tween the two forms of 1,1,2,2-tetrachloroethane is less than 200 cal./mole. The parallelism between these two compounds and 2-methylbutane and 2,3-dimethylbutane is striking. Thomas and Gwinn's discussion of the energy differences between the rotational isomers of the chlorine compounds in terms of steric repulsions and distortions of bond angles from tetrahedral values applies equally well to the methyl compounds studied in this work. The similar results for the polar and relatively non-polar pairs of compounds supports the idea that bond dipole interactions are unimportant in determining configurational stability.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE CATHOLIC UNIVERSITY OF AMERICA]

Substituent Effects in the Acid and Base Hydrolyses of Aromatic Amides[1]

BY ISABEL MELOCHE AND KEITH J. LAIDLER

A kinetic study has been made of the acid and base hydrolyses of benzamide, *p*-nitrobenzamide, *p*-chlorobenzamide, *p*-methylbenzamide and *o*-methylbenzamide. Activation energies, frequency factors and entropies of activation have been obtained. The changes in rate are found to be influenced mainly by changes in activation energy, but in both series ΔS^* increases approximately linearly with E. It is found that in alkaline hydrolysis electron-attracting groups lower E, while electron-repelling groups raise it; in acid solution electron-attracting groups raise E and electron-repelling ones lower it. A mechanism is proposed which explains the substituent effect and also the different effects observed in the acid and base hydrolyses of esters and the acid hydrolysis of anilides.

Introduction

In contrast to the situation with the aromatic esters,[2,3] very little information has been available with respect to substituent effects on the acid and base hydrolyses of amides. Emmet Reid[4] made some studies of this type, in aqueous solution and at 100°, but it seems likely that at least in some cases he was measuring the rate of solution of the amide rather than that of its hydrolysis. Various studies of the catalysis of aliphatic amides have been made,[5] and Karve and Kelkar[6] have recently investigated the kinetics of the acid hydrolysis of a number of substituted anilides.

In the present paper are reported kinetic data for the acid and base hydrolysis, in a 60-40 (by volume) alcohol–water mixture, of benzamide and four substituted benzamides.

Experimental

The amides used were benzamide, *p*-nitrobenzamide, *p*-chlorobenzamide, *p*-methylbenzamide (*p*-toluamide) and *o*-methylbenzamide (*o*-toluamide). All were obtained commercially except the *p*-chloro compound, which was prepared from the acid chloride. The amides were tested for purity by melting point determinations and were recrystallized when necessary.

The compounds are not sufficiently soluble in water, even at high temperature, to allow a reasonable concentration to be obtained. The 60-40 ethyl alcohol–water mixture was found to be suitable in all cases. Both the amide and the acid or base were put into solution at concentrations of 0.05 *M*, and as equal amounts (5 cc.) were mixed together in the reaction tubes the final concentration of each was 0.025 *M*. For the alkali sodium hydroxide was used; for the acid, benzene sulfonic acid. The latter has been found to be completely dissociated at the concentrations used, but unlike the mineral acids it does not esterify the alcohol present.[3]

The reactions were carried out in sealed tubes maintained for various lengths of time in thermostatically controlled oil-baths. Pyrex glass was used for the acid hydrolysis, but was unsuitable for the alkaline hydrolysis, being seriously etched, with marked removal of hydroxyl ions, at the higher temperatures used (80 and 100°). Corning brand alkali-resistant glass, no. 728, was used and was found to be entirely satisfactory.

Runs were carried out at four temperatures except with the very slowly hydrolyzed *o*-toluamide, which was hydrolyzed at three temperatures only with both acid and base. Tubes were removed after various periods of time and analyzed colorimetrically for ammonia after Nesslerization. It was established by separate experiments that the reaction gave mainly the acid and only to a negligible extent the ethyl ester.

Results

In all cases the second-order law was found to be obeyed accurately, constants being calculated using the equation $k = x/ta(a - x)$. Activation energies and frequency factors were obtained from the variation of log k with $1/T$, the method of least squares being used in all cases. The entropy of activation, ΔS^*, was calculated from the frequency factor A by means of the equation[7]

$$A = e(kT/h)e^{\Delta S^*/R} \qquad (1)$$

The rate constants obtained at the temperatures used are collected in Table I, while the values of E, A and ΔS^* are given in Table II. Some typical Arrhenius plots are shown in Fig. 1.

The least square treatment of the data indicates that the probable error in the activation energies is in all cases ±0.15 to ±0.20 kcal., and that the probable error in the entropies of activation is 0.4 to 0.55 entropy unit. In view of this the variation of ΔS^* with E, to be discussed in the next section, is entirely significant with respect to the experimental uncertainty.

Discussion

General.—It is to be noted from Table I that (except with the ortho compound) the alkaline

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[1] Abstracted from a dissertation submitted by Sister Isabel of Carmel Meloche, S.H.M., to the faculty of the Graduate School of Arts and Sciences of the Catholic University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] C. K. Ingold and W. J. Nathan, *J. Chem. Soc.*, 222 (1936).

[3] E. W. Timm and C. N. Hinshelwood, *ibid.*, 862 (1938).

[4] E. Emmet Reid, *Am. Chem. J.*, **21**, 284 (1899); **24**, 397 (1900).

[5] J. C. Crocker, *J. Chem. Soc.*, **91**, 593 (1907); J. C. Crocker and F. H. Lowe, *ibid.*, **91**, 952 (1907); S. F. Acree and S. Nirdlinger, *Am. Chem. J.*, **38**, 489 (1907); W. J. Taylor, *J. Chem. Soc.*, 2741 (1930); V. K. Krieble and K. A. Holst, THIS JOURNAL, **60**, 2976 (1938); B. S. Rabinovitch and C. A. Winkler, *Can. J. Research*, **B20**, 73 (1942).

[6] D. D. Karve and B. W. Kelkar, *Proc. Indian Acad. Sci.*, **24**, 254 (1946).

[7] S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 417.

TABLE I

SPECIFIC RATE CONSTANTS FOR THE HYDROLYSIS OF AMIDES

I. Alkaline Hydrolysis

$k \times 10^6$ (liter mole^{-1} sec.$^{-1}$)

Amide	100.1°	90.0°	80.3°	64.5°	52.8°
p-Nitrobenzamide	2270	..	582	217	93.9
p-Chlorobenzamide	502	..	125	39.7	16.1
Benzamide	338	..	76.4	23.9	8.54
p-Methylbenzamide	188	..	47.5	13.1	4.66
o-Methylbenzamide	13.5	5.57	2.37	...	...

II. Acid Hydrolysis

	99.6°	79.5°	65.0°	52.4°
p-Methylbenzamide	197	35.0	9.43	2.99
Benzamide	195	43.6	8.17	2.41
			(64.5°)	
p-Chlorobenzamide	206	38.5	7.78	1.99
	(100.1°)	(80.3°)	(64.5°)	(528°)
p-Nitrobenzamide	124	20.4	4.74	1.03
o-Methylbenzamide	13.9	1.34	3.61	..

TABLE II

ACTIVATION ENERGIES, FREQUENCY FACTORS AND ENTROPIES OF ACTIVATION

Amide	*E* (kcal.)	*A* (liter mole^{-1} sec.$^{-1}$)	ΔS^* (entropy units)
I. Alkaline hydrolysis			
p-Nitrobenzamide	16.1	5.72×10^6	−30.0
p-Chlorobenzamide	17.6	9.26×10^6	−29.0
Benzamide	18.7	2.77×10^7	−26.8
p-Methylbenzamide	18.9	2.33×10^7	−27.2
o-Methylbenzamide	23.1	4.55×10^8	−21.3
II. Acid hydrolysis			
p-Methylbenzamide	22.0	1.46×10^9	−18.9
Benzamide	23.3	1.25×10^{10}	−14.7
p-Chlorobenzamide	23.7	1.69×10^{10}	−14.1
p-Nitrobenzamide	24.6	3.74×10^{10}	−12.5
o-Methylbenzamide	27.1	8.79×10^{10}	−10.8

hydrolysis is somewhat more rapid than the acid. This is seen from Table II to be related to lower activation energies in alkaline hydrolysis. The frequency factors are lower by $\sim 10^3$ in alkaline hydrolysis, but this is not sufficient to offset the effect on the rates of the lower activation energies. The above remarks also apply to the ester hydrolyses.[2,3]

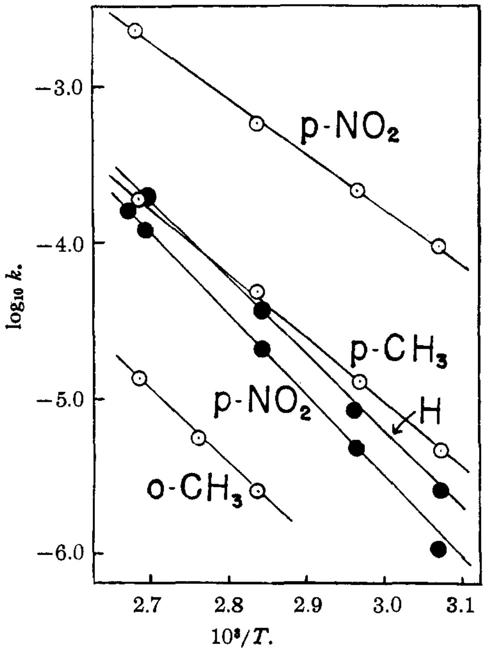

Fig. 1.—Plots of $\log_{10} k$ *vs.* $1/T$ for the hydrolysis of various substituted benzamides: full circles, acid hydrolysis; open circles, alkaline hydrolysis.

Figure 2 shows a plot of *E vs.* $T\Delta S^*$ for both the acid and alkaline hydrolyses. This plot shows, as may also be seen from Table II, that there is a tendency for ΔS^* to increase with increasing activation energy. In the alkaline series the ortho compound appears to conform to the linear relationship, but in the acid it does not: in the acid series ΔS^* is less than the linear relationship would require.

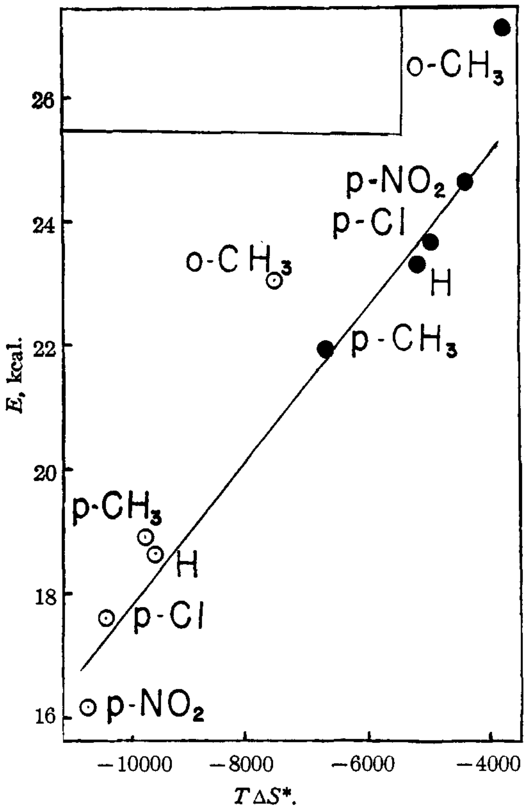

Fig. 2.—Plot of *E vs* $T\Delta S^*$ for acid and alkaline hydrolysis of benzamides: open circles, base hydrolysis; ●, acid hydrolysis.

Similar relationships to the above apply to the ester hydrolyses and many other reactions.[8]

The Substituent Effect.—The influence of substituents may be considered with reference to the substituent constants σ and ρ introduced by Hammett.[9] Plots of $\log_{10} k_{100°}$ against σ showed a roughly linear relationship in both the acidic and basic series, the values of ρ being −0.15 and 0.7, respectively. These values are to be contrasted with the figures 0.118 and 1.055 calculated by Hammett using Reid's data,[4] which do not refer to reaction in a homogeneous solution.

It may be seen from Table II that in alkaline hydrolysis the activation energy is lowered and the

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(8) K. J. Laidler and H. Eyring, *Ann. N. Y. Acad. Sci.*, **39**, 303 (1940).

(9) L. P. Hammett, *Chem. Revs.*, **17**, 125 (1935); *Trans. Faraday Soc.*, **34**, 156 (1938); "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940.

rate increased by the withdrawal of electrons from the seat of reaction; this is exemplified by the effect of the *p*-nitro group. On the other hand electron-releasing substituents (*e.g.*, CH_3, OCH_3) increase the activation energy in alkaline hydrolysis. This type of behavior is also exhibited by the esters in both alkaline and acid hydrolysis.

In the acid hydrolysis of the amides, on the contrary, the activation energy is seen to be lowered by electron-releasing substituents, and to be raised by electron-attracting ones.

The behavior of the amides, anilides and esters in both acid and alkaline solution is summarized in Table III, which shows the effect of introducing an electron-attracting substituent such as $-NO_2$.

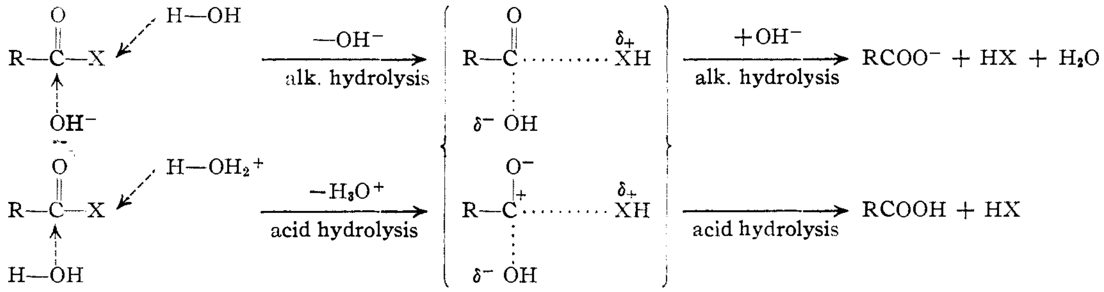
TABLE III

INFLUENCE OF AN ELECTRON-ATTRACTING SUBSTITUENT (*e.g.*, $-NO_2$) ON THE ENERGY OF ACTIVATION

Hydrolysis of	Alkaline hydrolysis	Acid hydrolysis
Amides	Decrease[b]	Increase[b]
Anilides	(No data)[a]	Decrease[c]
Esters	Decrease[d]	Decrease[e]

[a] A decrease is to be predicted on the basis of the treatment in the present paper. [b] Present work. [c] Karve and Kelkar, ref. 6. [d] Ingold and Nathan, ref. 2. [e] Timm and Hinshelwood, ref. 3.

The facts represented in this table appear to admit of explanation in terms of the following general mechanism of hydrolysis of a molecule of structure RCOX



(activated complex, two possible resonance forms shown)

Here X represents NH_2 in amide hydrolysis, OR in ester hydrolysis, and NHR in anilide hydrolysis. It is to be noted that reaction involves (1) the approach of OH^- or H_2O to the carbonyl carbon atom, (2) the ionic splitting of the C–X bond, and (3) the approach of H_2O or H_3O^+ to X.

An electron-attracting substituent in R facilitates effect (1), but hinders effects (2) and (3). The net effect of a substituent therefore depends on the importance of effect (1) relative to (2) and (3).[10]

The experimental results obtained in the present investigation indicate that in alkaline solution effect (1) is more important than (2) and (3). This is attributed to the fact that effect (1) involves interaction of an ion (OH^-) with the substrate molecule, and it is generally found[10] that such interactions are more important than those involving two molecules. In acid solution effects (2) and (3) are together more important than (1): this is attributed to the fact that effect (3) now involves an ion-molecule interaction. It is significant that the substituent effects are less pronounced in acid hydrolysis than in alkaline; this is due to the fact that the nitrogen atom, where the predominating attack occurs, is further removed from the substituted ring than is the carbonyl carbon atom which is important in alkaline hydrolysis.

The fact that the substituent effects on esters in acid solution are the reverse of those of the amides may be attributed to the fact that oxygen is a much weaker base than nitrogen. There is much less interaction between the oxygen and H_3O^+ (effect (3)), and effect (1) therefore predominates.

The anilides represent an intermediate case. The basicity of the nitrogen atom is weakened by substitution of the benzene ring (aniline is a weaker base than ammonia), so that the $N-H_3O^+$ interaction (effect (3)) will be weaker than in the amides. There is thus an approach to the situation with the acids, and in fact the influence of the H_2O-C interaction (effect (1)) is found to predominate.

Thanks are due to Dr. Barbara Van Tassel for valuable suggestions in connection with this work.

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[10] *Cf.* C. N. Hinshelwood, K. J. Laidler and E. W. Timm, *J. Chem. Soc.*, 848 (1938); K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., New York, N. Y., 1950, pp. 137-143.