TABLE I

TOXICITY AND THERAPEUTIC ACTIVITY COMPARED TO SULFANILAMIDE IN STREPTOCOCCAL INFECTIONS OF MICE

MTD = Maximum tolerated dose; MED = Minimum effective dose.

Compound	Toxicity to mice g. per kg.	Therapeutic activity g. per kg.
Sulfanilamide	MTD subcut. (oil) 2.5; orally 2.5	MED subcut. 0.5; oral 0.75
Sodium sulfanilamide formaldehyde sulfoxylate		Inferior
4,4'-Diaminodiphenyl sulfone	MTD orally 0.15	MED 0.025
4,4'-Diacetyldiaminodiphenyl sulfone	MTD orally >4.0	MED 0.2
Sodium 4,4'-diaminodiphenyl sulfone *bis*-formaldehyde sulfoxylate	MTD subcut. 3.0	MED 0.2
Sodium 4,4'-diaminodiphenyl sulfone diformaldehyde bisulfite		Little activity

of alcohol to the neutralized aqueous solution, the reaction product crystallized in fine needles; the needles contain two molecules of water of crystallization. The compound is readily soluble in water.

Anal. Calcd. for $C_{14}H_{14}O_6N_2S_3Na_2 + 2H_2O$: N, 5.78; S, 19.86; Na, 9.50. Found: N, 5.64; S, 19.80; Na, 9.24.

To keep the formaldehyde sulfoxylate derivatives stable either in solution or in a solid state, a small amount of sodium bicarbonate must be added.

Sodium 4,4'-Diaminodiphenyl Sulfone *bis*-Formaldehyde Bisulfite.—A mixture of 4,4'-diaminodiphenyl sulfone (2.5 g.), sodium formaldehyde bisulfite (3.5 g.) and water (15 cc.) was heated on a steam-bath for about two hours, until solution occurred. Upon cooling, a part of the condensation product crystallized out; the main portion was precipitated in fine needles by addition of alcohol. The colorless crystals are freely soluble in water; they contain 4 molecules of water of crystallization which can be removed by heating on a steam-bath. Upon standing in air, the water-free material attracts again 4 molecules of water.

Anal. Calcd. for $C_{14}H_{14}O_8N_2S_3Na_2 + 4H_2O$: S, 17.41; H_2O, 13.05. Found: S, 17.17; H_2O, 12.82.

Summary

A new method of preparing sodium formaldehyde sulfoxylates of aromatic amino compounds has been described. The method was used for the preparation of the derivatives of sulfanilamide and 4,4'-diaminodiphenyl sulfone. Results of their chemotherapeutic action are given. The sodium formaldehyde bisulfite derivative of 4,4'-diaminodiphenyl sulfone also has been prepared.

WASHINGTON, D. C. RECEIVED DECEMBER 28, 1938

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

The Influence of Substituents on the Rates of Decomposition of the Potassium Salts of Dihydroxamic Acids. The Lossen Rearrangement

BY ROBERT D. BRIGHT AND CHARLES R. HAUSER

The general course for the Hofmann and Lossen reactions of compounds of the type RCONHX (where X is halogen, benzoate, etc.) in the presence of alkali, may be represented as follows

$$\mathrm{RCONHX + KOH \longrightarrow (RCONX)^-K^+ + HOH}$$

$$\mathrm{(RCONX)^-K^+ \longrightarrow (RCON) + K^+X^-}$$

$$\mathrm{(RCON) \longrightarrow RNCO}$$

First, an acid–base reaction occurs forming the salt $(RCONX)^-K^+$; many salts of this type can be isolated. Second, the anion of the salt releases X with a complete octet of electrons (*i. e.*, as an anion) leaving the nitrogen atom with only a sextet of electrons. Third, the molecule is stabilized by rearrangement to an isocyanate[1]; this is considered to involve a shift of an electron pair, together with the group R attached, from carbon to nitrogen.[2] It is possible that the "univalent nitrogen derivative," although never isolated, might have a brief existence; on the other hand, it is also possible that the release of X from the anion of the salt and the migration of R are simultaneous processes. Regardless of the intimate mechanism, however, there seems little doubt that the rate measured[3] in the decomposi-

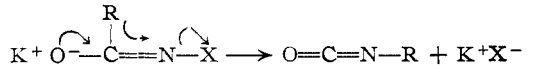
(1) Generally, the isocyanate is decomposed under the experimental conditions employed; in the presence of excess alkali, the corresponding primary amine is formed, while, in the presence of ammonia, which is used in the experiments described in this paper, urea derivatives are formed.

(2) See Whitmore, THIS JOURNAL, **54**, 3281 (1932).

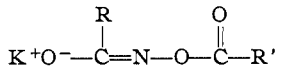
(3) The release of X may be the rate determining step, and the rearrangement of the "univalent nitrogen complex," a relatively rapid or simultaneous process. On the other hand, the experimental results might also be accounted for on the basis that the irreversible rearrangement of the "univalent nitrogen complex" is the relatively slow step. This would be possible, however, only if the release of X were a reversible reaction whose equilibrium is far on the side of unchanged dihydroxamate anion; the concentration of the "univalent nitrogen complex" would then be dependent upon the ease of release of X.

tion of the salt depends upon the release of X with a complete octet of electrons.

The decomposition (and rearrangement) of the anion[4] of the salt may be represented schematically as follows[5]



The facility of this decomposition should depend upon the electron attraction of X or the anionic stability of the potential anion X, and upon the capacity for electron release of the remainder of the molecule.[6,7] In agreement with this it has been shown recently that the rates of decomposition of the potassium salts of a series of substituted dibenzhydroxamates



in which R is phenyl and R′ contains certain meta and para substituents, are directly related to the ionization constants of the acids corresponding to R′COOH[8]; whereas, when R′ is phenyl and R contains certain meta and para substituents, the rates are roughly inversely related to the ionization constants of the acids corresponding to RCOOH.[8] Also, the rates of decomposition of the potassium salts of a series of meta and para substituted bromobenzamides, in which X is bromine, are roughly inversely related to the ionization constants of the corresponding benzoic acids.[9]

The purpose of this paper has been to make a more complete study of the effects of various groups R and R′ on the stabilities of potassium dihydroxamates. The rates of decomposition and energies of activation of a number of these compounds have been determined and the results discussed in terms of the polar effects of substituents.

Results

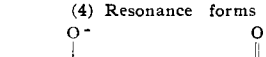
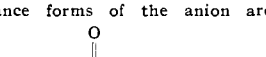
In Table I are given the average rates of decomposition at various temperatures of the potassium salts of the dihydroxamic acids studied, the energies of activation and the yields of primary amine obtained. In the rate determinations of sixteen of the compounds listed in Table I the potassium salts were isolated, while in the remaining rate experiments the potassium salts were prepared in aqueous solution from equal molecular quantities of the dihydroxamic acids and potassium hydroxide, an excess of the latter being avoided.[10] All reactions were carried out in the presence of four times the equivalent amount of ammonia, which reacted with the isocyanates formed to give urea derivatives. The concentration of the potassium salts was 0.025 molar, that of ammonia, 0.10 N. The temperatures of the thermostats were maintained constant to within $\pm 0.02°$.

The rates were determined gravimetrically by removing after suitable time intervals, 100-cc. aliquots of the reaction mixture and precipitating unchanged dihydroxamic acids by acidification with acetic acid. The rate constants were calculated from the first order equation,[11] $K = \frac{2.303}{t} \log \frac{a}{a - x}$, in which a is grams of dihydroxamic acid per 100 cc. of the reaction mixture at the time the first aliquot was removed, and $a - x$ is grams per 100 cc. after time t. Two or three sets of measurements, each consisting of three to six points (precipitations), were made at each temperature with each compound. The rate constants given in Table I are the averages of points obtained at the temperature indicated, the first point of a run being discarded when its deviation from the average of the other points was too large. The average deviations of the points from the mean values are approximately 1%, unless otherwise indicated in Table I.

Energies of activation were calculated from the rates at two temperatures, using the Arrhenius equation

$$\log k_2 - \log k_1 = \frac{E}{2.303}\left(\frac{1}{T_1} - \frac{1}{T_2}\right) \qquad (I)$$

where $R = 1.9885$ cal. The values given in Table I are rounded off to the nearest hundred

(4) Resonance forms of the anion are represented by (a)  and (b)  . The normal structure for the anion probably resembles (a) more than (b).

(5) This is essentially the scheme for rearrangements proposed by Ingold. It is termed "the pinacolic electron displacement." See Baker, "Tautomerism," Routledge and Sons, London, 1934, p. 307.

(6) A third factor would be the dielectric constant (ionizing power) of the media, but this need not be considered when the reactions are carried out under the same conditions.

(7) See Ingold, Ann. Reports, *J. Chem. Soc.*, **25**, 134 (1928); Baker, "Tautomerism," Routledge and Sons, London, 1934, p. 287.

(8) Renfrow and Hauser, THIS JOURNAL, **59**, 2308 (1937).

(9) Hauser and Renfrow, *ibid.*, **59**, 121 (1937).

(10) Excess alkali would cause a side reaction, involving hydrolysis of the potassium dihydroxamate to form alkali salts of a carboxylic and a hydroxamic acid.[8]

(11) The reaction is first order with respect to the potassium dihydroxamate. In the presence of an appreciable excess of alkali the kinetics would probably involve a combination of first and second order reactions. Not only would the dihydroxamates undergo hydrolysis (see Note 10), but, similar to the decomposition of the bromoamide anion, the decomposition and rearrangement of the dihydroxamate anion might be facilitated by an attack of the hydroxyl ion. In this connection see Van Dam and Abersou, *Rec. trav. chim.*, **19**, 318 (1900).

TABLE I

AVERAGE RATE CONSTANTS,[a] ACTIVATION ENERGIES AND YIELDS OF AMINES OBTAINED IN THE DECOMPOSITION OF POTASSIUM DIHYDROXAMATES OF THE GENERAL FORMULA $\left(\begin{matrix} & O^- & O \\ & | & \| \\ R-C=N-O & & C-R' \end{matrix}\right)K^+$ IN 0.1 *N* AMMONIA AT VARIOUS TEMPERATURES

No.	Compound R	Compound R'	$K_{V\ 30°}$	$K_{V\ 12°}$	$K_{V\ 20°}$	$K_{V\ 40°}$	*E*, kcal.	Yield of amine, %
1	C_6H_5—	*o*-$NO_2C_6H_4$—		0.00684	0.0230		25.2	93
2	*o*-$CH_3OC_6H_4$—	C_6H_5—		.00541	.0187		25.7	94
3	*o*-BrC_6H_4—	*o*-ClC_6H_4—	0.0423[c]		.0098[b]		25.4	88
4	*o*-$CH_3C_6H_4$—	C_6H_5—	.0356[b]		.0187		11.3	96
5	*o*-ClC_6H_4—	*o*-ClC_6H_4—	.0333[b]		.00800[b]		25.2	86
6	C_6H_5—	*o*-BrC_6H_5—	.0225		.00550		25.0	95
7	C_6H_5—	*o*-ClC_6H_4—	.0192		.00468[b]		25.0	96
8	C_6H_{11}—	C_6H_5—	.0159		.00326		28.0	69
9	*o*-FC_6H_4—	*o*-ClC_6H_4—	.0124		.00301		25.0	79
10	*p*-$CH_3OC_6H_4$—	C_6H_5—	.00943[e]		.00220		25.8	96[e]
11	C_6H_5—	*m*-$NO_2C_6H_4$—	.00575[e]		.00130[b]	0.0231	26.3	91[e]
12	*p*-ClC_6H_4—	*o*-ClC_6H_4—	.00566			.0217[c]	25.3	97
13	*p*-BrC_6H_4—	*o*-ClC_6H_4—	.00529			.0202	25.3	96
14	*m*-$CH_3C_6H_4$—	*m*-FC_6H_4—	.00436[e]			.0176	26.3	93
15	*p*-$CH_3C_6H_4$—	C_6H_5—	.00359[e]			.0146	26.5	90[e]
16	C_6H_5—	*o*-$CH_3OC_6H_4$—	.00351			.0141	26.2	91
17	*o*-$NO_2C_6H_4$—	*o*-$NO_2C_6H_4$—	.00338[g]					87
18	*m*-BrC_6H_4—	*o*-ClC_6H_4—	.00285			.0114	26.1	94
19	*m*-ClC_6H_4—	*o*-ClC_6H_4—	.00267					86
20	C_6H_5—	*o*-$CH_3C_6H_4$—	.00265			.0109	26.7	90
21	*o*-ClC_6H_4—	C_6H_5—	.00227[c]					81
22	*p*-$CH_3OC_6H_4CH_2$—	C_6H_5—	.00216			.00938	27.7	
23	*m*-$NO_2C_6H_4$—	*o*-$NO_2C_6H_4$—	.00173			.00700	26.4	87
24	C_6H_5CH=CH—	C_6H_5—	.00155[d]			.00656[d]	27.2	
25	*p*-$NO_2C_6H_4$—	*o*-$NO_2C_6H_4$—	.00151			.00628[b]	26.8	86
26	*o*-$CH_3OC_6H_4CH_2$—	C_6H_5—	.00148			.00662[c]	28.3	
27	C_6H_5—	C_6H_5—	.00138			.00562	26.5	92[e]
28	$C_6H_5CH_2$—	C_6H_5—	.00117[c,f]			.00436[b]	27.7	47
29	C_6H_5—	$C_6H_5C_2H_4$—	.000706			.00263	24.7	62
30	$C_6H_5C_2H_4$—	C_6H_5—	.000443[c]			.00195[b]	28.5	49

[a] Average deviation from the mean of the points averaged was 1% unless specified by *b*, *c* or *d*. [b] Average deviation from mean of points averaged was 2%. [c] Average deviation from mean of points averaged was 3%. [d] Average deviation from mean of points averaged was 4%. [e] Values obtained by Renfrow and Hauser.[8] [f] Rate constant at 31 ± 0.02°. [g] Rate run in presence of 5% dioxane.

calories. In the case of the potassium salt of *m*-nitrobenzoyl benzhydroxamate, the only compound measured at three temperatures, the activation energy calculated from the rates at 20 and 30° is 26,250 cal., and that calculated from the rates at 30 and 40° 26,390 cal. The limits of error of the activation energies given in Table I may be calculated from the average deviation from the mean of the rate constants. A 1% average deviation from the mean of both rate constants corresponds to ±300 cal. in the activation energy. The activation energy for the dihydroxamate in which R is *o*-tolyl is exceptionally low. Although the limits of error are rather large, there seems little doubt that the activation energy for this compound is lower than that for any of the other compounds studied.

The yields of primary amine given in Table I were obtained from experiments carried out under conditions that were the same as those used in the determinations of the rates at 30° (at 20° with compounds 1 and 2). The urea derivatives formed were hydrolyzed with hydrochloric acid to give the amines. In most cases in which aromatic amines were formed, high or almost quantitative yields were obtained, but in those in which aliphatic amines were formed the yields were somewhat lower. The yields of amines of compounds 22, 24 and 26 in Table I were not determined satisfactorily.

Discussion

In discussing the effects of substituents and groups on the decomposition of potassium dihy-

droxamates, $K^+O^-—\underset{\displaystyle R}{\overset{|}{C}}=N—O—\overset{\displaystyle O}{\overset{\|}{C}}—R'$, two series of compounds are considered, those in which R is phenyl and R′ varied, and those in which R′ is phenyl and R varied.

Variations of R′.—In Table II are arranged in decreasing order the rate constants at 30° for the potassium salts of a series of dihydroxamic acids in which R is phenyl and R′ varied; in this table are also listed the energies of activation (E), and the ionization constants[12] at 25° of the acids corresponding to R′COOH. The value given for the rate constant of the compound in which R′ is o-$NO_2C_6H_4$, has been calculated from the rate constant at 20° and the activation energy, according to equation I.

TABLE II

RATE CONSTANTS AT 30° OF POTASSIUM DIHYDROXAMATES OF THE GENERAL FORMULA $\left(C_6H_5—\overset{O^-}{\overset{|}{C}}=N—\overset{O}{\overset{\|}{C}}—R'\right)K^+$ AND IONIZATION CONSTANTS OF ACIDS, R′COOH

No.	R′	$K_{V\,30°}$	K_AR′COOH (×10⁵)	E, kcal.
1	o-$NO_2C_6H_4$—	0.0957[b]	671	25.2
2	o-BrC_6H_4—	.0225	140	25.0
3	o-ClC_6H_4—	.0192	114	25.0
4	m-$NO_2C_6H_4$—	.00575[a]	32.1	26.3
5	o-$CH_3OC_6H_4$—	.00351	8.06	26.2
6	m-FC_6H_4—	.00272[a]	13.6	
7	o-$CH_3C_6H_4$—	.00265	12.3	26.7
8	C_6H_5—	.00138[a]	6.27	26.5
9	p-$CH_3OC_6H_4$—	.000821[a]	3.38	25.8
10	$C_6H_5C_2H_4$—	.000706	2.19	24.7

[a] Values obtained by Renfrow and Hauser.[5] [b] Calculated from E, obtained from 12 and 20° rate constants.

It can be seen from Table II that with the exception of potassium o-methoxybenzoyl benzhydroxamate (no. 5), the rate constants of dihydroxamates and the ionization constants of the corresponding acids are in the same relative order. Plotting the negative logarithms of the rate constants at 20, 30 and 40° against the negative logarithms of the ionization constants, the direct linear relationship shown in Fig. 1 is obtained. With the exceptions of the phenylethyl and o-methoxyphenyl derivatives, the points lie on or close to the line. Since the dihydroxamic acids in these two cases are slightly more soluble in water than the other compounds studied, solubility corrections could be applied, but this would bring the points only a little closer to the line.

(12) These values have been taken from data of Dippy and coworkers, *J. Chem. Soc.*, 357 (1938), and earlier papers.

It should be pointed out also that a rather low yield (62%) of aniline was obtained when R′ was phenylethyl, indicating that hydrolysis (giving benzhydroxamic acid) occurred to some extent.

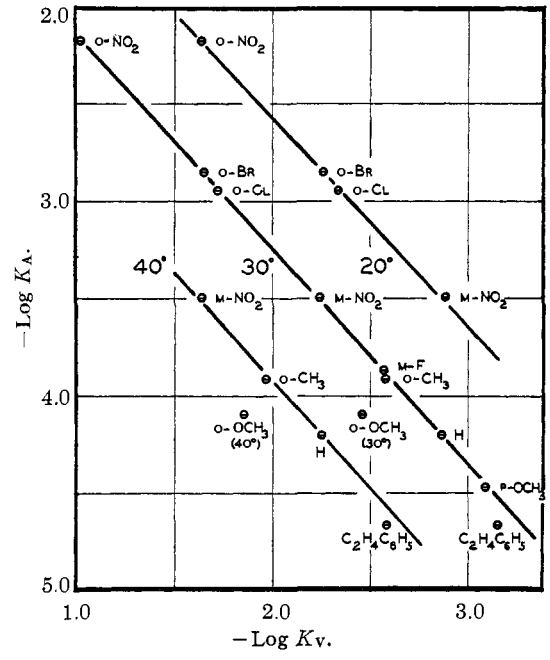


Fig. 1.

The fact that the rate constants for the ortho substituted phenyl derivatives (as well as the meta and para) can be correlated with the ionization constants of the corresponding acids is remarkable, and should be taken into account in any consideration of the "ortho effect." Apparently, the decomposition of potassium dibenzhydroxamates, in which R′ alone is varied, and the strengths of the corresponding benzoic acids (R′COOH) are influenced by the same factors. Since the unimolecular decomposition of dihydroxamates should be influenced primarily by polar factors, it might appear that the "ortho effect" exhibited by ortho substituted benzoic acids should be explained on the basis of polar factors. It should be pointed out, however, that the chelation process, which is assumed by Dippy and coworkers[13] to be a factor in the "ortho effect," could also operate in the decomposition of dihydroxamates if the release of X is a reversible reaction.[3]

The energies of activation for dihydroxamates in which R′ is varied fall into two groups. When R′ is o-$NO_2C_6H_4$, o-BrC_6H_4, o-ClC_6H_4 or C_6H_4-

(13) Dippy, Evans, Gordon, Lewis and Watson, *J. Chem. Soc.*, 1421 (1937).

TABLE III

RATE CONSTANTS AT 30° OF POTASSIUM DIHYDROXAMATES OF THE GENERAL FORMULA $\left(R-C(=N-O-C(=O)-C_6H_5)-O^-\right)K^+$, IONIZATION CONSTANTS OF ACIDS RCOOH, AND RATIO K_v DIHYDROXAMATE/K_v DIBENZHYDROXAMATE

No.	R	$K_{v\ 30°}$	E, kcal.	K_A RCOOH($\times 10^5$)[e]	$\frac{K_v \text{ Dihydroxamate}}{K_v \text{ Dibenzhydroxamate}}$
1	o-$CH_3OC_6H_4$—	0.0804[c]	25.7	8.06	58.3
2	o-$CH_3C_6H_4$—	.0356	11.3	12.3	25.8
3	C_6H_{11}—	.0159	28.0	1.34	11.5
4	p-$CH_3OC_6H_4$—	.00943[a]	25.8	3.38	6.83
5	p-$CH_3C_6H_4$—	.00359[a]	26.5	4.24	2.60
6	o-BrC_6H_4—	.00304[b]		140	2.20
7	o-ClC_6H_4—	.00227		114	1.61
8	m-$CH_3C_6H_4$—	.00216[a]		5.35	1.56
9	p-$CH_3OC_6H_4CH_2$—	.00216	27.7	4.36	1.56
10	C_6H_5CH=CH—	.00155	27.2	3.65	1.12
11	o-$CH_3OC_6H_4CH_2$—	.00148	28.3		1.07
12	C_6H_5—	.00138[a]	26.5	6.27	1.00
13	$C_6H_5CH_2$—	.00101[d]	27.7	4.88	0.732
14	m-$CH_3OC_6H_4$—	.000926[a]		8.17	.671
15	o-FC_6H_4—	.000891[b]		54.1	.646
16	$C_6H_5C_2H_4$—	.000443	28.5	2.19	.321
17	p-ClC_6H_4—	.000407[b]		10.5	.295
18	p-BrC_6H_4—	.000381[b]		10.7	.276
19	m-BrC_6H_4—	.000204[b]		15.4	.148
20	m-ClC_6H_4—	.000192[b]		14.8	.139
21	o-$NO_2C_6H_4$—	.0000428[b]		671	.031
22	m-$NO_2C_6H_4$—	.0000248[b]		32.1	.018
23	p-$NO_2C_6H_4$—	.0000193[b]		37.6	.014

[a] Values previously obtained by Renfrow and Hauser. [b] Rates calculated from disubstituted dibenzhydroxamic acids. [c] Rate calculated from 12 and 20° rates and E. [d] Rate calculated from 31 and 40° rates and E. [e] With the exception of K_A for compound 3, these are thermodynamic values determined by Dippy (see ref. 12).

CH_2CH_2, the energy of activation is more than a thousand calories less than when R′ is C_6H_5, o-$CH_3C_6H_4$, o-$CH_3OC_6H_4$ or m-$NO_2C_6H_4$. Although the first three compounds listed in Table II have the fastest rates of decomposition and the lowest values for E, the differences in rates of dihydroxamates in which R′ is varied cannot be accounted for only on the basis of variations in the energies of activation.

Variations in R.—In Table III are arranged in decreasing order the rate constants at 30° for a series of potassium dihydroxamates in which R′ is phenyl and R is varied. In this table are also listed the energies of activation (E), the ionization constants of the acids[12] corresponding to RCOOH, and the ratio of each rate constant at 30° to that of potassium dibenzhydroxamate.

Several of the rate constants in Table III are calculated values. The constant at 30° for compound number 13 was calculated from the activation energy and the constant at 40°, according to equation I. The constant of compound 1 was calculated similarly from the activation energy and the rate constant at 20°.

Since the presence of halogen (in m- or p-position) or of the nitro group (in o-, m- or p-position), in the phenyl of R greatly retards the decomposition of the dibenzhydroxamate, it was found desirable to introduce a negative group into the phenyl of R′ in order to obtain a convenient rate at 30°. The rates for a series of disubstituted compounds in which R is a halogen or nitro substituted phenyl group, and R′ is o-chloro- or o-nitrophenyl, are given in Table I. From these rates, constants have been calculated for a series of dibenzhydroxamates (nos. 6, 15 and 17 through 23 of Table III), in which R contains a halogen or nitro group and in which R′ is phenyl. The following equation was used in these calculations

$$K_{\text{subst. R}} = \frac{K_{\text{subst. R and R'}} \times K_{\text{unsubst.}}}{K_{\text{subst. R'}}} \qquad \text{(II)}$$

In this equation $K_{\text{subst. R}}$ is the rate constant for the dibenzhydroxamate anion substituted in R only, $K_{\text{subst. R and R'}}$ is the rate constant for the dibenzhydroxamate ion substituted in both R and R′, $K_{\text{unsubst.}}$ is the rate constant for unsubstituted dibenzhydroxamate ion, and $K_{\text{subst. R'}}$

TABLE IV

CALCULATED AND EXPERIMENTALLY DETERMINED CONSTANTS FOR CERTAIN POTASSIUM DIBENZHYDROXAMATES SUBSTITUTED IN R ONLY

	Substituents	$K_{\text{subst. R and R'}}$	$K_{\text{unsubst.}}$	$K_{\text{subst. R'}}$	$K_{\text{subst. R}}$ Calcd.	$K_{\text{subst. R}}$ Found	Diff., %
1	R *p*-CH_3O R' *m*-NO_2	0.0390[a]	0.00138[a]	0.00575[a]	0.00936	0.00943[a]	<1
2	R *p*-CH_3 R' *m*-NO_2	.0150[a]	.00138[a]	.00575[a]	.00360	.00359[a]	<1
3	R *m*-CH_3 R' *m*-F	.00436[a]	.00138[a]	.00272[a]	.00221	.00216[a]	2
4	R *o*-Cl R' *o*-Cl	.0333	.00138[a]	.0192	.00239	.00227	5[b]

[a] Values obtained by Renfrow and Hauser.[8] [b] This greater difference is probably due to experimental difficulties.

is the rate constant for the dibenzhydroxamate ion substituted only in R'.

It has been possible to test the validity of this equation with certain other dibenzhydroxamates whose rates could be determined with or without substituents in R'. In Table IV are given the experimentally determined constants and the calculated values of certain dibenzhydroxamates substituted only in R. In this table are also given the experimentally determined values, $K_{\text{subst. R and R'}}$, $K_{\text{unsubst.}}$ and $K_{\text{subst. R'}}$, which were used in the calculation of $K_{\text{subst. R}}$ according to equation II.

The close agreement between the calculated and experimentally determined values for the constants of $K_{\text{subst. R}}$ given in Table IV appears to justify the use of equation II for the calculation of the rate constants for dibenzhydroxamates in which R' is phenyl and R contains a halogen or nitro group.

It can be seen from Table III that although the rate constants and the ionization constants are not well correlated when regarded as a whole, a rough inverse relationship is exhibited when the meta and para substituted phenyl derivatives alone are considered. Thus, the rates of decomposition of compounds 4, 5, 8, 12, 14, 17, 18, 19, 20, 22 and 23 decrease in this order, while, with the exception of the *m*-bromo and *m*-chloro derivatives,[14] the ionization constants of the corresponding acids RCOOH increase in this order. This inverse relationship is made clearer when the negative logarithms of the rate constants are plotted against the negative logarithms of the ionization constants as shown in Fig. 2. The points of the meta and para substituted phenyl derivatives would lie close to a line that might be drawn if these compounds alone were considered. It is obvious that the rates of the ortho substituted phenyl derivatives are much faster, and those of the derivatives with aliphatic character slower, than would be expected from a consideration of the approximate correlation that is exhibited between the rates of the meta and para derivatives and the ionization constants of the corresponding acids.

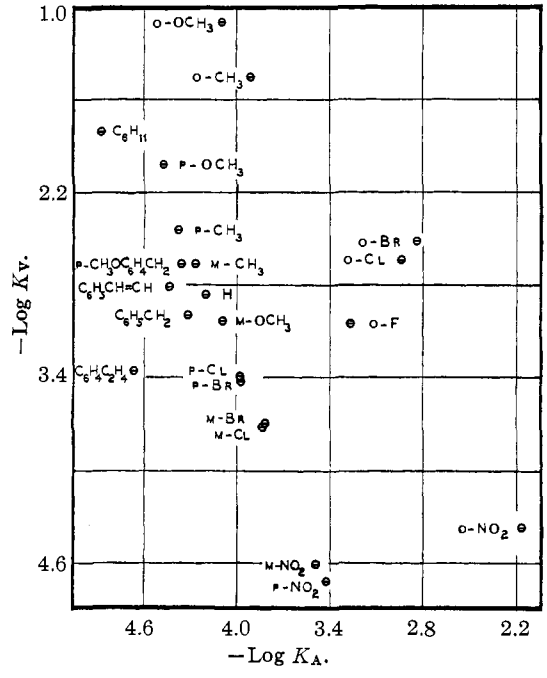


Fig. 2.

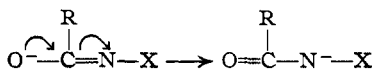
A consideration of the I and T effects[15] of various groups R of potassium dihydroxamates gives a rather good qualitative account of the influences

(14) It is of interest to note that the corresponding bromobenzamides likewise are out of order (see Ref. 9).

(15) At present there is no general agreement on the signs that should be attached to these effects. For this reason it seemed best in this paper to state in each case whether an electronic attraction or release is exerted. See Johnson, Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 1616.

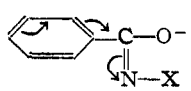
of R on the rates of decomposition.[16] In order to present a simple picture of these effects, which operate in a rather complex system, certain arbitrary assumptions have been made; this simplified treatment is to be regarded as a first approximation.

Electron displacements leading to the development of a high electron density at the N–X bond should facilitate the release of X as an anion and, consequently, the decomposition of the potassium dihydroxamate. On this basis an electromeric change of the enolic form[4] of the triad portion of the molecule (common to all dihydroxamates)



System A

should facilitate the decomposition. If R is in conjugation with the triad, as when R is phenyl, an electromeric or T effect of R will be superimposed on that of the triad system; the tautomeric electron-release effect of the phenyl group (as R), indicated as



System B[17]

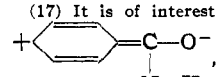
should facilitate the decomposition of the dihydroxamate anion. Moreover, T effects of ortho or para substituents of the ring will be superimposed on those of System B; the decomposition of the dihydroxamate anion should be facilitated by substituents that exert a tautomeric electron-release effect.

Inductive or I effects of R or its substituents are considered to act mainly by enhancing or restraining the electromeric (T) effects of the molecule; an inductive electron-release effect should facilitate, and an inductive electron-attractive effect retard, the decomposition of the dihydroxamate anion. In all cases the I effects of R are considered to influence the electromeric change of the triad portion of the molecule (System A), and in those compounds in which R is phenyl as represented by System B, I effects of ortho and para substituents are considered to influence mainly the electromeric effects of this system; I effects of meta substituents may be considered to increase or decrease the electron attractive effect that is generally attributed to the phenyl group.

The influence of substituents in the phenyl group of System B will be considered first. It can be seen from Table III (last column) that, in agreement with the ideas presented above, the introduction of methyl, an inductive electron-releasing group, facilitates the decomposition, whereas the introduction of nitro, an inductive electron-attracting group, retards the decomposition. With the methyl derivatives the order of the rates is o-CH_3 > p-CH_3 > m-CH_3 > H. As would be anticipated, the methyl group when in the ortho or para positions facilitates the decomposition more than when in the meta position. It could hardly have been predicted, however, that the methyl group in the ortho position would facilitate the decomposition so much more than in the para position. The fact that the methyl group in the meta position facilitates the decomposition to some extent may be attributed to a decrease in the inductive electron-attraction of the ring. The order of the rates with the nitro derivatives is p-nitro < m-nitro < o-nitro < H. While the order for the para and meta derivatives is that expected from the hypothesis that the inductive electron-attractive effect of the nitro group acts primarily by restraining the electromeric effects of the ring, the rate for the o-nitro derivative is relatively greater than would be anticipated on this basis alone;[18] obviously other factors are involved in the case of the ortho derivative. The fact that the nitro group in the meta position retards the decomposition may be attributed to an increase in the inductive electron-attraction of the ring.

It is generally recognized that the methoxy group and the halogens are capable of exerting T and I effects that oppose one another; the tautomeric electron-release effect is opposed by the inductive electron-attractive effect. It can be seen from Table III that the methoxy group, when substituted in the ortho or para position of the phenyl (as R) facilitates the decomposition of the dihydroxamate, but when substituted in the meta position, retards the decomposition. This may be

(16) These results can also be considered in terms of resonance in a manner similar to that recently discussed by Nixon and Branch, THIS JOURNAL, **58**, 492 (1936).

(17) It is of interest to note that if the resonance structure,  , is an "active" form, it would be difficult to represent the release of X and the migration of R as simultaneous processes.

(18) In this connection see Renfrow and Hauser, THIS JOURNAL, **59**, 124 (1937); Baker, *J. Chem. Soc.*, 447 (1938).

explained on the assumption that in the ortho or para position the tautomeric electron-release effect predominates, whereas in the meta position, where the T effect of methoxy cannot be superimposed on System B (above), the I effect of the methoxy predominates.[19] It can be seen from the table that chlorine or bromine, when substituted in the ortho position of the phenyl (as R), facilitates the decomposition of the dihydroxamate, but when substituted in the para or meta positions, retards the decomposition. Apparently the T effect of these halogens predominates in the ortho position, whereas the I effect predominates in the para and meta positions. It is noteworthy that chlorine and bromine in the meta position retard the decomposition more than in the para.

The rate for the *o*-fluoro derivative is of particular interest. In contrast to chlorine and bromine, which in the ortho position facilitate the decomposition of the dihydroxamate, fluorine in this position retards the decomposition. This indicates that the inductive electron-attractive effect of fluorine predominates over its T effect, which is generally considered to be very slight. It should be noted that the rates of the ortho substituted halogen derivatives increase in the order, *o*-F < *o*-Cl < *o*-Br, which is the order of increasing polarizabilities of these halogens.

It should be pointed out that the rates for all ortho-substituted phenyl derivatives are faster than those for the corresponding meta or para isomers. With the *o*-nitro derivative I and T effects alone do not account even qualitatively for the rate. It is possible that with other ortho derivatives, also, certain factors in addition to I and T effects operate.

The influences of various groups R of System A will now be discussed. It is convenient to consider that an aliphatic group as R exerts its usual inductive electron-release effect, although the rate for the dihydroxamate in which R is hydrogen, the common standard of reference, is not available for comparison. The phenyl group as R may be considered to exert two opposing effects, an inductive electron-attraction and a tautomeric electron-release.

It can be seen from Table III that as R is varied the following order of rates is exhibited: cyclohexyl > phenylvinyl > phenyl > benzyl > β-phenylethyl. Qualitative work by Jones and co-workers[20] has indicated that as R is varied, the ease of decomposition of potassium dihydroxamates decreases in the following order: triphenylmethyl > diphenylmethyl > benzyl > methyl.

While the dihydroxamate in which R is benzyl decomposes at a slower rate than the one in which R is cyclohexyl, the former decomposes at a faster rate than the derivative in which R is methyl. Apparently the cyclohexyl group exerts a considerably greater inductive electron-release effect (*i. e.*, is more polarizable) than the methyl group.

The fact that the substitution of successive phenyl groups for the hydrogen atoms of the methyl group increases the rate indicates that, although not in conjugation with the triad portion of the molecule, the phenyl group nevertheless exerts an electron-release effect. This may be accounted for on the basis of the idea discussed by Dippy and co-workers,[21] that the electron-release effect of the benzene ring can be transmitted inductively in a saturated side chain; in this manner the electron-release effects of the group progressively increase as the hydrogen atoms of the methyl group are substituted by phenyl. As would be anticipated on the basis of this idea, the substitution of the methoxy group, which exerts a tautomeric electron-release effect, in the ortho or para position of benzyl, facilitates the decomposition of the dihydroxamates. This can be seen from a comparison of the rates of compounds 9 and 11 with that of compound 13 in Table III.[22] The order of rates, benzyl derivative > β-phenylethyl derivative, also indicates that the phenyl group exerts an electron-release effect in benzyl, since the inverse order of rates would be expected if the phenyl group exerted only an inductive electron-attractive effect.

A comparison of the rates for phenylvinyl and phenylethyl derivatives is of especial interest. The much greater rate for the phenylvinyl is attributed primarily to a tautomeric electron-release effect which can operate in this compound but not in the phenylethyl derivative.

It can be seen from Table III that as R is varied the energies of activation (*E*) are not well correlated with the rates. Thus, for example, when R is cyclohexyl, the rate is eleven times faster than when R is phenyl, yet the cyclohexyl derivative

(19) In this connection see Dippy and co-workers, *J. Chem. Soc.*, 348 (1935).

(20) See especially Jones and Hurd, THIS JOURNAL, **43**, 2422 (1921).

(21) See Ref. 19, and *J. Chem. Soc.*, 648 (1936).

(22) It is rather surprising that, in contrast to the ortho and para methoxyphenyl derivatives, the para methoxybenzyl derivative decomposes more readily than the ortho isomer.

has the higher energy of activation. There appears to be a relationship, however, between the T and I effects and the energies of activation. At least in certain cases, the energy of activation is diminished with an increase of the tautomeric electron-release effect, but becomes greater with an increase of the inductive electron-attractive effect.

It can be seen from Table III that the highest values for the energy of activation are found in the cases in which R is not conjugated with the triad portion of the molecule (*i. e.*, when R is phenylethyl or cyclohexyl). Introducing conjugation into R lowers the energy of activation. Thus, when R is phenylvinyl, the energy of activation is approximately 1300 calories lower than when R is phenylethyl; and when R is phenyl, the energy of activation is 1500 calories lower than when R is cyclohexyl. It is to be observed that the energy of activation when R is benzyl, although greater than that when R is phenyl, is less[23] than that when R is phenylethyl; this appears to support the idea discussed above that in benzyl the electron-release effects of the ring are partly transmitted.

It can be seen from Table III that the energy of activation for potassium dibenzhydroxamate is 26,500 cal. Introducing the methoxy group into the ortho or para position of R lowers the energy of activation 700–800 cal.; this may be attributed to the T effect of the methoxy group, which is superimposed on the T effects of the ring. The methyl group, which exerts an inductive electron-release effect, when introduced into the ortho position, considerably lowers the energy of activation, but when introduced into the para position, apparently has no influence on this factor.

Although the energies of activation for the halogen and nitro derivatives listed in Table III are not available (the rates being calculated values), the effect on the energy of activation produced by the introduction of halogen or nitro group into the phenyl (as R) can be deduced from data listed in Table I. It can be seen from this table that when R′ is *o*-chlorophenyl and R is phenyl, the energy of activation is 25,000 cal. With R′ remaining the same (*o*-chlorophenyl), the introduction of chlorine, bromine or fluorine into the ortho position, or chlorine or bromine into the para position of the phenyl group (as R), has no appreciable effect on the energy of activation. In the ortho and para positions, halogens exert I and T effects that oppose one another and, perhaps for this reason, no appreciable change in the energy of activation results with the introduction of halogen into the ortho and para positions. In the meta position, however, halogens are able to exert only the inductive electron-attractive effect, and this appears responsible for the larger energy of activation that is exhibited by the *m*-bromo derivative.

The influence of the nitro group on the energy of activation is more obvious. It can be seen from Table I that when R′ is *o*-nitrophenyl and R is phenyl, the energy of activation is 25,200 cal. With R′ remaining the same (*o*-nitrophenyl), the introduction of the nitro group into the meta or para position of the phenyl group (as R), increases the energy of activation 1400–1800 cal.; this may be attributed to the inductive electron-attractive effect of the nitro group.

(23) The *o*-methoxybenzyl derivative (no. 11) is an exception, having a higher energy of activation.

Experimental

The acid chlorides used in this work were Eastman products or were prepared from the corresponding acids by means of thionyl chloride. Most of the esters were Eastman products or were prepared from the corresponding acid chlorides by reaction with alcohol or sodium alcoholate in alcohol solution, or from the corresponding acid by reaction with alcohol in the presence of concentrated sulfuric acid. The ethyl esters of *p*-methoxyphenylacetic and *o*-methoxyphenylacetic acids were prepared by a combination of the methods of Mauthner[24] and Cain, Simonsen and Smith.[25] A mixture of *p*-methoxyphenylacetic and benzoic acids was obtained from anisaldehyde, hippuric acid, anhydrous sodium acetate and acetic anhydride through the intermediate formation of the azlactone and keto-acid as described by Mauthner.[24] The crude acids were esterified with absolute ethyl alcohol in the presence of concentrated sulfuric acid, and the resulting mixture of esters was separated by distillation at reduced pressure according to the manner of Cain, Simonsen and Smith.[25] The ethyl *p*-methoxyphenylacetate boiled at 134–136° at 6 mm.; the boiling point given by Cain, Simonsen and Smith was 138–140° at 7 mm. The yield, calculated from anisaldehyde, was 25%. Ethyl *o*-methoxyphenylacetate, prepared by the same method, boiled at 127–129° at 7 mm. An 18% yield, calculated from *o*-methoxybenzaldehyde, was obtained.

Preparation of Hydroxamic Acid Salts.—Hydroxamic acid salts were prepared from the methyl or ethyl ester of the appropriate acid, hydroxylamine and potassium hydroxide in absolute methyl alcohol solution, according to the general method of Renfrow and Hauser.[26] In certain cases the potassium salt of the hydroxamic acid

(24) Mauthner, *Ann.*, **370**, 373–374 (1909).
(25) Cain, Simonsen and Smith, *J. Chem. Soc.*, **103**, 1036 (1913).
(26) Renfrow and Hauser, THIS JOURNAL, **59**, 2312 (1937).

precipitated from the methanol solution, while in others no precipitate formed. The potassium salt, if precipitated in appreciable amount, was filtered off, washed with a little absolute methyl alcohol, dried and weighed. The hydroxamic acid that did not precipitate as the potassium salt was precipitated as the barium salt, either as described previously,[26] using an amount of barium chloride equivalent to the theoretical amount of hydroxamic acid in solution, or, in the cases of compounds 2–8 and 17–19 listed in Table V, by the following modified procedure. The methyl alcohol solution of the potassium salt was added slowly with shaking to three times its volume of water containing an amount of barium chloride equivalent to the calculated quantity of hydroxamic acid present. The barium salt which precipitated at once was filtered off and washed with water and then with alcohol and ether to facilitate drying. The dry salt was kept in an air-tight bottle in a refrigerator. Since the barium salt of compound 17 in Table V was quite soluble in water, the methyl alcohol solution of the potassium salt was poured into only half its volume of water containing an equivalent of barium chloride.

The yields of potassium and barium salt of the hydroxamic acids, calculated from the ester used, are given in Table V. The only colored salts were the nitro-substituted compounds and the cinnamhydroxamates; these were yellow or orange. Barium *p*-nitrobenzhydroxamate was obtained as an orange precipitate which on standing became red-brown in color.

TABLE V

PERCENTAGE YIELDS OF THE SALTS OF HYDROXAMIC ACIDS OBTAINED FROM METHYL OR ETHYL ESTERS

No.	Hydroxamic acid	Ester used	% Yield of K salt	% Yield of Ba salt	Total yield, %
1	Benz-	Et	60	22	82
2	*o*-Bromobenz-	Me		75	75
3	*m*-Bromobenz-	Me	75	16	91
4	*p*-Bromobenz-	Me	53	29	82
5	*o*-Chlorobenz-	Me		65	65
6	*m*-Chlorobenz-	Me	17	54	71
7	*p*-Chlorobenz-	Me	51	32	83
8	Cinnam-	Et	41	33	74
9	*o*-Fluorobenz-	Me		86	86
10	Hexahydrobenz-	Me		96	96
11	*o*-Methoxybenz-	Me		82	82
12	*p*-Methoxybenz-	Et	70	4	74
13	*o*-Methoxyphenylacet-	Et		64	64
14	*p*-Methoxyphenylacet-	Et	55		55
15	*o*-Methylbenz-	Me		63	63
16	*p*-Methylbenz-	Me	42	28	70
17	*o*-Nitrobenz-	Et		76	76
18	*m*-Nitrobenz-	Et		87	87
19	*p*-Nitrobenz-	Et		72	72
20	Phenylacet-	Et		68	68
21	β-Phenylpropion-	Me		87	87

Preparation and Analysis of Dihydroxamic Acids.—The dihydroxamic acids were prepared by boiling for five minutes a suspension of the pulverized potassium or barium salt of the hydroxamic acid in dioxane with the equivalent amount of the acid chloride, according to the method of Renfrow and Hauser.[26] The potassium salts were more soluble in boiling dioxane than the barium salts, entering into reaction with the acid chloride more easily and completely to give somewhat better yields of dihydroxamic acids. The crude dihydroxamic acids were recrystallized from 95% or absolute ethyl alcohol or from a mixture or dioxane and ligroin. Benzoyl *o*-methoxybenzhydroxamate and, to a smaller degree, benzoyl *p*-methoxyphenylacethydroxamate decomposed when boiled with 95% alcohol, giving off a strong odor of isocyanate; these compounds appeared to be more stable in absolute alcohol, from which they were recrystallized. Phenylacetyl benzhydroxamate and β-phenylpropionyl benzhydroxamate separated from hot alcohol solution as supercooled oils. Seeding with a crude crystal induced crystallization, but in the case of the former compound the oil did not solidify for about a week. Benzoyl acethydroxamate was prepared according to the method of Jones.[27] The melting points (with decomposition in some cases) of the dihydroxamic acids were determined as described previously.[26]

The dihydroxamic acids were analyzed by the neutral equivalent method.[26] These determinations were carried out by titrating the alcoholic solutions of weighed amounts of acids with standard sodium hydroxide in an ice-bath at 0°, using thymol blue as indicator.

In Table VI are given the recrystallizing media, the melting points and the neutral equivalents of the dihydroxamic acids prepared in this work. The yields of recrystallized dihydroxamic acids obtained from hydroxamate salts are also given in this table.

Potassium Salts of Dibenzhydroxamic Acids.—The potassium salts of the first sixteen dihydroxamic acids listed in Table VI were prepared (in yields of 85–98%) by adding an alcoholic solution of potassium hydroxide to a solution of the dihydroxamic acid in a mixture of absolute alcohol and dry dioxane as described previously.[26] The somewhat soluble salt of compound 5 was obtained by evaporating part of the solvent. These salts were used in the rate studies described in the next section.

It is of interest to note that benzoyl *o*-methoxybenzhydroxamate, unlike its meta[26] and para isomers, did not precipitate when an alcoholic solution of potassium hydroxide was added to the hydroxamic acid dissolved in a dry alcohol mixture, even when dry ether was added. This greater solubility of the ortho isomer in organic solvents may have been due to chelation. The potassium salts of benzoyl phenylacethydroxamate and benzoyl *o*-methylbenzhydroxamate were isolated, but within a few minutes they decomposed spontaneously with a mild explosion, yielding lachrymous fumes which were apparently the isocyanate rearrangement product. The potassium salt of *o*-chlorobenzoyl *o*-chlorobenzhydroxamate, although quite soluble in organic solvents, was isolated in small amounts by the addition of ligroin to the alcohol–dioxane solution. The solid decomposed spontaneously within a few minutes, giving fumes which appeared to be isocyanate.

Rates of Reaction.—The potassium salts of dihydroxamic acids 1–16 (Table VI) were dissolved in 0.1 *N* ammonia solution and the rates determined as described previously.[26]

Potassium salts of dihydroxamic acids 16–30 and 32 were not isolated but were prepared in solution according to the following procedure. A sample (0.0158 mole) of dihydroxamic acid was powdered and suspended in 75–100 cc. of 0.1 *N* ammonia solution in a beaker cooled in an

(27) Jones, *Am. Chem. J.*, **20**, 6 (1898).

TABLE VI

RECRYSTALLIZATION MEDIA, YIELDS, MELTING POINTS AND NEUTRAL EQUIVALENTS OF DIHYDROXAMIC ACIDS

No.	Dihydroxamic acid	Recryst. media	Percentage yield from K salt	Percentage yield from Ba salt	Melting point, °C.	Neutral equiv. Found	Neutral equiv. Calcd.
1	Benzoyl benzhydroxamate	95% alc.		76	163–164	240.7	241.1
2	*o*-Chlorobenzoyl benzhydroxamate	95% alc.	73		130–131	275.8	275.6
3	*o*-Bromobenzoyl benzhydroxamate	95% alc.		73	132–133	319.5	320.0
4	*o*-Nitrobenzoyl benzhydroxamate	95% alc.	79	71	131–132	286.2	286.1
5	*o*-Methylbenzoyl benzhydroxamate	95% alc.		69	125–126	256.0	255.1
6	*m*-Nitrobenzoyl benzhydroxamate	95% alc.	64		149–150	286.5	286.1
7	*m*-Fluorobenzoyl *m*-methylbenzhydroxamate	Dioxane–ligroin		61	114–116		
8	Benzoyl cinnamhydroxamate	Abs. alc.	59		156–157	267.4	267.1
9	*o*-Chlorobenzoyl *m*-chlorobenzhydroxamate	Abs. alc.		59	147–147[a]	310.3[a]	310.1
10	*o*-Chlorobenzoyl *m*-bromobenzhydroxamate	Abs. alc.	80		142–143	354.0	354.5
11	*o*-Chlorobenzoyl *p*-chlorobenzhydroxamate	95% alc.	80	63	147–148	309.3	310.1
12	*o*-Chlorobenzoyl *p*-bromobenzhydroxamate	Abs. alc.	80		154–155	354.3	354.5
13	*o*-Nitrobenzoyl *m*-nitrobenzhydroxamate	Abs. alc.		42	159–160	330.0	331.1
14	*o*-Nitrobenzoyl *p*-nitrobenzhydroxamate	Abs. alc.		49	162–163	330.5	331.1
15	Benzoyl *p*-methoxybenzhydroxamate	Dioxane–ligroin	83		164–165	271.3	271.1
16	Benzoyl *p*-methylbenzhydroxamate	95% alc.	74		163–164	255.3	255.1
17	*o*-Methoxybenzoyl benzhydroxamate	95% alc.	73		112–114	270.8	271.1
18	Phenylacetyl benzhydroxamate	95% alc.		40	69–70	253.6	255.1
19	β-Phenylpropionyl benzhydroxamate	95% alc.	68		99–101	269.2	269.1
20	Benzoyl hexahydrobenzhydroxamate	95% alc.		69	148–149	248.2	247.2
21	Benzoyl phenylacethydroxamate	95% alc.		70	121–122	254.7	255.1
22	Benzoyl *p*-methoxyphenylacethydroxamate	Abs. alc.		66	123–124	284.7	285.1
23	Benzoyl *o*-methoxyphenylacethydroxamate	95% alc.		50	116–117	286.0	285.1
24	Benzoyl β-phenylpropionhydroxamate	95% alc.		70	132–133	269.3	269.1
25	Benzoyl *o*-methylbenzhydroxamate	Abs. alc.		53	108–109	255.8	255.1
26	Benzoyl *o*-methoxybenzhydroxamate	95% alc.		73	91–92	272.4	271.1
27	*o*-Chlorobenzoyl *o*-fluorobenzhydroxamate	Abs. alc.		61	124–125	293.6	293.6
28	Benzoyl *o*-chlorobenzhydroxamate	Abs. alc.		60	120–121	275.2	275.6
29	*o*-Chlorobenzoyl *o*-chlorobenzhydroxamate	Abs. alc.		44	144–145	309.3	310.1
30	*o*-Chlorobenzoyl *o*-bromobenzhydroxamate	Abs. alc.		50	141–143	354.3	354.5
31	*o*-Nitrobenzoyl *o*-nitrobenzhydroxamate	Abs. alc.		43	163–164	331.1	331.1
32	Benzoyl acethydroxamate	Ether–ligroin		40	98–99	178.6	179.1

[a] Values obtained from recrystallized dihydroxamic acid recovered from aliquots of the rate determinations.

ice-bath. An equivalent amount of potassium hydroxide (5–7 cc. of 2.5–3.0 *N*)[28] solution was added and the mixture stirred briskly until complete solution was effected. When necessary, additional 0.1 *N* ammonia was added to dissolve the salt formed. In order to make certain that no excess alkali was present, a small additional amount of the powdered dihydroxamic acid was added, the mixture stirred thoroughly and filtered. The filtrate was added to sufficient 0.1 *N* ammonia to make 630 cc. of 0.025 molar potassium dihydroxamate. A 430-cc. check run was made up in a similar manner. The reaction mixtures were placed in the thermostat and the procedure continued as described previously.[26] The thermostats maintained temperatures which were constant within ±0.02°.

The salts of dihydroxamic acids 8–14 and 16, which were isolated, and those of compounds 20, 22, 24, 25 and 28–30, which were prepared in solution as described above, gave on decomposition insoluble ureas that precipitated from the reaction mixture. In these cases the reaction mixture was stirred frequently during the course of the run and especially within about a minute before an aliquot was removed, in order to minimize supersaturation by the substituted urea. Before precipitation of the substituted ureas occurred, the 100-cc. aliquots were removed and run into 3 cc. of glacial acetic acid in 15 cc. of water. The flask containing the precipitate of unchanged dihydroxamic acid was placed in the thermostat for an hour, being shaken occasionally. The coagulated precipitate was filtered rapidly and quantitatively into a weighed sintered-glass crucible, washed and dried in an oven, generally at 70–80°.

When substituted urea had precipitated during the course of the decomposition, the aliquots were removed and filtered rapidly with strong suction through a sintered-glass crucible into the dilute acetic acid warmed to the temperature of the thermostat; the filtration was facilitated by tilting the suction flask and running the solution into one corner of the crucible. The acidified filtrate, containing the precipitate of unchanged dihydroxamic acid, was transferred quantitatively to a 250-cc. Erlenmeyer flask, using wash water warmed to thermostat temperature. The flask was suspended in the thermostat and,

(28) In several of the earlier experiments the alkali was dissolved in alcohol, but in the majority of the runs aqueous alkali was used. We consider that the runs in the presence of the very small amount of alcohol (about 1%) are comparable to within 1–2% with those carried out in the absence of this solvent. It was found by experiment that the rate of decomposition of potassium dibenzhydroxamate in the presence of 1% alcohol was only 1.4% lower than the rate in the absence of the solvent.

after coagulation, the dibenzhydroxamic acid was filtered and dried at 70–80°.

Certain compounds required special treatment. The potassium salt of benzoyl cinnamhydroxamate, half-way through the course of the decomposition, formed an unfilterable, gelatinous precipitate; aliquots were therefore removed only during the first part of the reaction. The methods described above were not applicable to *o*-nitrobenzoyl *o*-nitrobenzhydroxamate. An approximate reaction rate of the potassium salt of this dihydroxamic acid was obtained as follows. The compound (0.0158 mole) was dissolved in 30 cc. of dioxane, an equivalent amount of 3 *N* alcoholic potassium hydroxide solution added, followed immediately by 600 cc. of 0.1 *N* ammonia; the rate was determined in the usual manner. This rate of reaction in the presence of 5% dioxane may not be entirely comparable with the rates determined in the absence of this solvent.

It should be mentioned also that with dihydroxamic acids melting below 110° the precipitates obtained from the aliquots of the reaction rates were dried at approximately 40° below their melting points. Phenylacetyl benzhydroxamate, m. p. 69–70°, was dried to constant weight in a vacuum desiccator at room temperature.

The average values of the rate constants obtained for the potassium salts of the dihydroxamic acids listed in Table VI (with the exception of compounds 18 and 32) are tabulated in decreasing order of rate in Table I. The solubility of most of the dihydroxamic acids was negligible, but phenylacetyl benzhydroxamate (no. 18) and benzoyl acethydroxamate (no. 32) were too soluble to give acceptable rate constants.

Determination of Yields of Amine Produced through Rearrangement.—The yields of amine were determined from experiments that were carried out under the same conditions as those used in the rate determination. With the potassium salts of dihydroxamic acids 1–16 in Table VI, the procedure of Renfrow and Hauser[26] was used. With the potassium salts of compounds 17–31 in Table VI the following procedure was used. An accurately weighed sample (approximately 1 g.) of the powdered dihydroxamic acid was suspended in 0.1 *N* ammonia and an equivalent of aqueous potassium hydroxide (2.5–3.0 *N*) was added. Sufficient 0.1 *N* ammonia solution was added to make the solution 0.025 molar in potassium dihydroxamate. The solution was placed in a thermostat and after complete decomposition of the salt (usually three to seven days were allowed, depending on the compound) the reaction mixture was refluxed with hydrochloric acid, made basic and extracted with ether.[26]

The yield of aniline from compounds 1–6 and 17–19 was determined by extracting with 3 *N* hydrochloric acid and titrating with standard bromate solution.[26] The amines obtained from compounds 14, 30 and 31 were isolated and weighed as free amines. The amines obtained from compounds 7, 9–13, 15, 16, 20, 21 and 24–27 were isolated as hydrochloride salts as previously described.[26] With compounds 28 and 29, because of the low basicity of the amine obtained, the ether solution of the amine was evaporated to dryness in a weighed beaker in the presence of 5–6 cc. of concentrated hydrochloric acid to give hydrochloride salts.

In cases in which aliphatic amines were obtained, the aqueous solution of the reaction mixture was saturated with sodium chloride before extracting with ether. Even with this procedure, however, yields of the aliphatic amines were abnormally low.

The amines were identified by their melting points or by the melting points of suitable derivatives.

The yields of amines obtained are given in Table I.

Summary

1. The rates of decomposition of the potassium salts of thirty dihydroxamic acids $(RCONOCOR')^-K^+$, have been determined at two temperatures, and the energies of activation calculated.

2. When R is phenyl and R′ varied, the rates are in general directly related to the strengths of the acids corresponding to R′COOH. This direct relationship holds even when R′ is an ortho substituted phenyl group. These results are of interest in connection with the "ortho effect."

3. When R′ is phenyl and R a meta or para substituted phenyl group, the rates are roughly inversely related to the strengths of the acids corresponding to RCOOH.

4. The relative rates obtained when R′ is phenyl and R varied are accounted for on the basis of I and T effects. The energies of activation may be correlated with these effects.

5. A number of new hydroxamic acid salts and dihydroxamic acids have been synthesized.

DURHAM, NORTH CAROLINA

RECEIVED NOVEMBER 14, 1938