[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

Kinetics of Oxime Formation; Temperature Coefficients of Rate of Formation of Several Oximes

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The rates of oxime formation of eleven carbonyl compounds, some of relatively high reactivity and of a variety of structural types, have been measured at zero and twenty five degrees in aqueous solution buffered at *p*H 7. Oxime formation for all the compounds investigated is unambiguously a second-order reaction, irreversible under the experimentol conditions employed in this investigation. Determination of temperature coefficients allowed the calculation of relative thermodynamic activation quantities. A predicted correlation between presumed rigidities of carbonyl compounds and their corresponding activation entropies was not observed. However, a satisfactory linear free energy relationship was obtained for a series of seven of the carbonyl compounds when the logarithms of the specific rates for oxime formation were plotted against the logarithms of previously reported specific rates for semicarbazone formation. The linear free energy relationship suggests the essential soundness of the experimental method, the essential similarity of the semicarbazone and oxime reactions, and the necessity for further examination of the problem of structure and reactivity.

Introduction

As early as 1882, the striking differences in the ease of reaction of carbonyl compounds with hydroxylamine were observed and discussed. In the succeeeding years, the considerable practical and theoretical significance of oxime formation stimulated numerous investigators[2] to study the rates of oximation of a variety of compounds. An appreciable portion of this effort was directed primarily at obtaining relative rates only; in some few instances attention was focused on catalytic effects in carbonyl reactions. In a considerable number of these studies inadequate purification of reactants and solvents, indifference to temperature control, utilization of analytical methods of uncertain reliability, failure to isolate the major reaction from complicating, concomitant reactions of the reagent, hydroxylamine, and lack of cognizance of the importance of trace impurities, particularly those of an acidic or basic nature, render doubtful the value of the experimental results obtained. A critical examination of the literature concerning oxime formation reveals that there is a predominance of approximate, confusing, and in some instances, contradictory data.

Much of this work, particularly the earlier efforts, was stimulated by a desire to find some simple correlation between structure and reactivity, since the condensation of carbonyl compounds with hydroxylamine showed a dependence of rate upon structure for which there was apparently no consistent and all-inclusive explanation.

Of special interest because of its pertinence is the more recent work of Stempel and Schaffel[3] concerning the kinetics and mechanism of phenylhydrazone, semicarbazone and oxime formation. Rates of reaction of the optically active ketone, *d*-carvone, with phenylhydrazine, semicarbazide and hydroxylamine, were measured by observing the change in optical activity during the course of the reaction, thus avoiding the analytical difficulties and uncertainties encountered by earlier investigators. Stempel and Schaffel established for phenylhydrazone, semicarbazone and oxime formation of *d*-carvone the absence of a primary salt effect, the presence of general acid catalysis, and the unambiguous second-order nature of the reaction. These results were in sharp contrast with the data of some previous investigators who reported complex reaction orders for oxime formation; it is noteworthy that these results were in agreement with the work of Conant and Bartlett[4] who established similar findings in the case of semicarbazone formation for a variety of carbonyl compounds.

The apparent similarity of semicarbazone formation and oxime formation,[3,4] the unavailability of many precise and concordant kinetic data on oxime formation, the availability of precise data on the kinetics of semicarbazone formation[3–5] valuable for comparative purposes, and the existence of a satisfactory theoretical interpretation of the effect of structure on reactivity for semicarbazone formation,[5] suggested the desirability of re-examining the relationship between structure and reactivity for oxime formation.

The stoichiometric equation for oxime formation is

$$\begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>C{=}O + H_2NOH \longrightarrow \begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>C{=}NOH + H_2O \quad (1)$$

and the kinetics of this reaction was of prime importance during the current research.

Experimental

Materials.—Eastman Kodak Co. hydroxylamine hydrochloride was further purified by dissolving in a minimum of water and saturating with hydrogen chloride. Three such recrystallizations yielded a product which, when dried *in vacuo* over calcium chloride and sodium hydroxide, possessed an acidimetric titer which was within 2 parts per 1000 of its iodometric titer. Periodic determinations of purity indicated that the compound was perfectly stable when stored under the conditions of drying outlined above.

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(2) (a) A. Janny, *Ber.*, **15**, 2778 (1882); (b) F. Kehrmann, *ibid.*, **21**, 3315 (1888); (c) K. Auwers, *ibid.*, **22**, 604 (1889); (d) P. Petrenko-Kritschenko, *et al.*, *ibid.*, **34**, 1702 (1901); *ibid.*, **39**, 1452 (1906); (e) A. W. Stewart, *J. Chem. Soc.*, **87**, 410 (1905); (f) A. W. Stewart and E. E. Bailey, *ibid.*, **89**, 489 (1906); (g) S. F. Acree and J. M. Johnson, *Am. Chem. J.*, **38**, 308 (1907); (h) S. F. Acree, *ibid.*, **39**, 300 (1908); (i) E. Barrett and A. Lapworth, *J. Chem. Soc.*, **93**, 85 (1908); (j) A. Olander, *Z. physik. Chem.*, **129, 1** (1927); (k) L. Ruzicka and J. B. Buijs, *Helv. Chim. Acta*, **15**, 8 (1932); (l) P. Anziani and G. Vavon, *Bull. soc. chim.*, **4**, 2026 (1927); (m) P. Anziani, *ibid.*, **6**, 1945 (1939); (n) A. R. Poggi, *Gazz. chim. ital.*, **77**, 536 (1947); (o) E. C. Suratt, J. R. Proffit and C. T. Lester, THIS JOURNAL, **72**, 1561 (1950).

(3) G. H. Stempel and G. S. Schaffel, *ibid.*, **66**, 1158 (1944).

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

(5) F. P. Price and L. P. Hammett, *ibid.*, **63**, 2388 (1941).

All ketones were carefully distilled in all-glass apparatus before use.

Eastman Kodak Co. acetone was redistilled; b.p. 56.0°. Eastman Kodak Co. diethyl ketone was redistilled; b.p. 101.5°. Matheson, Coleman and Bell, Inc., pinacolone was redistilled; b.p. 105–106°. Eastman Kodak Co. methyl ethyl ketone was redistilled; b.p. 79–80°. Eastman Kodak Co. cyclohexanone was redistilled; b.p. 154–155°. Matheson Coleman and Bell, Inc., cyclopentanone was redistilled; b.p. 130–132°. Matheson, Coleman and Bell, Inc., di-*n*-propyl ketone was redistilled; b.p. 142–144°. Eastman Kodak Co. methyl isobutyl ketone was redistilled; b.p. 114–116°. Eastman Kodak Co. methyl isopropyl ketone was redistilled; b.p. 93–94°. Eastman Kodak Co. acetophenone was purified by vacuum distillation; middle fractions were retained and found to melt at 19–20°. Eastman Kodak Co. furfural was repurified according to the method of Evans and Aylesworth[6] except that the final distillation was made under vacuum; b.p. 59–60° (15 mm.).

Because of the nature of the analytical method and the well-known tendency of some ketones to peroxidize, the freshly distilled samples, and also samples which had been stored for a time in sealed glass ampoules after purification were subjected to the usual test for peroxides.

Since the mathematical treatment of the experimental results would be determined and possibly considerably complicated by reversal of the oximation reaction, it was essential to determine the extent of hydrolysis in aqueous solution, buffered at *p*H 7, of the oximes of the carbonyl compounds under investigation. To accomplish this, it was required to prepare pure samples of the oximes. This was done essentially by the methods of Shriner and Fuson.[7] After careful purification, the melting or boiling points were determined and found to agree with previously reported literature values.

Preparation of Solutions.—Baker and Adamson sodium phosphates were used to prepare buffer solution. Each buffer solution was prepared by weighing calculated amounts of Na_2HPO_4 and NaH_2PO_4 on an analytical balance. The salts were dissolved in, and the resulting solution was diluted to the proper volume with sterile distilled water. The *p*H of each volume of buffer solution thus prepared was confirmed by measurement with a Beckman *p*H meter, Model G. Periodic measurements indicated that there was no variation in *p*H during the usual short intervals of storage.

For each kinetic experiment a solution of hydroxylamine of known concentration was prepared by dissolving a weighed amount of the purified salt in a weighed amount of buffer solution. Each solution of hydroxylamine was standardized immediately before use.

Solutions of carbonyl compounds of known concentration were prepared in the following manner. A sample of freshly redistilled carbonyl compound was introduced into a previously cleaned, dried and weighed 5-ml. amber glass ampoule by means of a hypodermic syringe. The ampoules were then sealed and weighed. When it was desired to prepare a solution of known concentration of a particular compound, an ampoule containing a known weight of the compound was broken in a previously calculated and weighed amount of buffer solution.

Standard iodine and standard sodium thiosulfate solutions of approximately 0.004 *M* concentration and starch indicator solutions were prepared essentially by the method of Pierce and Haenisch.[8]

Apparatus.—The twenty-five degree thermostat was of conventional design and with proper care and adjustment a temperature of 25.00 ± 0.002° could be maintained.

The zero degree thermostat consisted of a cubical shaped wooden vessel, twenty inches on an edge, lined with copper sheet. The bath liquid was an aqueous methanol mixture. The thermostat was fitted with a vertical propeller type stirrer, a mercury regulator and a plunging mercury relay. The latter controlled the action of an American Instrument Company Portable Cooling Unit, a mechanical refrigerating device, the coil of which was immersed in the bath liquid. By proper adjustment of controls a temperature of 0.00 ± 0.002° could be maintained.

The timing of the kinetic experiments was done with an A.R. & J.E. Meylan one-fifth second split timer.

The thermometers used in the thermostats were of the Beckmann type. The exact operating temperature was determined by standardizing the thermometers used at that temperature against a Bureau of Standards calibrated thermometer.

Calibration of volumetric equipment and weights met customary standards for precision work.

The reaction flasks were 250-ml. Pyrex flasks fitted with 50-ml. side-bulbs and standard taper ground glass stoppers.

Analytical Method.—The analytical method for the determination of hydroxylamine as employed by previous workers necessitated an empirical correction for concentration effects and has been subjected to severe criticism.[9] However, a careful preliminary investigation indicated that when the reaction was followed by iodine titration of the unreacted hydroxylamine essentially according to the method reported by Conant and Bartlett[4] and refined by Price and Hammett[5] for semicarbazide determination, excellent results were obtained. This method consists of pipetting an aliquot of reaction mixture into an iodine flask containing an excess of standard iodine in a phosphate buffer of *p*H 7, adding an excess of standard sodium thiosulfate solution and starch indicator solution and back titrating with iodine. In order to ensure the precision required for the measurement of temperature coefficients, it was necessary to determine whether any hydrolysis of the oxime occurred under conditions prevailing during analytical manipulations. The procedure used to detect any possible hydrolysis was essentially that employed by Price and Hammett,[5] and for all the compounds here studied no hydrolysis was detected during analytical manipulations.

Procedure.—Preliminary experiments confirmed the observations of previous investigators that a great disparity existed among the rates of reaction of different carbonyl compounds with hydroxylamine. This disparity necessitated the utilization of two general experimental techniques: one for compounds for which only low rates of reaction could be obtained practicably; the other for compounds for which only high rates of reaction could be obtained practicably.

In any kinetic experiment when the reaction rate was relatively low, as in the case of most of the carbonyl compounds, the following procedure was used. Into the main section of a 250-ml. glass stoppered reaction flask was pipetted an aliquot of carbonyl compound of known concentration in buffer of *p*H 7. Into the side-bulb of the flask was pipetted an aliquot of hydroxylamine in the same buffer. The flask was then placed in a thermostat for a sufficient time to come to temperature. During this time, measured volumes of standard iodine solution were run into a series of iodine flasks containing buffer. The reaction was initiated by removing the solution-containing flask from the thermostat, inverting to mix the solutions contained in the two sections, shaking and immediately replacing in the thermostat. As soon as possible thereafter, an aliquot was rapidly withdrawn with a fast draining 10-ml. pipet, discharged into one of the iodine flasks, an excess of standard sodium thiosulfate solution and a definite volume of starch indicator solution added, and the resulting mixture back titrated with standard iodine solution. The time was noted when the pipet started delivering, and, since the time required for the pipet to deliver half its contents had been previously determined, the time at which the pipet was half emptied was known and was taken as the time, *t*, in the rate equation. The initial volume of the reacting system was usually of such magnitude that it was possible to remove as many as twelve or thirteen successive samples for analysis during the course of the reaction. The sampling pipet used for the zero degree experiments was kept in a well in the thermostat.

To avoid the experimental difficulties experienced by previous investigators in their studies of oxime formation of carbonyl compounds which possessed high rates of reaction, which difficulties can safely be assumed to be a considerable source of error, a different technique was developed and used. Into the side bulb of a reaction flask there was pi-

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(6) W. V. Evans and M. B. Aylesworth, *Ind. Eng. Chem.*, **18**, 24 (1926).

(7) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, pp. 167–168.

(8) W. C. Pierce and E. L. Haenisch, "Quantitative Analysis," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 241.

(9) W. C. Bray, M. E. Simpson and A. A. MacKenzie, THIS JOURNAL, **41**, 1363 (1919).

petted an aliquot of standard iodine solution, and into the other section of the flask there was pipetted an aliquot of carbonyl compound of known concentration in buffer of *p*H 7. The system was then allowed to come to temperature. To initiate the reaction an aliquot of hydroxylamine in buffer was discharged from a fast draining pipet into the solution of the carbonyl compound. The time was observed when the pipet started delivering, and since the time required for the pipet to deliver half its contents had been determined previously, the time at which the pipet was half emptied was known and was taken as zero time in the rate equation. The reaction was allowed to proceed for a predetermined interval of time and then quenched. To accomplish this, an aliquot of buffer solution was added all at once to the mixture, and immediately thereafter the flask was so tilted that the iodine solution contained in the side bulb mixed thoroughly with the carbonyl compound–hydroxylamine mixture and quenched the reaction. An aliquot of standard sodium thiosulfate solution was immediately added, followed by a definite volume of starch indicator solution, and the resulting solution was back-titrated with standard iodine solution. Patently, the procedure immediately described above was instrumental in providing but one of several necessary experimental points. Repetition of the method as frequently as the reaction velocity made practicable, using varied intervals of time before quenching, furnished the necessary number of experimental points to permit the calculation of precise rate constants. The excellent reproducibility among the rate values secured by this method indicates its essential soundness.

In the formation of the oxime of any carbonyl compound under study, there was always the possibility of concomitant reversal of oxime formation, or hydrolysis of the oxime. Such a hydrolysis, if present, would necessarily complicate the mathematical treatment of the experimental data. In all cases studied there was found to be no measurable hydrolysis. This was determined in the following manner. A known weight of pure oxime of the carbonyl compound under investigation was dissolved in a known amount of buffer solution at either 0 or 25°. Immediately after complete solution, which generally occurred very rapidly, an aliquot was removed and subjected to analysis as described above. At subsequent times aliquots were removed and analyzed.

Because of the known significant effect of *p*H on the rate of this type reaction[4] care was taken to establish the constancy of the *p*H during the course of any one kinetic experiment. Samples of the reaction mixture were withdrawn at appropriate intervals and the *p*H was measured. In all cases the adequacy of the buffer system was confirmed, establishing the invariance of the environment with regard to *p*H during the progress of the reaction.

Results

The specific rate constants obtained during the course of this research are presented in Tables I and II. These data indicate clearly that oxime formation is a second-order reaction, first order with respect to the carbonyl function and first order with respect to hydroxylamine. The unambiguous second-order character of the reaction has been established for some eleven carbonyl compounds of rather diverse character. This contrasts strikingly with the results of some previous investigators[2k,2n] which apparently indicated a more complex reaction order type in the case of certain compounds here investigated and reported.

Table I

Furfural Oxime Formation

Medium: 0.0571 M Na_2HPO_4; 0.0286 M NaH_2PO_4; temp., 0.03°; initial concentration, furfural 0.02059 M, hydroxylamine 0.01647 M.

Time, sec.	$[NH_2OH]$ $(a - x)$	[Furfural] $(b - x)$	log $b(a - x)/a(b - x)$	k, l./mole sec.
300	0.01483	0.01895	0.00945	0.0176
600	.01350	.01762	.01862	.0173
900	.01195	.01607	.03161	.0197
1500	.01021	.01433	.05015	.0187
1800	.009572	.01369	.05847	.0181
2100	.008737	.01285	.07078	.0188
2400	.008186	.01230	.08005	.0186
2700	.007710	.01182	.08895	.0184
3000	.007234	.01135	.09878	.0184
3300	.006758	.01087	.10972	.0186
3600	.006351	.01046	.12005	.0186
4200	.005691	.009809	.13950	.0186
			Av.	0.0184

Table II

Rate constants, k, in l./mole sec. for oxime formation in buffer of *p*H 7.0; buffer, 0.0571 M Na_2HPO_4, 0.0286, M NaH_2PO_4.

Compound	Temp., °C.	[Compound]	$[NH_2OH]$	k
Acetone	0.00	0.003678	0.008512	0.155
		.004705	.01527	.164
		.004725	.01562	.153
			Av.	.157
	25.01	0.004559	0.005115	0.293
		.003304	.008422	.280
		.002618	.006523	.276
			Av.	.283
Diethyl ketone	0.02	0.01528	0.01569	0.0325
		.01039	.01609	.0329
		.005170	.01693	.0344
			Av.	.0332
	25.00	0.004969	0.005275	0.0578
		.01041	.009199	.0567
		.01391	.008918	.0540
			Av.	.0563
Pinacolone	0.03	0.006536	0.01569	0.00188
		.01719	.01610	.00200
		.006860	.01648	.00190
			Av.	.00193
	25.02	0.01292	0.01030	0.00684
		.01302	.01043	.00646
		.01321	.01063	.00657
			Av.	.00662
Cyclopentanone	0.00	0.01431	0.01420	0.0306
		.01005	.01328	.0325
		.005211	.01452	.0314
			Av.	.0315
	25.00	0.01485	0.01058	0.0639
		.01448	.01081	.0670
		.01365	.01002	.0652
			Av.	.0654
Cyclohexanone	0.02	0.001810	0.003980	1.51
		.001163	.002576	1.39
		.001493	.001792	1.47
			Av.	1.46
	25.00	0.001169	0.003847	1.79
		.001002	.002410	1.68
		.001200	.004320	1.77
			Av.	1.75

TABLE II (*Continued*)

Compound	Temp., °C.	[Compound]	[NH$_2$OH]	k
Furfural	0.00	0.01124	0.01003	0.0197
		.02059	.01647	.0188
		.01175	.007512	.0199
			Av.	.0195
	25.02	0.008218	0.01324	0.0810
		.01184	.01391	.0761
		.01172	.01340	.0795
			Av.	.0789
Acetophenone	0.03	0.009977	0.1586	0.000919
		.009149	.01605	.000925
		.008114	.01563	.000928
			Av.	.000924
	25.01	0.01015	0.01001	0.00300
		.01539	.01570	.00294
		.01528	.01024	.00293
			Av.	.00296
Methyl isopropyl ketone	0.00	0.01518	0.01308	0.0330
		.01014	.01312	.0342
		.004956	.01308	.0320
			Av.	.0331
	25.00	0.004494	0.01647	0.0860
		.005116	.01656	.0889
		.009988	.01639	.0902
			Av.	.0884
Methyl isobutyl ketone	0.00	0.01484	0.01134	0.0189
		.009977	.01051	.0194
		.01499	.01112	.0195
			Av.	.0193
	25.02	0.005544	0.01252	0.0578
		.005135	.01599	.0544
		.007524	.01725	.0555
			Av.	.0559
Methyl ethyl ketone	0.01	0.01127	0.01651	0.0826
		.005247	.01594	.0783
		.006951	.01569	.0813
			Av.	.0807
	25.00	0.009199	0.008299	.190
		.008674	.01563	.186
		.008457	.01569	.180
			Av.	.185
Di-*n*-propyl ketone	0.02	0.01001	0.01178	0.0151
		.01028	.01489	.0158
		.00800	.1037	.0150
			Av.	.0153
	25.01	0.009679	0.01347	0.0463
		.01361	.004577	.0456
		.01366	.006774	.0428
			Av.	.0449

The data necessary for the calculation of the rate constants were determined by measuring the concentration of hydroxylamine remaining at convenient intervals of time. For all the compounds investigated, exacting preliminary experimental study indicated no measurable reversibility. Therefore the rate constants were determined on the basis of an irreversible second-order reaction using the equation

$$kt = 2.303/(a - b)\ [\log b(a - x)/a(b - x)] \qquad (2)$$

where k is the second-order rate constant; t, the time in seconds; x, the hydroxylamine concentration at time, t; and a and b, the initial concentrations of hydroxylamine and ketone, respectively. The value of k was determined by the application of least squares methods to a plot of $\log b(a - x)/a(b - x)$ against t.

In practically all cases, the kinetic experiment was carried to at least 70% completion of reaction. In many cases, 80% completion was realized. Most experiments involved the plotting of a minimum of twelve experimentally determined points. In all compounds investigated the irreversibility was so complete that a least squares plot showed no falling off of the rate constant during the time the reaction was studied.

The extent of possible decomposition of the reagent, hydroxylamine, was determined by preparing solutions of hydroxylamine hydrochloride in buffer of the approximate concentration as those used in actual kinetic experiments, periodically removing samples and analyzing for hydroxylamine. Even in the case of greatly prolonged runs, such as acetophenone at 0°, the amount of decomposition was negligible.

The variety of carbonyl compounds investigated was limited by such practical considerations as stability, solubility in the aqueous buffer medium purposely selected to minimize the effect of environmental changes, and the possibility of comparison with data of a related reaction.[5]

The deviation of the mean of the rate constants was taken as the precision measure of the average since the reproducibility was considered a better measure of the accuracy of the rate constant than the probable error in the least squares slope of any individual measurement. This error ranged from 1 to 2%.

The problem under consideration is one involving the effect of a structural change upon reaction. Therefore the pertinent quantities are not the absolute values of the free energy, ΔG, entropy, ΔS, and heat, ΔH, 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 selected. The equations employed for the calculation of these relative quantities are

$$\Delta G^{\ddagger} - \Delta G_0^{\ddagger} = -RT \ln k/k_0 \qquad (3)$$

$$\Delta S^{\ddagger} - \Delta S_0^{\ddagger} = \frac{\partial}{\partial T}(RT \ln k/k_0) \qquad (4)$$

$$\Delta H^{\ddagger} - \Delta H_0^{\ddagger} = RT^2 \frac{\partial}{\partial T}(\ln k/k_0) \qquad (5)$$

In these equations symbols with the subscript zero refer to acetone, the standard substance, those without subscript to the carbonyl compound in question.

In the computations finite increments were substituted for differentials in equations 4 and 5.

From equations 4 and 5 and the data listed in Table II the values of the relative entropies and heats of activation for oxime formation were calculated and the values of the relative free energies were calculated from these. They are given in Table III.

TABLE III

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

$\Delta H_0^{\ddagger} = 4500$ cal.

Compound	$(\Delta S^{\ddagger} - \Delta S_0^{\ddagger})$, 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	−4.50	−400	900
Pinacolone	7.10	4300	2300
Cyclopentanone	0.20	900	1000
Cyclohexanone	−5.30	−2600	−1100
Furfural	15.00	5200	1000
Acetophenone	3.00	3700	2900
Methyl isopropyl ketone	6.30	2600	800
Methyl isobutyl ketone	7.10	3200	1100
Methyl ethyl ketone	4.50	1600	300
Di-*n*-propyl ketone	−15.10	−3100	1200

Discussion

The results of some previous investigators[2k,2n] indicating that oxime formation for several of the carbonyl compounds here considered was of a complex reaction order type is obviously not substantiated by the results of the present investigation. The use of a precise analytical technique, the care exercised to vary the initial concentrations of reactants, the effort applied in following the course of the reaction far toward completion, and the unsuccessful attempts to fit the experimental data to reaction order types other than second order, all lead to the conclusion, in the present research, that oximation for all compounds investigated is unambiguously a second-order reaction. The use in the present research of an aqueous solution buffered at *p*H 7, as opposed to the use of unbuffered organic solvents by some previous investigators, apparently eliminated, or at least minimized to an immeasurable extent, the indeterminate interferences of trace impurities, of fortuitous acid or base catalysis, and of possible decomposition reactions of hydroxylamine. In all probability, it was the operation of a combination of the insidious interferences indicated above which led to the observation of apparent complex reaction order types for oxime formation reported by previous investigators.

Furthermore, it was observed that for all the carbonyl compounds studied under the experimental conditions employed there was an absence of detectable reversibility, and an absence of any appreciable variation in the specific rate with varition in the initial concentrations of the reactants. No significant trend in the values of the rate constant, or, equivalently, no apparent change in the slope of a plot of appropriate variables for any one particular kinetic experiment was observed. This suggests the absence of any environmental effect of appreciable magnitude such as a change in the dielectric properties of the reacting system caused by the disappearance of reactants and accumulation of products.

A comparison of data obtained in this research with available data on semicarbazone formation[5] for the first seven compounds listed in Table II is of interest and indicates that the rates of oxime formation and semicarbazone formation both decrease in the order cyclohexanone, acetone, cyclopentanone, furfural, diethyl ketone, pinacolone and acetophenone.

In Table IV there are listed some data derived from the rates of oxime formation and semicarbazone formation for the seven carbonyl compounds mentioned immediately above. Columns two and three contain the ratios of the rate of oxime formation to that of semicarbazone formation at 0 and 25°, respectively. Columns four and five list the temperature coefficients of oxime formation and semicarbazone formation, respectively.

TABLE IV

Compound	$(k_O/k_S)_0$	$(k_O/k_S)_{25}$	$(\Delta k/\Delta t)_O 10^4$	$(\Delta k/\Delta t)_S 10^4$
Acetone	2.47	3.28	504	90.1
Diethyl ketone	4.82	6.58	92.4	6.68
Pinacolone	2.50	6.58	18.8	0.940
Cyclopentanone	3.81	4.27	135	28.2
Cyclohexanone	3.34	3.41	1160	300
Furfural	2.97	6.41	238	22.9
Acetophenone	4.53	7.16	8.14	0.836

The above data emphasize several differences between oxime formation and semicarbazone formation. Both at zero and twenty-five degrees the ratio of the rate of oxime formation to that of semicarbazone formation is consistently and appreciably greater than unity. For example in the case of acetone at zero degrees the rate of oximation is approximately two and one-half times greater than that of semicarbazone formation; at twenty-five degrees for acetophenone the rate of oxime formation is more than seven times greater than the rate of semicarbazone formation. Moreover, it can be seen that the temperature coefficients of oxime formation for the seven compounds considered are substantially greater than the temperature coefficients of semicarbazone formation.

Another objective of the present research was to establish a correlation between structure and reactivity. Considerable effort had been exerted in the past to explain the differences in rates of oximation in terms of steric effects, cyclic strain, ease of enolization and other factors. In light of more recent and sounder theory[5,10] much of the earlier theoretical interpretation was necessarily erroneous, because it emphasized potential energy effects to the complete exclusion of the all-important internal kinetic energy effects of the reacting species. These latter kinetic energy effects are implicitly contained in the entropy of activation, $\Delta S^{\ddagger}$. The temperature coefficients of reaction rate obtained experimentally allowed the calculation of pertinent thermodynamic quantities for oxime formation of eleven carbonyl compounds (Table III). Relative entropies of activation for oxime formation of seven of these compounds are compared with corresponding data on semicarbazone formation in Table V.

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(10) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 194–238.

TABLE V

RELATIVE ENTROPIES OF ACTIVATION FOR SEMICARBAZONE FORMATION[5] AND OXIME FORMATION AT 12.5°

	($\Delta S^{\neq} - \Delta S_0^{\neq}$), cal./°C.	
Compound	Semicarbazone formation	Oxime formation
Cyclopentanone	3.30	0.20
Furfural	3.20	15.00
Cyclohexanone	0.40	−5.30
Acetone	0.00	0.00
Acetophenone	−1.90	3.00
Diethyl ketone	−6.50	−4.50
Pinacolone	−9.70	7.10

An examination of the above two sets of relative entropies shows a striking difference. In the case of semicarbazone formation there is with the exception of acetophenone, a parallelism between the presumed rigidity of the carbonyl compound involved and the relative entropy of activation. The most rigid of these substances, cyclopentanone and furfural show the highest relative entropies of activation, while the lowest value is exhibited by pinacolone, whose molecules possess a larger number of internal degrees of freedom. The other compounds fit reasonably well into the sequence except that acetophenone would be expected to be relatively rigid and to occupy a position in the sequence above acetone.

There is no such parallelism for oxime formation. However, there are some points of similarity between the two sets of data. The compounds cyclopentanone, furfural and diethyl ketone occupy roughly comparable positions in each series. The values of the relative activation entropies for these three compounds are of different magnitudes in both series, but this is of small consequence since there is no immediately apparent reason to expect that they should be identical in magnitude. The relative entropy value for acetophenone in semicarbazone formation is negative in magnitude; however theory would have it positive in sign and above acetone in the sequence since acetophenone is presumably more rigid than acetone. For oxime formation, acetophenone in terms of its positive entropy value occupies a more nearly expected position. The relative entropies of activation for oxime formation in the case of the compounds listed in Table V vary over some twenty entropy units, which is equivalent to approximately five orders of magnitude in the rate of reaction. It is safe to assume that the variations are many times greater than the probable error in the measurement of the relative activation entropy. This variation of twenty entropy units is approximately twice the variation in the case of semicarbazone formation.

An examination of the data of Table III reveals that among the alkyl ketones diethyl ketone, di-*n*-propyl ketone, pinacolone, methyl isopropyl ketone, methyl isobutyl ketone and methyl ethyl ketone there is no uniformity involving the sign of the relative entropies of activation. All these compounds are presumably rather non-rigid and possess many degrees of freedom and would be expected to possess negative relative entropies of activation. However, for oxime formation it is found that diethyl ketone and di-*n*-propyl ketone possess negative entropies of activation while the remaining four possess positive entropies of activation.

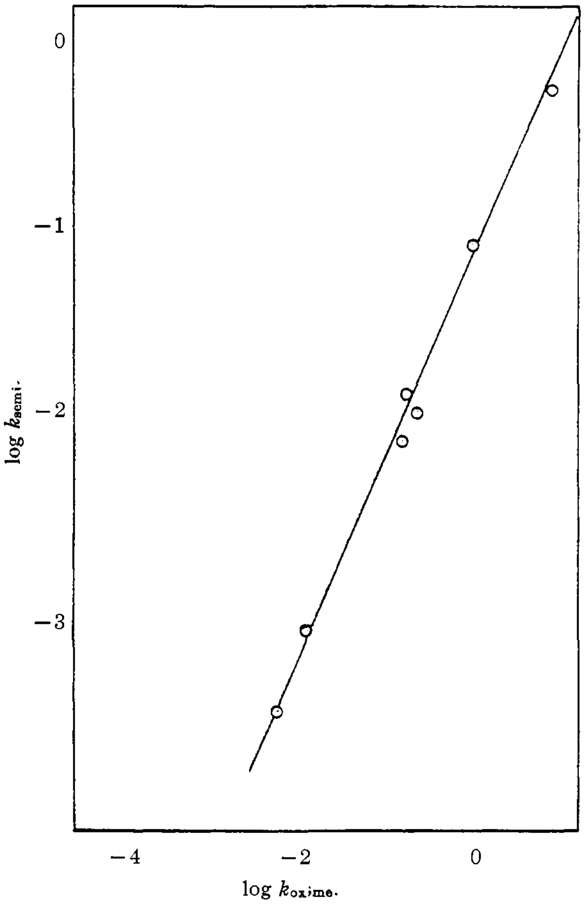

Fig. 1.—Plot of log *k* for semicarbazone formation *versus* log *k* for oxime formation at 25°. Reading from the uppermost point of the plot downward the points correspond successively to cyclohexanone, acetone, cyclopentanone, furfural, diethyl ketone, pinacolone and acetophenone.

Figure 1 illustrates a plot of the logarithm of the rate constants for semicarbazone formation[5] *versus* the logarithm of the rate constants for oxime formation both taken at 25°. This plot constitutes a "linear free energy" relationship.[10,11] The median deviation of the points from the straight line of the plot is 0.060. The degree of linearity in the present situation is especially striking in view of the wide variation in the structure of the seven carbonyl compounds concerned which include a heterocyclic aldehyde, an aromatic ketone, and aliphatic and cyclic ketones. Furthermore a plot of the same quantities for 0° possesses just as high a degree of linearity. This satisfying linearity arises, in part, from a suggested existence of some degree of internal resemblance between semicarbazone formation and oxime formation such as similarity of transition states, and, in part, from the innate compressive features of logarithmic plotting, generally. This same linearity suggests the essential soundness of the two sets of experimental data under comparison,

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(11) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 218.

which soundness is especially impressive since each set was obtained independently by two different pairs of observers. It also suggests the necessity of re-examination of the problem of structure and reactivity.

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Sedimentation Coefficient Determinations with Some Sugars and Dextrins[1]

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The sedimentation coefficients of glucose, sucrose, raffinose, amyloheptaose, cyclohexaamylose and cycloöctaamylose were determined and converted to correspond to the sedimentation rate which would have been observed in water at 20°. The results were reproducible to ±0.03 Svedberg unit. They agreed well with the theoretical values which were computed from molecular weight and diffusion data. For the open chain compounds the dependence of sedimentation coefficient on molecular weight may be represented by the expression $s_{20,\mathrm{w}} = 0.0087M^{0.56}$ Svedberg unit. For the cyclic compounds the sedimentation coefficients may appear to be somewhat larger than would be predicted by the above relationship for a molecule with open chain structure and the same molecular weight, but the point is not established with certainty.

Introduction

In a normal experiment for measuring a sedimentation rate with the ultracentrifuge the solute separates entirely away from the meniscus; when it does not the procedure is unreliable since the conditions for free diffusion in the sedimenting boundary do not exist in the ultracentrifuge cell.

Three approaches to the problem of obtaining the sedimentation coefficient, s, of slowly sedimenting solutes have been made. (1) Ultracentrifuge cells have been partitioned into top and bottom compartments. The amount of solute which moves through the partition during the experiment may be determined by analyzing the solutions in the two compartments; from which data the coefficient s can be computed.[2] (2) "Synthetic boundary cells" have been designed with which the sedimentation displacement of a freely diffusing boundary may be observed for a *short* period of time.[3] (3) Methods have been found for obtaining the sedimentation coefficient from the refractive index gradient which develops in the ultracentrifuge cell when the experiment is carried out in the usual way.[4–6]

In this paper a modified method based on procedure (3) is presented. It has been used to determine experimentally the sedimentation coefficients of several sugars and dextrins. The values obtained are compared with the theoretical figures which were computed from molecular weight and diffusion data.

Theory

By applying the reasoning of Goldberg[7] to the case in which the concentration at the meniscus does not become zero during a sedimentation experiment, one arrives at the equation

$$c_{\mathrm{t}}x_{\mathrm{b}}^2 - c_{\mathrm{x_0}}x_0^2 = \int_{x_0}^{X} x^2 \frac{\mathrm{d}c}{\mathrm{d}x}\,\mathrm{d}x \qquad (1)$$

in place of his equation 59. Here x is the distance from the axis of rotation, x_0 is the position of the meniscus, x_{b} is the position the boundary would have if there were no diffusion of the sedimenting solute and if all the sedimenting particles had identical sedimentation coefficients, X is an arbitrary plane in the "plateau region" (*i.e.*, that part of the cell where concentration is independent of x), c is the concentration of the solute, with $c_{\mathrm{x_0}}$ corresponding to that at the meniscus and c_{t} to that in the plateau region at time t.

By substituting the expressions

$$c_{\mathrm{t}} = c_0e^{-2s\omega^2t} \qquad (2)$$

$$x_{\mathrm{b}} = x_0e^{s\omega^2t} \qquad (3)$$

$$c_{\mathrm{x_0}} = c_{\mathrm{t}} - \int_{x_0}^{X} \frac{\mathrm{d}c}{\mathrm{d}x}\,\mathrm{d}x \qquad (4)$$

into equation 1 and rearranging one obtains

$$e^{-2s\omega^2t} = 1 - \frac{1}{c_0x_0^2}\int_{x_0}^{X} (x^2 - x_0^2)\frac{\mathrm{d}c}{\mathrm{d}x}\,\mathrm{d}x \qquad (5)$$

Here ω is the angular velocity of the rotor. Except for rearrangement this expression is identical with equation 3 of Baldwin.[6] It can also be obtained from equation 6a of Gutfreund and Ogston[5] by changing the order of integration in the double integral and integrating once. Taking logarithms of each side of equation 5 one obtains

$$\frac{-2s\omega^2t}{2.303} = \log\left[1 - \frac{1}{c_0x_0^2}\int_{x_0}^{X} (x^2 - x_0^2)\frac{\mathrm{d}c}{\mathrm{d}x}\,\mathrm{d}x\right] \qquad (6)$$

When s is very small this equation may be replaced by the statement

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[1] More complete details of this investigation may be obtained from the Ph.D. dissertation, 1954, of the writer filed in the library of the University of Wisconsin.

[2] A. Tiselius, K. O. Pedersen and T. Svedberg, *Nature*, **140**, 848 (1937).

[3] G. Kegeles, THIS JOURNAL, **74**, 5532 (1952); *cf.* also G. E. Pickles, W. F. Harrington and H. K. Schachman, *Proc. Nat. Acad. Sci.*, **38**, 943 (1952).

[4] T. Svedberg and K. O. Pedersen, "The Ultracentrifuge," Clarendon Press, Oxford, 1940, p. 283.

[5] H. Gutfreund and A. G. Ogston, *Biochem. J.*, **44**, 163 (1949).

[6] R. L. Baldwin, *ibid.*, **55**, 644 (1953).

[7] R. J. Goldberg, *J. Phys. Chem.*, **57**, 194 (1953).