 4b. [f] ΔS^* calculated from E_a by $E_a = \Delta H^* - RT$ and $\Delta S^* = R \ln k_T - R \ln kT/h + \Delta H^*/T$.

TABLE II

ABSORPTION DATA FOR KETONES AND DERIVATIVES

	Ketone		Thiosemicarbazone		
	ϵ[a]	λ_{max}, mμ[a]	ϵ[b]	λ_{max}, mμ[b]	M.p. (cor.), °C.
Butyrophenone	12000	244	23300	298	99
2-Methyl-	8500	244	22200	273	138
2,5-Dimethyl-	7800	248	22200	274	97
2-Methyl-5-isopropyl-	7600	238	22200	273	142
Butyrophenone semicarbazone			15900	274	

[a] In ethanol–water (1:1). [b] In reaction solvent and buffer diluted 100 times with ethanol–water (1:1).

(1) M.A. Thesis of M. Joanne Brownlee (1960) and A.B. Thesis of Maretta T. Paige (1958), Mount Holyoke College.

(2) (a) D. S. Noyce, A. T. Bottini and S. G. Smith, *J. Org. Chem.*, **23**, 752 (1958); (b) W. P. Jencks, THIS JOURNAL, **81**, 475 (1959); (c) B. M. Anderson and W. P. Jencks, *ibid.*, **82**, 1773 (1960); (d) J. D. Dickinson and C. Eaborn, *J. Chem. Soc.*, 3036 (1959); (e) J. D. Dickinson and C. Eaborn, *ibid.*, 3641 (1959).

(3) F. P. Price, Jr., and L. P. Hammett, THIS JOURNAL, **63**, 2387 (1941).

(4) (a) E. C. Suratt, J. R. Proffitt, Jr., and C. T. Lester, *ibid.*, **72**, 1561 (1950); (b) M. J. Craft and C. T. Lester, *ibid.*, **73**, 1127 (1951).

(5) F. W. Fitzpatrick and J. D. Gettler, *ibid.*, **78**, 530 (1956).

are recorded in Table I. The results show an increase in E_a with a methyl substituent in the 2-position; no change in E_a greater than the probable error occurs with further methyl substitution in the 5-position, but the 5-isopropyl group lowers E_a considerably. The data show no difference in the entropy of activation, ΔS^*, due to 2-methyl or subsequent 5-methyl substitution; however, the 5-isopropyl group produces a large change to a more negative ΔS^*. These results are in accord with the data on the oximes[4] of Lester and co-workers included in Table I.

o-Substitution reduces the rate of this reaction to about one-twentieth. This slower rate is shown to be due almost entirely to the greater energy of activation, since there is little change in the entropy of activation. The contributions of both polar and steric effects to changes in E_a have been discussed[6] by Taft and by Ingold. For the polar contribution of the *o*-methyl substituent, an approximation can be made by analogy to the *p*-methyl group which Dickinson and Eaborn[2d] found causes a slight increase in E_a and a slight decrease in rate for oxime formation. Brown and Barbaras[7] proposed that the increase in strain of the transition state from the *o*-substituent should increase the energy of activation over that of the unsubstituted ketone. Thus steric and polar effects should act in the same direction to slow the reaction. The large negative value for ΔS^* for the semicarbazide reaction has been interpreted by Price and Hammett[3] to mean that the formation of the transition state involves a considerable loss in degrees of freedom even for the unsubstituted ketone. The lack of a significant change here in ΔS^* due to the *o*-substituent must mean that the *o*-methyl group does not interfere in internal motions of the transition state to any greater extent than it does in the reactant ketone.

The data for 2,5-dimethylbutyrophenone are in accord with the report of Dickinson and Eaborn[2d] that the *m*-methyl group makes no significant contribution to E_a or to the rate of reaction (the differences shown in Table I being of the order of the probable error). In the light of these data, the differences in E_a and ΔS^* produced by the change from *m*-methyl to *m*-isopropyl are of special interest. The decrease in E_a and increase in the negative value of ΔS^* occur in both the hydroxylamine and thiosemicarbazide reactions. It is possible that the presence of the larger isopropyl group in the *m*-position in conjunction with the *o*-methyl makes such spatial requirements that the additional interference in internal motion of the transition state becomes quite serious, thus accounting for the larger negative value of ΔS^*.

The lowering of the energy of activation by the 5-isopropyl group is unexpected. It is of interest, however, to note from the absorption data for the series of ketones that, though the 2-methyl substituent does not affect the λ_{max}, the shift to a shorter wave length due to the 5-isopropyl group is in contrast to the shift toward a longer wave length shown by the 5-methyl group. Both kinetic and spectral data might indicate some steric inhibition by the isopropyl group to resonance of the carbonyl group and the ring.

The reaction of butyrophenone with semicarbazide is faster than that with thiosemicarbazide with a less negative ΔS^* and no difference in E_a. Thiosemicarbazide hydrochloride in water has a pK_a of 2.25 and semicarbazide hydrochloride a pK_a of 3.36[8]; thus the stronger base (the oxygen compound) reacts faster.

Experimental

Materials.—**2-Methylbutyrophenone** was prepared by the dropwise addition of *o*-methylphenylmagnesium bromide (from 25 g. of halide) to 100% excess of butyryl chloride (30 g.) in ether solution. After addition was completed, the reaction mixture was poured over ice and washed with sodium hydroxide solution. The ether solution was dried, the ether distilled off, and the product distilled through a Todd column (yield 10 g. (42%), b.p. 92.5° at 5 mm., $n^{24}D$ 1.5149).

2,5-Dimethylbutyrophenone was prepared by the Friedel-Crafts reaction using *p*-xylene (m.p. 13.2°). Final distillation was with a Todd column, b.p. 80–82° at 1.5 mm., $n^{24.2}D$ 1.5142 (reported[9] 119° at 7 mm., $n^{30}D$ 1.5124).

2-Methyl-5-isopropylbenzoic acid, prepared as previously described,[10] was purified further by recrystallization of the salt formed with S-benzylthiuronium chloride[11] (m.p. 143.2–143.8°). The acid recovered by hydrolysis with dilute hydrochloric acid melted at 69.7–71.0° (lit.[10] 71°). The acid chloride (b.p. 112–114° at 12 mm.) was prepared using thionyl chloride in benzene solution.

2-Methyl-5-isopropylbutyrophenone was obtained by refluxing the acid chloride and dipropylcadmium in benzene for 3 hours before working up in the usual way.[12] The ketone was distilled through a small vacuum-jacketed column packed with a tantalum coil, b.p. 95–96° at 1 mm., $n^{24}D$ 1.5047 (reported[4b] 102° at 2 mm.). The yield of ketone from 7.8 g. of acid chloride was 5.9 g. (72%).

Butyrophenone (Eastman Kodak Co. white label) had a boiling range of 74–75° at 2 mm. and was used without purification. Fisher A 412 methanol was dried by distillation from magnesium methoxide.[13] Fisher reagent pyridine was dried by distillation from barium oxide.

Pyridine hydrochloride was precipitated from a solution of dry pyridine in anhydrous ether by dry hydrogen chloride gas. The precipitate was filtered rapidly, washed repeatedly with dry ether and stored in a vacuum desiccator over phosphorus pentoxide.

Thiosemicarbazide hydrochloride was precipitated from a solution of 10 g. of thiosemicarbazide in 50 ml. of water and 50 ml. of concd. hydrochloric acid by saturating with hydrogen chloride gas. This and semicarbazide hydrochloride were recrystallized and titrated immediately before use according to Price and Hammett.[3]

The thiosemicarbazones were prepared by reaction of the ketones with thiosemicarbazide in alcohol slightly acidified with dilute hydrochloric acid. All derivatives were crystallized repeatedly from alcohol or water–alcohol until successive samples melted at the same temperature. The melting points given in Table II are corrected.

The pK_a of thiosemicarbazide hydrochloride was determined to be 2.25 by potentiometric titration of the salt in water with 0.1 *N* NaOH.

Method.—The reaction was followed using a Beckman model DU spectrophotometer at the wave length of maximum absorption of the product (Table II). Before each run 250 ml. of buffer solution was prepared. Pyridine hydrochloride was dissolved in about 100 ml. of dry methanol to give an approximately 1.5 *M* solution; a sample was titrated with 0.1 *N* NaOH and the volume of pyridine hy-

(6) (a) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 556; (b) C. K. Ingold, *Quart. Revs.*, **11**, 1 (1957).

(7) H. C. Brown and G. K. Barbaras, THIS JOURNAL, **69**, 1137 (1947).

(8) J. B. Conant and P. D. Bartlett, *ibid.*, **54**, 2881 (1932).

(9) C. T. Lester and E. C. Suratt, *ibid.*, **71**, 2262 (1949).

(10) C. T. Lester and C. F. Bailey, *ibid.*, **68**, 375 (1946).

(11) J. J. Donleavy, *ibid.*, **58**, 1004 (1936).

(12) J. Cason and F. S. Prout, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 601.

(13) L. F. Fieser, "Experiments in Organic Chemistry," 3rd edition, D. C. Heath and Co., Boston, Mass., 1955, p. 289.

drochloride solution necessary to give a 0.500 M solution was transferred to a 250-ml. volumetric flask; the solution also was made 0.500 M with respect to pyridine; final addition of methanol was made at the reaction temperature. The ketone solution ($4.00 \times 10^{-2}M$) and the thiosemicarbazide hydrochloride solution ($2.00 \times 10^{-2}M$) were made up in the buffered methanol. Equal volumes of the two solutions were mixed for the reaction. Samples of 1 ml. were removed at intervals and diluted 100 times with ethanol–water (1:1), and the optical density was read against a similarly diluted sample of the original buffer solution. Runs were made at 24.97 and 38.90 ± 0.02° (34.83° for the semicarbazone). The reading of the solution on a Beckman pH meter was 3.49 ± 0.02 throughout the reaction. The rate constants were reproducible within 1–2%; activation energies are believed to be accurate to ±0.4 kcal./mole.

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The Mechanism of Solvolysis of Nitrostyrenes

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The kinetics of hydrolysis of 3,4-methylenedioxy-β-nitrostyrene, to piperonal and nitromethane, are characteristic of two consecutive, pseudo-first-order reactions over the pH range −0.8 to 6. The first is reversible and shows general base catalysis, with the rate constant a non-linear function of the acetate ion concentration. The rate of the second is pH dependent. A mechanism is proposed consistent with these observations.

The base-catalyzed cleavage of 3-methoxy-4-hydroxy-β-nitrostyrene in strongly alkaline solution was shown by Stewart[1] to proceed with attack of a hydroxyl ion *via* the colorless intermediate nitroalcohol. The fact that this cleavage will take place slowly in acid solution[2a] proves, however, that a slightly different mechanism must be possible. In the course of some preliminary work on nitrostyrene formation in acetate buffers (our previous work dealt only with amine catalysis[2]) we had occasion to study the hydrolysis in acid solution and can report new kinetic features.

Experimental

The nitrostyrene used in this work was 3,4-methylenedioxy-β-nitrostyrene (piperonylidenenitromethane), which was prepared by condensation of piperonal and nitromethane.[3] Buffer solutions and hydrochloric acid solutions were prepared from reagent-grade chemicals and distilled water. The ionic strength, here equal to the sodium ion concentration, was kept constant at 0.1 M by adding sodium chloride, except for a series of runs at 0.3 M.

The kinetic runs were started by adding 1 ml. of a freshly prepared 0.002 M methanol solution of nitrostyrene to the aqueous buffer components and adding water to make 100 ml. The flasks were placed in the thermostat and samples analyzed spectrophotometrically without further dilution, at 372 mμ. The optical density at this wave length decreased as the nitrostyrene hydrolyzed, and at first no peak at 312 mμ appeared to indicate the presence of piperonal unless the pH was as high as 6. Piperonal gradually was produced at lower pH, however, but only after a considerable quantity of an intermediate had formed.

In very acidic solution (3 and 6 M HCl) the λ_{max} of the nitrostyrene shifted to 385 mμ.

Results

The hydrolysis of nitrostyrene showed complex kinetics, though all the reactions involved were pseudo first order because of the high dilution of the substrate in comparison with the buffer components. Figure 1 shows typical logarithmic plots of concentration *vs.* time. At very low pH, equilibrium is reached when about 60% of the nitrostyrene has reacted, and a plot of log $(x_e - x)$ is linear, indicating opposing first-order reactions.

TABLE I

RATE CONSTANTS (SEC.$^{-1}$) FOR NITROSTYRENE HYDROLYSIS

[HAc], M	HCl, M	[Ac$^-$], M	pH[a]	10^6k_1	10^6k_{-1}	10^6k_2	k_1/k_{-1}
0.005		0.05	5.6	3.22	3.86	4.36	0.83
.003		.03	5.6	4.25	6.37	3.72	.67
.001		.01	5.6	1.92		[c]	
.1		.1	4.6	6.34	8.94	0.44	.71
.05		.05	4.6	5.08	7.78	.42	.65
.03		.03	4.6	4.03	6.42	.47	.63
.01		.01	4.6	2.16	3.47	.43	.62
.3		.3	4.5[b]	6.94			
.2		.2	4.5[b]	6.94			
.12		.12	4.5[b]	6.83			
.07		.07	4.5[b]	6.04			
.02		.02	4.5[b]	3.84			
.01		.01	4.5[b]	2.03			
.008		.008	4.5[b]	1.69			
.006		.006	4.5[b]	1.39			
.004		.004	4.5[b]	0.91			
.002		.002	4.5[b]	.58			
.25		.025	3.6	3.16	4.83	0.075	0.65
.05		.005	3.6	1.24	2.13	.103	.58
	0.0012		2.9	0.181	0.42	.114	.44
	0.012		1.9	.186	.42	.114	.44
	0.12		0.9	.181			.53
	3.0		−0.5	.091		[c]	
	6.0		−0.8	.086		$k_2 > k_1$	
	0.0012		2.9[d]	1.92			
	.012		1.9[d,e]	0.15			
	.006		2.2[d,e]	.12			

[a] Using 2.8×10^{-5} for K_{HAc} in 0.1 M NaCl (M. Kilpatrick and R. D. Eanes, *J. Am. Chem. Soc.*, **75**, 586 (1953)). [b] Ionic strength 0.3, $K_{HAc} = 3.2 \times 10^{-5}$. [c] k_2 to close to k_1 for accurate determination. [d] Temperature 45°. [e] Solvent 99% D_2O.

At a slightly higher pH, a slow reaction becomes apparent after the first equilibrium is established. This reaction is so rapid at pH 7 that the first step is rate controlling and simple first-order kinetics are obtained. These observations may be represented by the scheme

$$\mathrm{I} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{II} \xrightarrow{k_2} \mathrm{III} \qquad (1)$$

which is confirmed by the spectral changes described in the Experimental section.

(1) R. Stewart, *J. Am. Chem. Soc.*, **74**, 4531 (1952); see also a study of nitrochalcones by E. A. Walker and J. R. Young, *J. Chem. Soc.*, 2045 (1957).

(2) (a) T. I. Crowell and F. A. Ramirez, *J. Am. Chem. Soc.*, **73**, 2268 (1951); (b) T. I. Crowell and D. W. Peck, *ibid.*, **75**, 1075 (1953).

(3) N. A. Lange and W. E. Hambourger, *ibid.*, **53**, 3865 (1931).