4-Chlorophenyl disulfide (2.87 g) was dissolved in 100 ml of absolute ethanol, 15 ml of 5.5 *N* NaOH was added, and the solution was held for 24 hr at 35.2° under nitrogen. Upon working up as above, a 65% yield of 4-chlorobenzenesulfinic acid, melting at 90–92°, was recovered. Elemental analyses for all three sulfinic acids are given in Table III.

Alkaline Decomposition of Benzyl Disulfide.—Benzyl disulfide (2.46 g, 10 mmoles) was dissolved in about 60 ml of EtOH in a 100-ml spherical flask equipped with a gas-diffusing inlet tube with diffusing disk near the bottom of the flask, an outlet tube, and a dropping funnel. The solution was aspirated with nitrogen for 30 min, then 2.4 g of sodium hydroxide dissolved in 10 ml of water was added and the solution was stirred for a few minutes with nitrogen while the solution took on a pink color. The flask was held at room temperature and sealed for 18 hr; 6 *N* HCl (10 ml) was added through the dropping funnel and a slow stream of nitrogen was started which was conducted from the outlet tube to a flask containing 2.5 g of $CuSO_4 \cdot 5H_2O$ in 50 ml of water. A copious black precipitate accumulated during 9 hr. The assembly was dismantled and the clear pink solution was decanted from the sodium chloride crystals into a 500-ml erlenmeyer flask. After dilution with an equal volume of water, the turbid solution was titrated with 0.62 *N* iodine in aqueous potassium iodide. The end point at 23.7 ml corresponds to 14.7 mequiv of iodine. A heavy red oil (1.99 g) settled and soon solidified. The striking red color persisted on recrystallization from aqueous EtOH, but the product melted at 65–67° and a mixture melting point with authentic benzyl disulfide (70–72°) was 68–70°. The solution, at the completion of the iodometric titration, smelled strongly of benzaldehyde. Further acidification of the solution, extraction with ethyl ether, and evaporation of the ether concentrated the benzaldehyde, but furnished no benzoic acid.

Registry No.—4,4′-Dithiodiphenol, 15015-57-3; 4-chlorophenyl disulfide, 1142-19-4; *o*-tolyl disulfide, 4032-80-8; *p*-tolyl disulfide, 103-19-5; 2-Sulfinobenzoic acid, 13165-80-5; 3-sulfinobenzoic acid, 15451-00-0; 4-chlorobenzenesulfinic acid, 100-03-8; 4,4′-dithiodibenzoic acid, 1155-51-7; benzyl disulfide, 150-60-7.

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The Alkaline Hydrolysis of Benzamide and N-Methyl- and N,N-Dimethylbenzamide[1]

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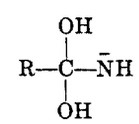
The alkaline hydrolyses of benzamide and N-methylbenzamide, but not of N,N-dimethylbenzamide, are accompanied by extensive oxygen exchange between water and the amide. The values of k_e/k_h for benzamide decrease with increasing hydroxide ion concentration and are greater in deuterium than in protium oxide. For hydrolysis of benzamide, k_{H_2O}/k_{D_2O} is 1.4, and for N,N-dimethylbenzamide it is 0.88. These differences arise because of the solvent isotope effect upon partitioning of the tetrahedral intermediate derived from benzamide.

The mechanism of the alkaline hydrolysis of carboxylic amides is similar to that of esters, except that the concomitant oxygen exchange is generally faster than hydrolysis.[2,3] In the simplest reaction scheme, an intermediate (I) is assumed to partition to give products or regenerate reactants and, provided that the oxygen atoms in I become equivalent by virtue of rapid proton transfers, this reverse step will lead to oxygen exchange.[2,4] The rate constants for exchange and hydrolysis are then related to k_{-1} and k_2 by

$$k_e/k_h = k_{-1}/2k_2 \quad (1)$$

In the alkaline hydrolysis of primary and secondary amides where $k_e/k_h > 1$, the rate of hydrolysis should therefore be considerably less than that of the formation of the intermediate (I).[2,3]

There is considerable evidence that the equilibration of the oxygen atoms in the tetrahedral intermediate is not always faster than its breakdown[5,6] and it has also been suggested that the relatively fast oxygen exchange during the alkaline hydrolysis of amides arose because the negative charge could be located on the nitrogen atom of the intermediate, as in II.[2c,3]



II

There is also direct kinetic evidence for the formation of tetrahedral intermediates in the alkaline hydrolysis of anilides.[7–9] The amide residue should be a poorer leaving group than either hydroxy or alkoxy groups and the ready return of I to reactants is to be expected.

We examined the alkaline hydrolysis of N,N-dimethylbenzamide, where structures like II could not be formed, and determined the effects of hydroxide ion concentration and the solvent isotope effect upon the rates of exchange and hydrolysis of benzamide. The alkaline hydrolysis of N-methylbenzamide was also examined to a limited extent.

(1) Partial support of this work by the National Science Foundation and award of a Fellowship from the New Zealand Federation of University Women are gratefully acknowledged.

(2) (a) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); (b) M. L. Bender and R. D. Ginger, *J. Am. Chem. Soc.*, **77**, 348 (1955); (c) M. L. Bender and R. J. Thomas, *ibid.*, **83**, 4183, 4189 (1961).

(3) C. A. Bunton, T. A. Lewis, and D. R. Llewellyn, *Chem. Ind.* (London), 1154 (1954).

(4) M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951).

(5) M. L. Bender, R. D. Ginger, and J. P. Unik, *ibid.*, **80**, 1044 (1958).

(6) C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1956).

(7) S. S. Biechler and R. W. Taft, *J. Am. Chem. Soc.*, **79**, 4927 (1957).

(8) P. M. Mader, *ibid.*, **87**, 3191 (1965).

(9) (a) R. L. Schowen and G. W. Zuorick, *ibid.*, **88**, 1223 (1966); (b) R. L. Schowen, H. Jayaraman, L. Kershner, and G. W. Zuorick, *ibid.*, **88**, 4008 (1966).

Experimental Section

Materials.—Benzamide was a commercial sample recrystallized from hot water, mp 128° (lit.[10] mp 128°). N-Methyl- and N,N-dimethylbenzamide were prepared from benzoyl chloride and the amine. N-Methylbenzamide was recrystallized from petroleum ether, bp 60–80°, and had mp 79° (lit.[10] mp 78°); N,N-dimethylbenzamide was vacuum distilled and then recrystallized from petroleum ether, mp 43° (lit.[11] mp 43°).

The isotopically labeled amides were prepared from [^{18}O] benzoyl chloride,[2b] by reaction with ammonia gas in benzene, or from the amines in 10% aqueous NaOH or in dry ether.[11]

After purification as described, they had the following melting points: benzamide, 127.5–128°; N-methylbenzamide, 78.5–79.5°; N,N-dimethylbenzamide, 43–43.5°. The isotopic abundance of ^{18}O was *ca.* 1.4 atom % excess.

Kinetics.—The hydrolyses were carried out at 100.4° in protium or deuterium oxide in alkali-resistant Jena glass ampoules. The reaction was stopped by adding hydrochloric acid, sufficient to neutralize the alkali, to the contents of ampoules. The hydrolysis of benzamide was followed by determining the evolved ammonia using Nessler's reagent. That of N-methylbenzamide was followed spectrophotometrically at 2300 and 2330 A. The hydrolysis of N,N-dimethylbenzamide was followed by adding an alcoholic solution of 1-fluoro-2,4-dinitrobenzene and alkali to the reaction solution. The N,N-dimethyl-2,4-dinitroaniline was determined spectrophotometrically at 3810 A.[12]

Oxygen Exchange.—The reaction was generally carried out in sealed ampoules with 0.1–0.2 *M* amide, but X-tubes, with an aqueous solution of the amide in one leg and alkali in the other, were used for the faster reactions. After a given time, the tubes or ampoules were cooled to −80° and excess acid was added. The amount of hydrolysis was determined as described above using a portion of the reaction mixture. The amide was then extracted from the solution after the acid was neutralized, using ether for benzamide and methylene chloride for the other amides. The amides were purified as already described and had melting points within 0.5° of those found for the original samples.

The isotopic abundances of the amides were determined either by the method of Dahn, Moll, and Menassé,[13] or by the modification of that method using a mixture of phenylenediamine hydrochloride and guanidine hydrochloride.[14]

The relative rates of exchange and hydrolysis were calculated from the relation

$$k_e/k_h = \frac{\log [100/(100 - \% \text{ exchange})]}{\log [100/(100 - \% \text{ hydrolysis})]}$$

Results

The second-order rate constants for the alkaline hydrolyses in both H_2O and D_2O are given in Table I. The reactions are first order in each reagent. The solvent isotope effect for the alkaline hydrolysis of benzamide is similar to that found for the alkaline hydrolysis of acetamide.[15]

In agreement with earlier work, we find extensive oxygen exchange between water and benzamide and N-methylbenzamide, but none for N,N-dimethylbenzamide (Table II). However, the values of k_e/k_h decrease with increasing hydroxide concentration. This result was not unexpected, because less exchange was observed during hydrolyses of benzamide in 0.1 *M* sodium hydroxide[2] than in 1 *M* barium hydroxide.[3] (However, temperature differences made comparison of these earlier experiments difficult.)

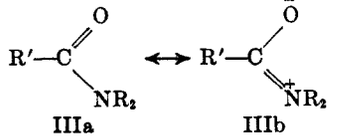
Discussion

Formulation of the hydrolysis mechanism requires consideration of the rates of both oxygen exchange and hydrolysis. On the simple assumption that proton transfers in the intermediate (I) are rapid compared with the rates of decomposition of it to reactants and products, the first-order rate constant for its formation, k_1, is given by[4]

$$k_1 = k_h(1 + 2k_e/k_h) \quad (2)$$

The values of k_1 calculated using eq 2 and assuming rapid proton transfer are given in Table III.

Although the reactivity sequence of the amides in hydrolysis is benzamide > N,N-dimethylbenzamide > N-methylbenzamide (Table I), the values of k_1/C_{OH^-} decrease with increasing methylation. N-Methyl groups should hinder nucleophilic attack upon the acyl group either sterically or inductively or by increasing the contribution of the classical structure (IIIb) to the structure of the resonance hybrid and so reducing the electrophilicity of the carbonyl group.



IIIa IIIb

TABLE I

ALKALINE HYDROLYSIS[a]

Amide	C_{OH^-}, *M*	C_{OD^-}, *M*	10^4k_ψ, sec^{-1}	$10^4k_\psi/C_{OH^-}$
Benzamide	0.010	...	0.158[b]	15.8
Benzamide	...	0.010	0.115[b,c]	11.5[c]
Benzamide	0.100	...	1.55	15.5
Benzamide	...	0.111	1.22[c]	11.0[c]
Benzamide	0.314	...	4.99	15.9
Benzamide	0.700	...	11.5	16.4
Benzamide	0.990	...	16.5	16.5
Benzamide	1.02	...	11.5[c]	11.2
N-Methylbenzamide	0.110	...	0.786	7.16
N-Methylbenzamide	0.467	...	3.37	7.23
N-Methylbenzamide	1.02	...	7.33	7.19
N,N-Dimethylbenzamide	0.198	...	3.03[b]	15.2
N,N-Dimethylbenzamide	...	0.196	3.41[b,c]	17.4[c]

[a] At 100.4°. [b] Mean of three determinations. [c] In D_2O.

TABLE II

OXYGEN EXCHANGE[a]

Amide	C_{OH^-}, *M*	C_{OD^-}, *M*	Hydrolysis, %	k_e/k_h
Benzamide	0.070	...	36.5	4.8
Benzamide	0.070	...	37.1	4.7
Benzamide	...	0.097	15.3	7.8[b]
Benzamide	0.100	...	13.9	4.7
Benzamide	0.116	...	19.9	4.3
Benzamide	...	0.125	18.8	7.5[b]
Benzamide	0.141	...	24.2	4.0
Benzamide	0.514	...	21.7	3.8
Benzamide	...	0.561	13.7	6.7[b]
Benzamide	0.990	...	19.5	3.7
Benzamide	1.02	...	36.1	3.6
Benzamide	...	1.08	17.1	5.2[b]
Benzamide	1.09	...	25.1	3.0
N-Methylbenzamide	0.150	...	52.2	1.38
N-Methylbenzamide	1.08	...	48.6	1.32
N,N-Dimethylbenzamide	0.40	...	14.7	0.04
N,N-Dimethylbenzamide	0.40	...	24.4	0.07
N,N-Dimethylbenzamide	0.40	...	58	0.02

[a] At 100.4°. [b] In D_2O.

(10) F. L. Dunlap, *J. Am. Chem. Soc.*, **24**, 758 (1902); O. L. Brady and F. P. Dunn, *J. Chem. Soc.*, 2414 (1926).
(11) A. Hallman, *Ber.*, **9**, 846 (1876).
(12) A. B. Thomas and E. G. Rochow, *J. Am. Chem. Soc.*, **79**, 1843 (1957).
(13) H. Dahn, H. Moll, and R. Menassé, *Helv. Chim. Acta*, **42**, 1225 (1959).
(14) C. A. Bunton and B. N. Hendy, *J. Chem. Soc.*, 627 (1963)
(15) O. Reitz, *Z. Physik. Chem.* (Leipzig), **A183**, 371 (1939).

TABLE III

RATE CONSTANTS FOR ATTACK OF HYDROXIDE ION[a]

Amide	Lyate ion	C_{OH^-}, M	10^4k_h, sec^{-1}	k_e/k_h[b]	10^4k_1, sec^{-1}	$10^4k_1/C_{OH^-}$
Benzamide	OH^-	0.100	1.55	4.4	15.2	152
Benzamide	OH^-	0.314	4.99	4.1	45.9	146
Benzamide	OH^-	0.700	11.5	3.7	96.8	138
Benzamide	OH^-	0.99	16.5	3.5	132	133
Benzamide	OD^-	0.11	1.22	7.6	19.8	180[c]
Benzamide	OD^-	1.02	11.5	5.3	134	131[c]
N-Methylbenzamide	OH^-	0.11	0.79	1.4	3.0	27
N-Methylbenzamide	OH^-	1.02	7.33	1.3	2.6	25
N,N-Dimethylbenzamide	OH^-	0.198	3.03	...	3.03	15.2
N,N-Dimethylbenzamide	OD^-	0.196	3.41	...	3.41	17.4[c]

[a] At 100.4°. [b] Values for benzamide interpolated from plot of k_e/k_h against C_{OH^-}. [c] In D_2O.

Kinetic, Isotopic, and Structural Effects on Exchange. —The deuterioxide ion in deuterium oxide is a better nucleophile than hydroxide ion in protium oxide[16-18] and this difference has been ascribed to changes in the vibrational frequencies of the hydroxide ion in going from the initial state to the transition state,[19] possibly caused by changes in hydrogen bonding interactions.[20]

On this basis the value of $k_{OH}/k_{OD} = 0.88$ for the alkaline hydrolysis of N,N-dimethylbenzamide (Table I) is understandable and similar solvent isotope effects have been observed for ester saponifications and SN2 reactions involving lyate ions.[17,18] If we consider only the values of k_h for the hydrolysis of benzamide in alkaline protium and deuterium oxide (Table I), where $k_{OH^-}/k_{OD^-} = 1.41$, we would assume that the isotope effect upon the nucleophilicity of the hydroxide ion is more than offset by some secondary structural isotope effect, because in deuterium oxide the substrate is $C_6H_5CO\cdot ND_2$. On the other hand, the values of k_1 for the alkaline hydrolysis of benzamide in both protium and deuterium oxide show that for the attack of lyate ion k_{H_2O}/k_{D_2O} is 0.85–1.0 (Table III). These results suggest that the kinetic isotope effect upon the hydrolysis of benzamide arises in the partitioning of the intermediate, because k_{-1}/k_2 (which is assumed to be given by $2k_e/k_h$) is larger in deuterium than in protium oxide. Kinetic analysis of the alkaline hydrolysis of 2,2,2-trifluoro-N-methylacetanilide suggests that k_{H_2O}/k_{D_2O} is close to unity for the actual attack of hydroxide ion upon this amide.[9b]

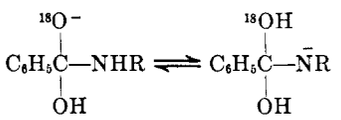
The extensive oxygen exchange during the alkaline hydrolysis of benzamide shows that at least partial equilibration of the oxygen atoms in I occurs during its lifetime. If this equilibration was limited by the rate of the proton transfers which are necessary for isotopic equilibration, we might expect the values of k_e/k_h to be less in deuterium than in protium oxide, particularly when, as in these reactions, the protons are transferred between bases (or basic centers) of similar strength.[20,21]

If we assume that isotopic equilibration is not limited by proton transfer, the values of k_e/k_h in protium and deuterium oxide give $(k_{-1}/k_2)_H(k_2/k_{-1})_D \sim 0.6$ (Table II). This value is similar to that estimated by a kinetic analysis of the alkaline hydrolysis of 2,2,2-trifluoro-N-methylacetanilide.[9b] However, in view of the structural differences between these two amides further evidence is needed before we can assess the mechanistic significance of these similarities in the isotope effects upon k_{-1}/k_2.

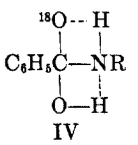
Although the solvent isotope effect upon k_e/k_h suggests that interoxygen proton transfers are fast for the alkaline hydrolysis of benzamide, there are many hydrolyses of anilides and esters for which proton transfers to or from the leaving group are kinetically important and there is strong kinetic evidence that slow proton transfers are involved in the decomposition of the tetrahedral intermediates.[2,7-9]

Bender and his co-workers have explained the structural effects upon k_e/k_h for anilide hydrolysis in these terms[2c] and noted that our observation of no exchange in the alkaline hydrolysis of N,N-dimethylbenzamide was evidence that the equilibration of the oxygen in I required proton transfer from a –NH residue.[22]

It was reasonable to suggest, therefore, that the isotopic equilibration in I occurs by a series of reactions such as

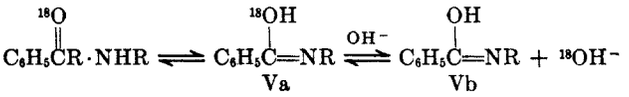


or by an intramolecular proton transfer as in IV.[23]



IV

Another possible explanation for the differences in oxygen exchange between these various amides, and for the generally greater oxygen exhange in amide as compared with ester hydrolysis, is that these are distinct reactions with exchange occurring by direct displacement on a (hypothetical) hydroxyimide (V). However, there is no evidence for hydroxyimide



Va Vb

(16) W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **32**, 1397 (1936).
(17) K. B. Wiberg, *Chem. Rev.*, **55**, 713 (1955).
(18) J. G. Pritchard and F. A. Long, *J. Am. Chem. Soc.*, **78**, 6008 (1956).
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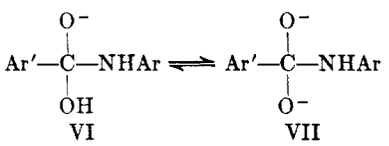
(20) C. A. Bunton and V. J. Shiner, *ibid.*, **83**, 3207, 3214 (1961).
(21) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).
(22) C. A. Bunton, personal communication quoted in ref 2c.
(23) We are indebted to Dr. J. Rocek for this suggestion.

structures in amides[24] and, if we assume that an imide (V) is formed in equilibrium with the amide, we would expect it to hydrolyze readily by attack of hydroxide ion. There would then be no real experimental distinction between these explanations because in each we would assume that the initial state was the amide plus hydroxide ion and that the transition state was generated by attack of hydroxide ion upon an unsaturated carbon atom. Also, if the hydroxyimide structure (V) played a major role in hydrolysis, N,N-dimethylbenzamide should be much less reactive than the primary and secondary amides.

Kinetic Form of Hydrolysis and Exchange.—For the three amides which we have examined, the second-order rate constant, k_h/C_{OH^-}, is independent of hydroxide ion concentration and the small decreases of k_e/C_{OH^-} and k_1/C_{OH^-} with increasing hydroxide ion concentration are probably caused by negative salt effects of the sodium hydroxide. (The results also suggest that the apparent second-order kinetic form of the alkaline hydrolysis arises because of a fortuitous cancellation of effects upon k_1/C_{OH^-} and k_e/k_h.) Orders either greater or less than unity have been observed for a number of amide hydrolyses.[2,7-9] An order less than unity is observed when the amide itself is sufficiently acidic to be partially ionized, as in the hydrolysis of trifluoroacetanilide,[7,8] and higher orders are observed in anilide hydrolyses in which it appears that the intermediate (I) can be further ionized (VI → VII). (In VI and VII



VI VII

we could alternatively assume that the nitrogen atom carried a negative charge.)

These conclusions are reasonable because I should exist as a monoanion for benzamide and N-methylbenzamide. The hydrate of benzamide should be a stronger acid than formaldehyde hydrate,[25] for which $K_a = 5.1 \times 10^{-14}$ and therefore it should behave as a monobasic acid at pH >13.

It is difficult to explain these particular isotope effects because isotopic substitution changes both the nature of the solvent and the structure of the tetrahedral intermediate because of the number of exchangeable hydrogen atoms in it. We had initially hoped to isolate some of these effects by measuring the solvent isotope effect upon k_e/k_h for the alkaline hydrolysis of N,N-dimethylbenzamide, but our plans were frustrated by the absence of oxygen exchange during this reaction.

Relative Reactivities.—Although there is a general decrease in the values of k_1 with increasing N-methylation, we should note that the true rate constants for the formation of the intermediate (I) may be greater than those calculated using eq 2, simply because this equation is valid only if proton transfer in I is sufficiently rapid to give isotopic scrambling within the lifetime of I. However, we have assumed that this condition is not fulfilled during the alkaline hydrolysis of N,N-dimethylbenzamide and have explained the absence of oxygen exchange in these terms (*cf.* ref 2c). Therefore, it is probable that the values of k_1, given in Table III, for the hydrolysis of N,N-dimethylbenzamide actually underestimate the rate constants for the formation of I in this reaction. This problem is quite general, because we can never be certain that isotopic scrambling is complete, even though there is extensive oxygen exchange during alkaline hydrolyses of primary and secondary amides (Table III and ref 2 and 3). However, the deuterium solvent isotope effect upon k_e/k_h for the hydrolysis of benzamide suggests either that scrambling of the oxygen label is not limited by the rates of proton transfer or that k_{-1} and k_2 both depend upon rate-limiting proton transfers between oxygen or nitrogen atoms, but we see no general method for deciding whether the absence of oxygen exchange during hydrolysis of a carboxyl derivative arises from an unfavorable partitioning of tetrahedral intermediate or from a slow isotopic scrambling of its oxygen atoms.

Registry No.—Benzamide, 55-21-0; N-methylbenzamide, 613-93-4; N,N-dimethylbenzamide, 611-74-5.

(24) S. Pinchas, D. Samuel, and M. Weiss-Broday, *J. Chem. Soc.*, 1688 (1961); A. Lapidot, S. Pinchas, and D. Samuel, *ibid.*, 1128 (1963); R. Stewart and L. J. Muenster, *Can. J. Chem.*, **39**, 401 (1961).

(25) R. P. Bell and P. T. McTigue, *J. Chem. Soc.*, 2983 (1960).