The Base-catalysed Hydrolysis of Certain Aliphatic Amides and p-*Alkylbenzamides.*

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[Reprint Order No. 6185.]

The aqueous alkaline hydrolysis of acetamide, propionamide, *iso*-butyramide, and trimethylacetamide has been followed at 50° and 70° over a range of concentrations of sodium hydroxide. The order of reactivity appears to be governed by the inductive effects of the alkyl groups. Hydrolysis of benzamide, *p*-toluamide, *p*-ethylbenzamide, *p-iso*propylbenzamide, and *p-tert.*-butylbenzamide under similar conditions has also been examined. Within the limits of experimental error, the rates of hydrolysis of these *p*-alkylbenzamides are the same.

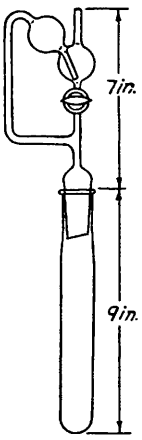
Kinetic studies (Reid, *Amer. Chem. J.*, 1899, **21**, 284; 1900, **24**, 397) indicate that the alkaline hydrolysis of a simple amide follows the mechanistic type summarised by Ingold as $B_{AC}2$. Electron-attracting substituents accelerate, and electron-donating substituents retard the reaction. Thus any *C*-alkylated acetamide would be expected to hydrolyse more slowly than the parent compound, even if steric retardation were absent. In the series, acetamide, propionamide, *iso*butyramide, and trimethylacetamide, the order of reactivity would depend on the relative contributions of the inductive and hyperconjugative effects, although related data (*e.g.*, alkaline hydrolysis of the corresponding ethyl esters; Davies and Evans, *J.*, 1940, **339**; Evans, Gordon, and Watson, *J.*, 1938, 1438) suggest that in the simple aliphatic amides the order would probably be dictated by the inductive effect. A kinetic study has now been made, at 50° and 70°, of the hydrolysis with sodium hydroxide in aqueous solution. Because similar hydrolysis of *p*-alkylbenzamides should be relatively free from primary steric effects and should also provide more favourable conditions for hyperconjugation, the series, *p*-toluamide, *p*-ethylbenzamide, *p-iso*propylbenzamide and *p-tert.*-butylbenzamide, was also examined.

Experimental and Results

Amides.—Of the purified materials acetamide had m. p. 81°, propionamide 81°, and *iso*-butyramide (prepared by Kent and McElvain's method; *Org. Synth.*, 1945, **25**, 58) 128°. Trimethylacetamide was prepared from the purified acid by Kent and McElvain's method. Repeated recrystallisations from ethyl acetate and from ether gave a sample melting at 157° (cf. m. p. 153—154°, Franchimont and Klobbie, *Rec. Trav. chim.*, 1887, **6**, 238; 155—156°, Haller and Barrer, *Compt. rend.*, 1909, **148**, 129). Benzamide melted at 129°, toluamide at 162°, unchanged after many recrystallisations (Beilstein records several values between 156° and 165°), and *iso*propylbenzamide (prepared from the corresponding acid by Berliner's procedure, *J. Amer. Chem. Soc.*, 1952, **74**, 4940) at 153°. *p-tert.*-Butylbenzamide, prepared from *p*-bromo-*tert.*-butylbenzene *via* the Grignard compound and the acid resulting from carboxylation, melted at 173° (cf. 171°; Kelbe and Pfeiffer, *Ber.*, 1886, **19**, 1726). Gattermann and Rossolymo (*Ber.*, 1890, **23**, 1195) recorded m. p. 115—116° for *p*-ethylbenzamide; our sample was obtained by a procedure similar to that used for the *tert.*-butyl compound and melted at 166°, although the acid had the accepted m. p., 114°. Gattermann and Rossolymo's preparation was therefore repeated; the resulting amide, after two recrystallisations from water, had m. p. 162°, and a mixed m. p. determination with our original preparation confirmed identity of the two samples (Found: C, 72·5; H, 7·35; N, 9·45. Calc. for $C_9H_{11}ON$: C, 72·5; H, 7·4; N, 9·4%).

Hydrolyses.—The bath temperatures were maintained to within 0·05° for all runs. For each run, a set of ten tubes (see Figure) was used. The reaction mixture was contained in the tube and in the bulb were placed 10 ml. of a sulphuric acid solution sufficiently concentrated to ensure slight residual acidity on mixing with the hydrolysate. Tubes were removed from the bath at appropriate intervals for analysis and placed in ice–salt to arrest hydrolysis, the tap being opened at the same time to effect mixing. After this neutralisation of the hydrolysate, the method for ammonia determination depended on whether or not the amide concerned interfered with the direct titration method (*J.*, 1952, 3264).

Aliphatic Amides.—There was no measurable reaction of acetamide or propionamide with hypobromite under the experimental conditions; *iso*butyramide reacted very slightly but the extent was insufficient to render uncertain the titration for ammonia. In each of these cases, therefore, ammonia determination was carried out in the presence of the amide. Trimethylacetamide reacted extensively with hypobromite; the distillation procedure was therefore followed and proved free from complications. The molar ratio of alkali to amide was >100 : 1 in every run and the kinetics were of first order with respect to amide. For each amide, variation of amide concentration confirmed pseudo-unimolecularity and runs with sodium chloride additions indicated a freedom from salt effect. The range of sodium hydroxide concentration was 0·03125—0·75M, and at least two runs were carried out at each of the concentrations, with the exception of the lowest. For each of the amides, when k_1 (first-order rate constant) was plotted against alkali concentration, the resulting graph (4—7 points) was linear and passed through the origin. Typical results, for acetamide at 50°, are given in Table 1.



The linear plots of k_1 against [NaOH] are described by the equation $k_1 = k_2 . m_{NaOH}$. The " catalytic coefficient " of the hydroxyl ion (k_2) is the second-order rate constant for the bimolecular reaction between amide and hydroxyl ion. Relevant values for k_2, the activation energy (E), and the temperature-independent term of the Arrhenius equation ($\log_{10} B$) are given in Table 2, together with the estimated errors.

Aromatic Amides.—With each of these amides the distillation method of analysis was used, because of the extensive reaction between amide and hypobromite. Procedure for kinetic work at 70° was similar to that adopted for the aliphatic amides, at least four values for [NaOH] being used, and linear k_1–[NaOH] plots were again obtained. Kinetics at 80° were followed for all four amides but alkali concentrations were limited to 0·25—0·50M-sodium

TABLE 1.

[NaOH] (mole/l.)	10^3k_1 (50°) (min.$^{-1}$) Individual values				Mean
0·03125		0·5			0·5
0·0625		1·03	0·94		0·99
0·125		1·96	2·10		2·03
0·250	4·13	4·13	4·10	4·10	4·10
	4·10	4·25	4·08	3·94	
	4·07				
0·375		6·88	6·83		6·86
0·500	9·80	8·80	9·25	9·58	9·33
	9·58	9·75	9·10	8·80	
0·625	12·1	11·4	11·2	11·4	11·5

TABLE 2.

	10^3k_2 (l. mole^{-1} min.$^{-1}$) 50°	70°	E (± 0·5) (kcal. mole^{-1})	$\log_{10} B$ (± 0·24)
Acetamide	18·4 ± 0·2	66·8 ± 0·3	14·3	6·15
Propionamide	16·6 ± 0·1	60·2 ± 0·6	14·4	6·17
*iso*Butyramide	6·58 ± 0·1	25·5 ± 0·6	15·0	6·18
Trimethylacetamide	1·53 ± 0·02	6·35 ± 0·2	15·7	6·02

TABLE 3.

	10^3k_2 (±0·2) (at 70°)	10^3k_1 in 0·50M-NaOH 80°	70°	60°	E (±1)	$\log_{10} B$ (±0·5)
Benzamide	16·3	15·6	8·20	—	12	6·0
p-Toluamide	10·4	9·5	5·30	2·80	13	6·4
p-Ethylbenzamide	10·8	9·7	5·28	—	13	6·2
*p-iso*Propylbenzamide	10·6	9·1	4·80	—	12	5·5
p-tert.-Butylbenzamide	10·8	9·1	5·60	2·75	11	5·1

hydroxide. In view of the results obtained at these two temperatures the hydrolyses of *p*-toluamide and *p-tert.*-butylbenzamide were followed at 60° in 0·50M-sodium hydroxide. Relevant data are collected in Table 3.

Results.—The order of reactivity of the aliphatic amides is apparently determined by the

inductive effects of the alkyl groups, the effect of hyperconjugation on the order being small and almost negligible. Steric effects appear to be constant, there being no appreciable difference between frequency factors within the series. Similar results have been observed in the alkaline hydrolysis of the corresponding esters (Davies and Evans, *loc. cit.*). In the aromatic series there is no definite reactivity order. All four substituted benzamides are hydrolysed more slowly than the parent amide but there are no significant differences between the reaction rates of the *p*-alkylbenzamides, the observed differences in rate constants being just within the limits of experimental error. It thus appears that the order is a mixed inductive–hyperconjugative order displaying an unusual balance of effects.

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[*Received, March 2nd,* 1955.]