property of the reacting system. However, it should be pointed out that the large positive entropies which Stearn and Eyring found for fast reactions do not appear in the present investigation. Quite possibly, the reaction under consideration is not fast enough for a large entropy of activation. In any case, the accuracy of ΔS^* as the difference between two large numbers is small enough that speculation seems fruitless.

In the case under consideration we seem to have a reaction which exhibits both the anomalies of the collision theory, that is, it may be either too fast or too slow for the simple theory. The changes when the base of the chlorimine is varied are very great, and difficult of explanation, since the type of reaction is essentially unchanged. When the activated complex concept is applied, the anomalies disappear, and instead regularities appear which are in accord with such other data as can be found. It would appear, then, as though the activated complex approach were the more fruitful attack in explaining the rate of reactions, at least those that deviate from the normal.

Conclusion

The rates of reaction of several chlorimines with various bases in several solvents have been measured, and the results calculated according to the two alternative procedures for explaining the dependence of rate on temperature. The activated complex explanation seems to be the more successful, admitting of several correlations with other data which do not appear in the collision theory.

DURHAM, NORTH CAROLINA RECEIVED JUNE 23, 1941

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Effect of Structure on Reactivity of Carbonyl Compounds; Temperature Coefficients of Rate of Formation of Several Semicarbazones[1]

BY FRASER P. PRICE, JR., AND LOUIS P. HAMMETT

The reaction of ketones and aldehydes with typical carbonyl reagents such as hydroxylamine, hydrazine, and semicarbazide shows a dependence of reaction rate upon the structure of the carbonyl compound with which existing theory is in no way competent to deal yet which is of large magnitude and is a characteristic concomitant of all reactions of this type.[2] Thus the lengthening of the carbon chain in an aliphatic ketone in proceeding from acetone to diethyl ketone lowers the rates of these reactions by an order of magnitude or so, yet cyclohexanone is considerably more reactive than acetone while cyclopentanone is only slightly more reactive than diethyl ketone.

In approaching a phenomenon as challenging as this, it is important to remember that the effect of a change in structure of reactant upon rate of reaction can be explained in terms of internal electron displacements or of external electrical fields due to a substituting group, in terms that is of potential energies alone, only when there is a cancellation of other effects due to the internal kinetic energies of the reactants[3]; further that the criterion of this cancellation is that the quantity

$$\Delta S_1^{\ddagger} - \Delta S_2^{\ddagger} = \frac{\partial}{\partial T}\left(RT \ln \frac{k_1}{k_2}\right) \qquad (1)$$

shall vanish (the subscripts 1 and 2 refer to two different reactants, k is specific reaction rate, $\Delta S^{\ddagger}$ is entropy of activation). The study of temperature coefficients of reaction rate is therefore prerequisite to a serious investigation of such a problem as the one in question, and the present paper furnishes the necessary data for the reaction of a variety of carbonyl compounds with semicarbazide in a phosphate buffer of pH 7.0. The stoichiometric equation for the reaction is

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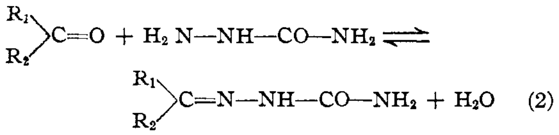
(1) Dissertation submitted by Fraser Pierpont Price, Jr., in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

(2) Among the more important papers on this subject are: (a) Westheimer, THIS JOURNAL, **56**, 1962 (1934); (b) Conant and Bartlett, *ibid.*, **54**, 2881 (1932); (c) Ölander, *Z. physik. Chem.*, **129**, 1 (1929); (d) Ardagh and Williams, THIS JOURNAL, **47**, 2976, 2983 (1925); (e) Bodforss, *Z. physik. Chem.*, **109**, 223 (1924); (f) Michael, THIS JOURNAL, **41**, 393 (1919); (g) Acree, *Am. Chem. J.*, **39**, 300 (1908); (h) Barrett and Lapworth, *J. Chem. Soc.*, **93**, 85 (1908); (i) Acree and Johnson, *Am. Chem. J.*, **38**, 308 (1907); (k) Stewart, *J. Chem. Soc.*, **87**, 410 (1905); (l) Petrenko-Kritschenko, *et al.*, *Ann.*, **341**, 150 (1905); *Ber.*, **34**, 1702 (1901); **39**, 1452 (1906).

(3) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 118–120.



$$R_1R_2C{=}O + H_2N{-}NH{-}CO{-}NH_2 \rightleftharpoons R_1R_2C{=}N{-}NH{-}CO{-}NH_2 + H_2O \quad (2)$$

but the work of Conant and Bartlett[2b] shows that the reaction is subject to a general acid catalysis and that the transition state is therefore composed of carbonyl compound, semicarbazide, and the catalyzing acid (in this case $H_2PO_4^-$).

Experimental

Method.—The reaction was followed by iodine titration of the unreacted semicarbazide, essentially according to the method of Conant and Bartlett,[4] which consists of pipetting an aliquot of reacting solution into a flask containing an excess of standard iodine dissolved in a strong phosphate buffer of *p*H 7 or 7.5, adding a small excess of standard thiosulfate and back-titrating with iodine. In order to obtain the precision required for the measurement of temperature coefficients, it is necessary to correct for the hydrolysis of semicarbazone which occurs during these manipulations or to adjust the prevailing conditions so that the hydrolysis is negligible. The value of this correction was determined as follows: an approximately 0.02 *M* solution of the semicarbazone in question of exactly known concentration was allowed to stand overnight for partial hydrolysis. Then a 10-cc. aliquot of this solution was run into a 250-cc. flask containing a known amount of phosphate buffer and an excess of standard iodine solution, the total volume being about 125–150 cc. The time was noted when the aliquot was introduced and when the titration was finished. Immediately about 1 cc. more of the iodine solution was introduced and the procedure repeated several times over a period of about five minutes. The whole procedure was done at least three times. The time was plotted against the volume of iodine used. In this manner the volume of iodine used per second due to the hydrolysis of the semicarbazone was found. The magnitude of this correction may be decreased by lowering the temperature, by decreasing the buffer concentration, and by increasing the *p*H of the solution. Table I contains the conditions actually used for the titration, together with the values of the correction. Whenever the conditions of the titration were changed a comparison was made between conditions that were known to be reliable and the new ones by determining the concentration of a known semicarbazide solution under the new conditions.

TABLE I

CONDITIONS FOR TITRATION OF SEMICARBAZIDE IN PRESENCE OF SEVERAL SEMICARBAZONES

10-cc. Aliquots of semicarbazone soln.

Semicarbazone	Medium Concn., *M*	Buffer, cc.	*p*H	Temp.	Rate of disappearance of 0.004 *M* I_2 soln., cc./sec.
Acetone	0.015	20 Buffer A	7.0	Ice	8.3×10^{-4}
Diethyl ketone	.004	10 Buffer A	7.0	Ice	0.0×10^{-4}
Pinacolone	.018	20 Buffer A	7.0	Room	0.0×10^{-4}
Cyclopentanone	.012	20 Buffer A	7.0	Ice	0.0×10^{-4}
Cyclohexanone	.009	10 Buffer B	7.5	Ice	30.0×10^{-4}
Furfural	.010	20 Buffer A	7.0	Room	0.0×10^{-4}
Acetophenone	...	20 Buffer A	7.0	Room	0.0×10^{-4}

Buffer A: 0.550 *M* Na_2HPO_4, 0.275 *M* NaH_2PO_4
Buffer B: 0.357 *M* Na_2HPO_4, 0.0564 *M* NaH_2PO_4

The solubility of acetophenone semicarbazone is so low that it was impossible to make up a 0.01 *M* solution. The rate of hydrolysis given is for the amount which did dissolve out of 0.001 mole in 100 cc. in three days of shaking. However, the fact that the actual concentration of this semicarbazone was unknown introduces no error because its concentration during a run could not be appreciably higher than that in the solution tested.

In calculating the corrections applied to titers in a rate determination the time of titration was noted and the rate of disappearance of iodine was taken as proportional to the concentration of the semicarbazone.

The procedure for making a run when the reaction rate was high as in the case of cyclohexanone or acetone was as follows. Into a 250-cc. glass-stoppered reaction flask was pipetted the reaction medium, a phosphate buffer of *p*H 7.0, and an aliquot of carbonyl compound of known concentration in that buffer and into the side-bulb of the flask an aliquot of semicarbazide in the same buffer. The semicarbazide solution was always made up, standardized and used on the same day. The flask was put in the thermostat for at least one hour to come to temperature. Then measured amounts of standard iodine solution were run into iodine flasks containing buffer and ice and these flasks set in ice water. The reaction was started by removing the flask from the thermostat, inverting, shaking well and replacing in the thermostat. As soon as possible an aliquot was taken with a fast draining 10-cc. pipet, run into one of the iodine flasks and titrated. The time was noted

TABLE II

SAMPLE DATA: CYCLOHEXANONE SEMICARBAZONE FORMATION

Medium: 0.0571 *M* Na_2HPO_4, 0.0286 *M* NaH_2PO_4; temp. 25.11°; initial concn., cyclohexanone 0.01055 *M*, semicarbazide 0.009254 *M*; I_2 0.004011 *M*; 9.939 cc. aliquots used; time in sec.

Time	Titration ended, sec.	Cc. I_2 used	Hydrolysis corrn.	Cc. I_2 used (cor.)	Semicarb. concn. $\times 10^3$	*k*
60.3	111	33.67	0.04	33.63	6.786	
181.7	231	22.87	.08	22.79	4.599	0.598
295.6	352	18.89	.10	18.79	3.791	.586
425.5	487	16.85	.12	16.73	3.376	.516
554.7	615	15.93	.12	15.81	3.190	.563
					Av.	.566

Medium: 0.0571 *M* Na_2HPO_4, 0.0286 *M* NaH_2PO_4; temp. 25.01°; initial concn., acetophenone 0.01009, semicarbazide 0.007888; I_2 0.003998 *M*; 9.939-cc. aliquots used; time in sec.

Time	Cc. I_2 used	Semicarb. concn. $\times 10^3$	$k \times 10^4$
101	38.93	7.830	
11,422	37.40	7.522	3.76
21,580	35.89	7.218	4.24
28,692	34.66	6.971	4.72
38,187	33.60	6.758	3.80
		Av.	4.13

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[4] Conant and Bartlett, THIS JOURNAL, 54, 2881 (1932).

when the pipet started delivering and when the titration was completed, the time for the pipet to deliver half its contents having previously been determined. The time at which the pipet was half emptied was used as the time, t, in the rate equation. With this procedure it was possible to do five titrations in ten to twelve minutes as in the data on cyclohexanone in Table II. Table II also contains sample data on a slow reaction, that of acetophenone.

Computation.—In those cases where a determination of the equilibrium constant was possible by analysis of a system which had attained equilibrium, the rate constants for semicarbazone formation were determined by the equation developed by Conant and Bartlett,[2b]

$$kt = \frac{1}{2x_e + c + K}\left[\ln\left(\frac{x + x_e + c + K}{x - x_e}\right)\right] + C \qquad (3)$$

which holds for a second order forward and first order reverse reaction. Here k is the second order formation constant; t, the time in seconds; x, the semicarbazide concentration at time, t; x_e, the equilibrium concentration of semicarbazide; c, the difference between initial concentrations of carbonyl compound and semicarbazide; K, the equilibrium constant for hydrolysis, *i. e.* $K = k_{\text{reverse}}/k_{\text{forward}}$; and C, a constant involving initial and final concentrations. The value of k was determined by least squares methods applied to a plot of the first term on the right against t. This method was used for acetone, diethyl ketone, cyclopentanone and cyclohexanone semicarbazone formation. The constants for pinacolone, furfural and acetophenone were determined on the basis of an irreversible second order forward reaction. This was done because of the fact that semicarbazide decomposes in solution into hydrazine and hydrazodicarbamide to an extent which is appreciable during the time required for equilibrium to be attained in these semicarbazone reactions. In the cases of furfural and acetophenone the equilibrium was so far toward completion that a least squares plot showed no falling off of the rate constant during the time the reaction was studied. Pinacolone, however, showed considerable curvature and the initial slope of the curve was obtained by a graphical method of numerical differentiation.

Since the problem under discussion is that of the effect of a change in structure upon reaction, the pertinent quantities are not the absolute values of the free energy, $\Delta G^{\ddagger}$, entropy, $\Delta S^{\ddagger}$, and heat, $\Delta H^{\ddagger}$, of activation for a single reaction, but rather the values of these quantities relative to that of a standard reactant, for which acetone has been used. The equations used for the calculation of these relative quantities are[3]

$$\Delta G^{\ddagger} - \Delta G_0^{\ddagger} = -RT \ln k/k_0 \qquad (4)$$

$$\Delta S^{\ddagger} - \Delta S_0^{\ddagger} = \frac{\partial}{\partial T}(RT \ln k/k_0) \qquad (5)$$

$$\Delta H^{\ddagger} - \Delta H_0^{\ddagger} = RT^2 \frac{\partial}{\partial T}(\ln k/k_0) \qquad (6)$$

In all these equations symbols with the subscript zero refer to the standard substance, those without subscript to the carbonyl compound in question. These relative free energies, entropies and heats of activation can be visualized as the thermodynamic functions of the process

$$\text{A} + \text{Acetone}^{\ddagger} \rightleftharpoons \text{A}^{\ddagger} + \text{Acetone}$$

with the starred symbols representing the transition states for semicarbazone formation of the substance referred to and A symbolizing any carbonyl compound.

In the computations finite increments were substituted for the differentials in equations 5 and 6. Rate constants k_h for hydrolysis of semicarbazones were computed from the equilibrium constants and rate constant for formation.

Apparatus.—The thermostat used at temperatures in the neighborhood of 25° was of conventional design; that employed at temperatures around 0° was a simple and effective apparatus, based upon a suggestion of Prof. G. H. Walden, and apparently not described elsewhere.

It consists of two cork insulated tanks containing an ethylene glycol–water mixture. One tank is maintained at about −5° by a large General Electric Type CK-35 refrigerating unit whose cooling coils are immersed in the liquid. The other tank is maintained at constant temperature by forcing the cold liquid into it as required by means of a gear pump which is controlled by a mercury regulator and a thermionic relay. The liquid returns to the first tank through a pipe set near the top of the constant temperature bath. The motor has a variable rheostat connected in series with it to cut down its power and also to prevent damage to the commutator by arcing. There is a 60-watt lamp bulb immersed in the bath which operates alternately with the pump to take up the thermal lag after the pump has stopped. Also there is a float device which automatically shuts off the pump if the level of liquid rises too high. It was found that the delivery of the $^3/_8$-in. pipe from the pump was too great for the temperature control desired and hence a by-pass of 8-mm. glass and rubber tubing was made so as to pass most of the liquid delivered by the pump back into the −5° tank with some being taken off through a T-tube into the constant temperature tank.

This thermostat gives very satisfactory results not varying more than ±0.002° over a period of about six months in the winter. In the summer it is necessary to cover it with a lid to get this control.

The timing of the kinetic runs was done with an A. R. & J. E. Meylan one-fifth second split timer. This type of stop watch was found very convenient for timing intervals of about two minutes to the precision desired.

The pipets used for taking aliquots of reaction mixtures were 10-cc. volumetric pipets with the tips slightly enlarged to make them drain in about eight seconds. In spite of this short drainage time it was found possible to obtain a reproducibility of better than 0.01 cc. For each pipet the time for half delivery was determined as it was found easier to record the time of start of delivery than that of half delivery. The pipet used in the 0° work was wrapped with asbestos paper and kept in a well in the thermostat. The pipets were calibrated as were all burets and volumetric flasks.

The reaction flasks were 250-cc. Pyrex flasks with a 40-cc. side-bulb and fitted with standard taper ground glass stoppers.

Materials.—Allen E. Rogers Labs C. P. semicarbazide hydrochloride was further purified in 10-g. lots by dissolving this weight in 19 cc. of water and saturating with hydrogen chloride. The recrystallized product was dried *in vacuo* over calcium chloride and sodium hydroxide. Two such recrystallizations yielded a product whose acidimetric titer was within 2 parts per 1000 of its iodometric titer; yield per recrystallization approx. 85%.

Eimer and Amend acetone was redistilled three times at atmospheric pressure in all-glass apparatus; b. p. 56.5°.

Du Pont Co. cyclohexanone was redistilled twice; b. p. 155°. Org. Prep. Lab. of Columbia Univ. cyclopentanone was redistilled; b. p. 130°.

Eastman Kodak Co. diethyl ketone was redistilled; b. p. 102.5–103.0°.

Eastman Kodak Co. pinacolone was redistilled; b. p. 106.0–106.5°.

Kahlbaum furfural was redistilled three times and used the next day; b. p. 161–162°.

Some acetophenone previously used in this Laboratory was purified by successive partial freezing and removal of the liquid center[5]; m. p. 19.65°.

Baker and Adamson sodium phosphates were used to make up buffer solution.

Dilatometer Experiments.—In some preliminary experiments the attempt was made to follow the rate both of semicarbazone formation and of oxime formation by dilatometer methods. With both these reactions the volume of the solution appeared first to expand and then to contract. The phenomenon was so reproducible in spite of many attempts to improve the quality of the stopcock closure used in the dilatometer that it may well be a real and significant property of these reactions.

The dilatometer had a capillary of 0.2-mm. diameter. In spite of these small dimensions, the meniscus could be seen easily with the aid of a Beckmann thermometer reading glass, provided the capillary was backed with a milk glass scale illuminated from behind.

TABLE III

Rate constants, k, in l./mole sec. for semicarbazone formation in buffer of pH 7.0; buffer, 0.0571 M Na_2HPO_4, 0.0286 M NaH_2PO_4

Acetone	0.04°	25.11°
	0.0612	0.0863
	.0630	.0873
	.0638	.0847
	.0661	
	Av. .0635	Av. .0861
Diethyl ketone	0.03°	25.00°
	0.00687	0.00827
	.00659	.00860
	.00716	.00878
	Av. .00688	Av. .00855
Pinacolone	0.04°	25.00°
	0.000741	0.000999
	.000753	.000992
	.000817	.001027
	Av. .000771	Av. .001006
Cyclopentanone	0.04°	25.10°
	0.00822	0.0152
	.00817	.0153
	.00814	.0147
	.00850	.0160
	Av. .00826	Av. .0153
Cyclohexanone	0.03°	25.11°
		0.506
	0.423	.495
	.430	.563
	.458	.485
	Av. .437	Av. .512
Furfural	0.03°	25.00°
	0.00647	0.0120
	.00645	.0122
	.00674	.0127
	Av. .00656	Av. .0123
Acetophenone	0.04°	25.01°
	0.000204	0.000417
	.000204	.000410
	.000203	.000414
	Av. .000204	Av. .000413

Results

The experimental results of this investigation are given in Tables III and IV.

From equations 5 and 6 and the data listed in Table III the values of the relative entropies and heats of activation for semicarbazone formation were calculated and the values of the relative free energies of activation were calculated from these. They are given in Table V.

From the data in Table IV the analogous functions for the reverse reaction were calculated and are given in Table VI. The thermodynamic functions for the total forward reaction are given in Table VII.

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[5] Flexser, Hammett and Dingwall, THIS JOURNAL, 57, 2103 (1935).

TABLE IV

EQUILIBRIUM CONSTANTS, K_H, AND RATE CONSTANTS, k_h, FOR HYDROLYSIS OF SOME SEMICARBAZONES. SAME MEDIUM AS IN TABLE III

	Temp., °C.	$K_H \times 10^3$	$k_h \times 10^4$, sec.$^{-1}$
Acetone	25.11	3.23	2.78
	0.04	0.804	0.511
Diethyl ketone	25.00	26.4	2.26
	0.03	8.86	0.609
Cyclopentanone	25.10	1.48	0.226
	0.04	0.461	0.0381
Cyclohexanone	25.11	2.06	10.6
	0.03	0.510	2.23

TABLE V

RELATIVE ENTROPIES, HEATS, AND FREE ENERGIES OF ACTIVATION FOR SEMICARBAZONE FORMATION AT 12.5°

$\Delta H_0^{\ddagger} = 2000$ cal.

	$\Delta S^{\ddagger} - \Delta S_0^{\ddagger}$, cal./°C.	$\Delta H^{\ddagger} - \Delta H_0^{\ddagger}$, cal.	$\Delta G^{\ddagger} - \Delta G_0^{\ddagger}$, cal.
Acetone	0.00	0	0
Diethyl ketone	−6.50	−600	1300
Pinacolone	−9.70	−200	2500
Cyclopentanone	3.30	2000	1100
Cyclohexanone	0.40	−900	−1100
Furfural	3.20	2100	1200
Acetophenone	−1.90	2600	3200

TABLE VI

RELATIVE ENTROPIES, HEATS AND FREE ENERGIES OF ACTIVATION FOR SEMICARBAZONE HYDROLYSIS AT 12.5°

$\Delta H_0^{\ddagger} = 11{,}000$ cal.

	$\Delta S^{\ddagger} - \Delta S_0^{\ddagger}$, cal./°C.	$\Delta H^{\ddagger} - \Delta H_0^{\ddagger}$, cal.	$\Delta G^{\ddagger} - \Delta G_0^{\ddagger}$, cal.
Acetone	0.00	0	0
Diethyl ketone	−8.70	−2500	0
Cyclopentanone	−3.20	600	1500
Cyclohexanone	−0.40	− 900	−800

TABLE VII

THERMODYNAMIC DIFFERENCES FOR SEMICARBAZONE FORMATION AT 12.5°

$\Delta H_0 = -9000$ cal.

	$\Delta S - \Delta S_0$, cal./°C.	$\Delta H - \Delta H_0$, cal.	$\Delta G - \Delta G_0$, cal.
Acetone	0.00	0	0
Diethyl ketone	2.20	1900	1300
Cyclopentanone	6.50	1500	−400
Cyclohexanone	0.70	0	−300

The deviation of the mean of the rate constants was taken as the precision measure of the average as the reproducibility was considered a better measure of the accuracy of the constant than the probable error in the least squares slope of any individual measurement. This error ranged from 1 to 2%. The error thus introduced into the entropy differences is about 0.70 cal./°C., into the energy differences about 125 cal., and into the free energy differences about 200 cal.

Discussion

The present results emphasize the complete hopelessness of any general theory of the effect of structure on reactivity which is based upon considerations of potential energy alone. The entropies of activation for semicarbazone formation of the limited series of carbonyl compounds here studied vary over a total range of 13 cal./degree which is equivalent to three orders of magnitude in the rate of reaction; the variations are many times greater than the probable error in the measurement of the activation entropy; and so typical and familiar a phenomenon as the decrease in reactivity of a carbonyl compound with substitution of methyl for hydrogen on the alpha carbon atom (the series acetone, diethyl ketone, pinacolone) may be attributed almost exclusively to an entropy effect, the variation in heat of activation being comparatively unimportant.

In its broader aspects the effect of changing structure upon the reactivity of aldehydes and ketones offers so consistent a picture[2] that these conclusions apply with high probability to the semicarbazone reaction in other buffer mixtures or in other solvents or, indeed, to other typical carbonyl reactions.

The entropies of activation for the whole series of reactions parallel to a marked extent the rigidity of the carbonyl compound involved. The most rigid of these substances are unquestionably cyclopentanone with its planar ring structure and slightly strained bond angles, and furfural with its rigid ring and the partial double bond character of the link between the carbonyl group and the ring. These substances show the highest entropies of activation, while the lowest value is exhibited by pinacolone $(CH_3)_3CCOCH_3$, whose molecule certainly possesses a large number of internal degrees of freedom. The other carbonyl compounds fit reasonably well into this sequence, except that acetophenone would be expected to be relatively rigid because of the partial double bond character of the link between the carbonyl and the phenyl group.

The parallelism suggests that for some reason the transition state in this reaction possesses a relatively rigid structure, so that a carbonyl compound possessing many degrees of freedom loses most of these on activation, whereas a more rigid carbonyl compound cannot do so. The freezing out of internal motion on formation of the activated state results in a less positive entropy of activation with the less rigid carbonyl compounds.

Such a freezing out is not unreasonable in view of the fact that the transition state system is a strongly polar one with a charge of significant magnitude probably resident in the neighborhood of the carbonyl carbon atom. Professor J. G. Kirkwood has pointed out in conversation that a charged body (the carbonyl group) immersed in a medium of high dielectric constant (the solvent) repels a body of low dielectric constant (methyl groups or the like). If this repulsion is strong enough to constrain the carbon chains in diethyl ketone and pinacolone to lie as far as possible from the carbonyl group in the transition state and hence to lose their freedom of rotation, the observed low entropy of activation is accounted for. Clearly no such effect would be possible with the cyclic compounds. An obvious test of this hypothesis will be to run the reaction in a solvent of lower dielectric constant. The variation in entropy of activation in this series of reactions is higher than is the case in the acid catalyzed ester hydrolysis, whose mechanism is probably similar to that of the semicarbazone formation. In the ester reactions the entropy differences do not exceed 3 cal./deg.[6]

In addition to the variations in entropies of activation and hence in the kinetic energy changes involved in the formation of the transition states, there are clearly important differences in the potential energy. The sequence cyclohexanone, acetone, cyclopentanone is particularly interesting. The first two have practically the same entropy of activation and the increase in potential energy involved in forming the transition state of the cyclic compound is therefore some 1000 calories less than that for acetone. The difference in entropy between acetone and cyclopentanone is in such a direction that the potential energy increase involved in the formation of the transition state for this cyclic derivative must be greater than that for acetone by more than the free energy of activation difference of 1000 cal., probably by more nearly 2000 cal.

The interpretation of this important phenomenon is complicated by the fact that Gordy's[7] measurements of the base strength of these three carbonyl compounds show a qualitative parallelism, although by no means a satisfactory quantitative relation of the linear free energy type, between the rate of the semicarbazone reaction and the equilibrium constant for the addition of a proton to the carbonyl compound. While the ring structure does constrain the atoms attached to two adjacent carbon atoms to have a quite different spatial relation in cyclopentane and in cyclohexane derivatives, it is difficult to see how any differences in energy thus created can account both for the difference in basicity and for that in rate of semicarbazone formation.

The Gordy relationship[7] between basicity and rate of semicarbazone formation was at best semiquantitative when applied to the range of carbonyl compounds available. The present data on the rate of reaction of acetophenone makes its general validity even more doubtful, since the actual rate is nearly two orders of magnitude slower than would be predicted from the basicity by this relationship.

The potential energy barrier opposing the reaction of acetophenone is nearly 3000 cal. higher than that in the case of acetone. This is reasonable since the resonance stabilization of the former ketone by the interaction of the carbonyl with the phenyl group increases the height of the barrier by the amount of the resonance energy, and no such coupling is possible in the transition state.

The nearly identical values of the heats of activation for furfural and acetophenone suggests, although it does not completely prove, that the characteristic difference in reactivity between aldehydes and ketones is largely an entropy effect.

This reaction is one which is very convenient to study. Its rates are fast enough so that considerable data may be obtained in a relatively short time, yet not so fast as to make accurate measurement impossible. The temperature coefficient of the rate is small enough to permit the use of a wide temperature range, which aids greatly in obtaining precision in the determination of heats and entropies of activation. The rate and its temperature coefficient vary sufficiently with varying structure of reactant to warrant considerable trust in the interpretation of the structural effects.

Summary

The Bartlett determination of semicarbazide in the presence of a semicarbazone has been refined by correcting for the error introduced by

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[6] H. A. Smith and others, THIS JOURNAL, **61**, 254, 1172, 1176, 1963 (1939); **62**, 1136, 2733 (1940).

[7] Gordy and Stanford, *J. Chem. Phys.*, **8**, 170 (1940); **9**, 204 (1941); Gordy, *ibid.*, **7**, 93 (1938).

hydrolysis of the semicarbazone during the titration. By this means the rates of semicarbazone formation of a variety of carbonyl compounds, some of them of relativly high reactivity, have been measured with sufficient precision to permit reliable determination of the effect of structure of carbonyl compound upon heat and entropy of activation.

The potential energy barrier opposing the formation of the transition state is of nearly the same height for acetone, diethyl ketone and pinacolone, and the ninety-fold variation in rate of reaction is essentially an entropy effect. The same consideration applies to the thirty-fold difference in rate between acetophenone and furfural.

On the other hand, there is a difference of well over 2000 cal. in the barrier height in the series cyclopentanone, acetone, cyclohexanone, for which no satisfactory explanation seems to be available. The similar difference in barrier height between acetone and acetophenone is no doubt due to resonance stabilization of the latter ketone.

For all the compounds studied the entropy of activation increases with increasing rigidity of the structure of the carbonyl compound, an effect for which an explanation is offered.

A thermostat of new design wherein temperatures around 0° can be obtained to a constancy of ±0.002° is described.

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Esterification Kinetics of Disubstituted Benzoic Acids in Methyl Alcohol

BY A. G. GASSMANN[1] AND R. J. HARTMAN

Investigations of the esterification of substituted benzoic acids have been carried out by Kellas,[2] Goldschmidt,[3] Sudborough and Turner,[4] Hinshelwood,[5] Hartman,[6] and others. The effect of substituents on the reaction velocity of various compounds has been explained in theories presented by Williams[7] and by Hammett.[8] Williams classified reactions into three groups according to the electronic shift toward or away from the point of reaction. The effect on the reaction velocity of a meta or para substituent on the benzene ring is expressed by the Hammett[8] equation

$$\log k = \log k_0 + \rho\sigma$$

where k is the velocity constant of the substituted reactant, k_0 the velocity constant of the unsubstituted reactant, ρ a constant depending on the reaction, medium, and temperature, and σ a constant depending upon the substituent. A prediction of the reaction rate of esterification of substituted benzoic acids is possible if the value of the substituent constant, σ, is known. Hammett[8] has determined values of σ for many mono-substituents from the data of Dippy.[9] However, no values of σ are given for the dichloro and dinitro substituents.

Since the investigations cited above are concerned primarily with mono-substituents, it is not possible to predict the velocities of the reactions of disubstituted compounds. The object of this investigation was to determine the velocity of esterification of 2,4-DiCl, 2,5-DiCl, 3,5-DiCl and 3,5-$DiNO_2$ benzoic acids with methyl alcohol and catalyzed by hydrions. From these data, the energies of activation of the reactions were determined, thus enabling an analysis of the results from the standpoint of the Arrhenius equation.

Experimental

Materials.—Absolute methanol was purified by the method of Bjerrum and Lund[10] with magnesium methylate. Water, aldehyde, and ketone tests were negative. The acids were obtained either from Eastman Kodak Company or from Professor C. S. Marvel of the University of Illinois. The melting points of the purified acids were as follows:

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(1) This paper represents a part of a thesis presented by Albert George Gassmann to the Faculty of the Graduate School of Indiana University in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry.

(2) Kellas, *Z. physik. Chem.*, **24**, 221 (1897).

(3) Goldschmidt, *et al.*, *ibid.*, **60**, 728 (1907); **81**, 30 (191); **143**, 139 (1929).

(4) Sudborough and Turner, *J. Chem. Soc.*, **101**, 237 (1912).

(5) Hinshelwood, *et al.*, *Trans. Faraday Soc.*, **30**, 935, 1145 (1934); *J. Chem. Soc.*, 587, 1588 (1935).

(6) Hartman, *et al.*, THIS JOURNAL, **59**, 2107 (1937); **61**, 2167 (1939); **62**, 1559 (1940).

(7) Williams, *J. Chem. Soc.*, 37 (1937).

(8) Hammett, THIS JOURNAL, **59**, 97 (1937).

(9) Dippy, *J. Chem. Soc.*, 644 (1936).

(10) Bjerrum and Lund, *Ber.*, **B64**, 210 (1931).