B. With 2 Equiv of Potassium Ethoxide.—Following procedure A, 1.0 g (0.00267 mole) of VI and 0.17 g (0.00534 g-atom) of sulfur in 10 ml of ethanol was treated with 0.44 g (0.00534 mole) of potassium ethoxide in 5 ml of ethanol to give 0.52 g (63.4%) of VII, mp 118–122°.

Registry No.—I, 2461-75-8; VI, 2786-92-7; VII, 15441-13-1; VIII, 15441-14-2; IX, 15441-15-3; XIII, 15441-16-4; XV, 2461-79-2; 2,3-mercapto-1,4-diphenyl-1,4-butanedione, 15441-18-6; XVI, 15441-19-7; XX, 1665-65-2; XXI, 15441-21-1; XXII, 925-47-3.

The Alkaline Decomposition of Organic Disulfides. III. Substituent Effects among Aromatic Disulfides[1]

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Eleven variously substituted aromatic disulfides have been found to undergo extensive cleavage at 35.2° in 0.1 N sodium hydroxide in water, aqueous ethanol, or aqueous 1,4-dioxane, according to the stoichiometry $2ArSSAr + 4OH^- \rightarrow 3ArS^- + ArSO_2^- + 2H_2O$. The relative speeds of decomposition correlate rather well with the pK_a values of the thiols which are conjugate to the thiolate anions displaced from the disulfides by the nucleophilic attack of the hydroxide ion: the more sensitive the disulfide, the more stable the thiolate anion. This generalization extends to those aliphatic disulfides which have previously been shown to decompose by nucleophilic attack, or not at all, in aqueous alkali. Benzyl disulfide decomposes more rapidly than would have been anticipated from the pK value of benzyl mercaptan, but the products of decomposition (benzyl mercaptan, hydrogen sulfide, and benzaldehyde) indicate the probability that it has decomposed by an α elimination. The behavior of 4,4′-dithiodiphenol is anomalous: stable for at least 10 days in 0.1 N NaOH, it decomposes readily in 1 N NaOH at 35.2°. The slow addition of aqueous hydrogen peroxide to an alkaline solution of an aromatic disulfide which is sufficiently sensitive to alkali, by oxidizing the thiolate anion back to disulfide, provides a convenient way for preparing aromatic sulfinic acids.

Recently, from a consideration of the relative speeds of decomposition, and of the products of decomposition, of variously substituted symmetrical alkyl disulfides, Danehy and Hunter[3] concluded that direct nucleophilic attack of hydroxide ion on one sulfur atom, with displacement of the other as thiolate anion, will take place unless attack is inhibited by a negative charge not too far removed from the sulfur atoms or, in rarer cases, by steric hindrance. It was suggested that the sulfenate anion immediately attacked disulfide to form more thiolate anion and thiolsulfinate, which underwent further alkaline decomposition to furnish sulfinate anion and more thiolate anion. Actually, under strictly anaerobic conditions, more of the oxidized sulfur was accounted for as sulfonate rather than as sulfinate, for which we as yet have no explanation (see Scheme I). Alternatively, if a sufficiently labile proton is bonded to a carbon atom which is α or β to a sulfur atom, decomposition may be initiated by proton abstraction followed by an α or β elimination reaction.

While in principle the displacement and elimination reactions could be competitive, the 17 cases examined were quite clean: evidence for elimination was observed only in those cases in which neighboring carboxylate anions inhibited direct nucleophilic attack by hydroxide ion.

In investigating further the extent and significance of inhibition of direct attack by negative charge, the three isomeric dithiodibenzoic acids seemed particularly suitable. Forty years ago, Smiles[4] reported that 3,3′-dithiodibenzoate anion was extremely susceptible to attack by aqueous alkali, while 2,2′-dithiodibenzoate anion was far less so. While he made some reference to 4,4′-dithiodibenzoic acid, he never completed a quantitative comparison of the three isomers in relation to alkali. He did report that the corresponding mercaptobenzoate anion is the major product in each case. By reinvestigation we have established that at 35.2° the 4,4′ and 3,3′ isomers are 80 and 46% cleaved, respectively, in 12–15 min in a 12:1 molar excess of 0.125 N NaOH, while the 2,2′ isomer under the same experimental conditions is only 6.6% cleaved in 6 hr and only 15.5% cleaved in 24 hr.

While these results placed the three isomers in the expected order of reactivity, they are surprising for another reason. There is a long-standing opinion that aromatic disulfides are considerably more resistant to alkaline attack than the suitably substituted, water-soluble alkyl disulfides. Smiles[4a] stated that "in this behavior with cold aqueous alkali, *m*-dithiobenzoic acid [*sic*] is exceptional: other aromatic disulfides which do not contain the acid group appear to be unattacked by the reagent." Earlier investigators[5] had established that some aromatic disulfides decompose under strongly alkaline conditions at elevated temperatures to give thiophenols and aromatic sulfinic acids, though they examined neither the differences in sensitivity to base of different disulfides nor the level of basicity required. The more recently published data of Pappalardo[6] imply support for the notion that relatively concentrated alkali and high temperature are required. Our data for the decomposition of the three dithiodibenzoic acids prompted us to investigate this previously neglected problem. We found that a dozen aromatic disulfides, with a single remarkable exception, decompose more or less readily in 0.1 N NaOH in an effective solvent at 35.2°.

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[1] Presented at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 11, 1967.

[2] Postdoctoral investigator, 1966–1967.

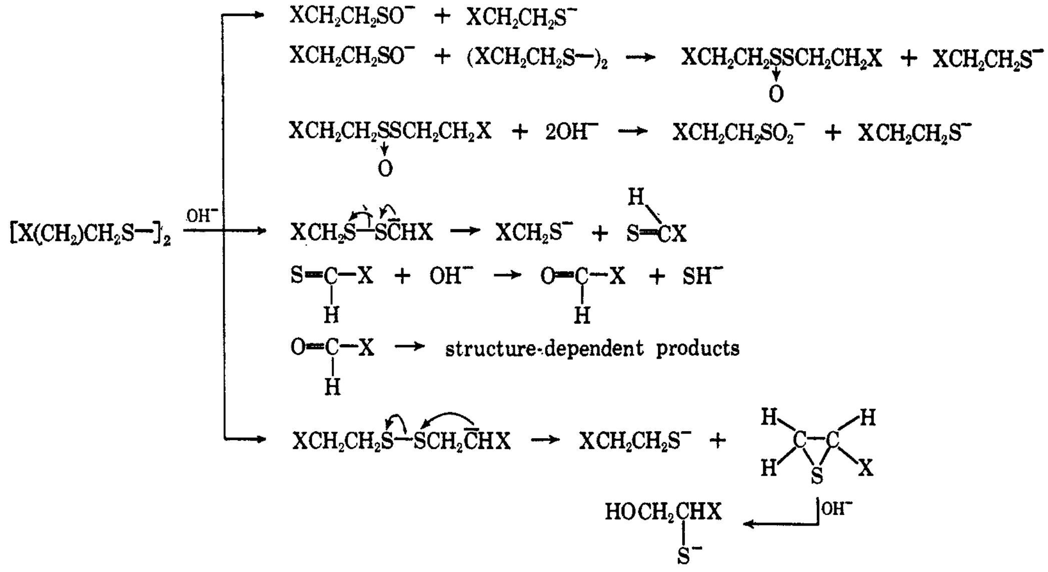
[3] J. P. Danehy and W. E. Hunter, *J. Org. Chem.*, **32**, 2047 (1967).

[4] (a) S. Smiles and J. Stewart, *J. Chem. Soc.*, **119**, 1792 (1921); (b) S. Smiles and D. C. Harrison, *ibid.*, **121**, 2022 (1922).

[5] (a) R. Schiller and R. Otto, *Ber.*, **9**, 1637 (1876); (b) E. Fromm and J. Wittmann, *ibid.*, **41**, 2266 (1908); (c) E. Fromm, *ibid.*, **41**, 3403 (1908).

[6] G. Pappalardo, *Gazz. Chim. Ital.*, **90**, 648 (1960); *Ann. Chim.* (Rome), **53**, 630 (1963).

SCHEME I



Schiller and Otto,[5a] almost a century ago, guided more by intuition than by data, proposed the stoichiometry which has since been generally accepted. This view

$$2ArSSAr + 4OH^- \longrightarrow 3ArS^- + ArSO_2^- + 2H_2O$$

has been adopted by us as a basis for an analytical method: excess alkali is back-titrated with standard acid to a phenolphthalein end point, the calculations being based on the consideration that the decomposition of each millimole of disulfide consumes 2 mequiv of base. This assumption has been justified by the results: the limiting titration values checked the stoichiometry in those cases in which decomposition had been completed and in no case did a titration exceed the stoichiometry. In several cases further qualitative checks were provided by carrying preparative runs to complete decomposition, diluting with water, neutralizing with acid to precipitate the thiophenol, and recovering the sulfinic acid from the filtrate.

The most generally convenient solvent was 80% by volume aqueous ethanol. Water alone was used for the three dithiodibenzoic acids. Eighty per cent by volume aqueous 1,4-dioxane was suitable for 4-nitrophenyl disulfide. It is the insolubility of the latter in ethanol which accounts for Fromm's misleading report that this disulfide is rather resistant to alkali.[5b]

In Table I the compounds are arranged in order of decreasing sensitivity to alkaline decomposition. The positions of the three dithiodibenzoic acids make it clear that the presence or absence of a negative charge on the disulfide is not in itself of the first importance. But it appears that there is a reasonably good correlation of sensitivity to alkaline decomposition with the pK values of the displaced thiols. Thus, the more susceptible the disulfide, the more stable is the thiolate anion displaced by nucleophilic attack of hydroxide ion on disulfide. Parker and Kharasch[7] demonstrated clearly that in the ionic cleavage of the sulfur–sulfur bond in unsymmetrical disulfides the thiol obtained is always the one with the lower pK. Here, where no choice is possible, it is a consistent extension of the earlier results that more stable thiolate ions are formed more rapidly than less stable ones.

TABLE I

CORRELATION OF SENSITIVITY TO DECOMPOSITION IN 0.125 *N* NAOH OF AROMATIC DISULFIDES WITH pK'S OF DISPLACED THIOLS[a]

Disulfide	Approx half-life	pK of displaced thiol at temp shown (°C) In H_2O	 In 40% EtOH
$(p\text{-}NO_2C_6H_4S\text{-})_2$	*b*	...	4.77 (30)
$(p\text{-}^-OOCC_6H_4S\text{-})_2$	7 min	5.85 (25)	7.85 (20–22)[e]
$(m\text{-}^-OOCC_6H_4S\text{-})_2$	12 min	6.20 (30)	7.0 (28)
$(p\text{-}ClC_6H_4S\text{-})_2$	0.5 hr	5.9 (23)	6.78 (23)
$(o\text{-}H_2NC_6H_4S\text{-})_2$	1.5 hr	6.59 (20)	...
$(PhS\text{-})_2$	16 hr	6.62 (23)	7.40 (23)
$(p\text{-}MeC_6H_4S\text{-})_2$	22 hr	6.52 (23)	7.40 (30)
$(o\text{-}MeC_6H_4S\text{-})_2$	24 hr	6.64 (26–27)	7.83 (25)
$(p\text{-}H_2NC_6H_4S\text{-})_2$	*c*	...	7.80 (30)
$(o\text{-}^-OOCC_6H_4S\text{-})_2$	*d*	8.20 (27)	10.69 (20–22)[e]
$(PhCH_2S\text{-})_2$	30 hr	9.4(25)	...

[a] 35.2°; in 80% (v/v) aqueous EtOH, except $(p\text{-}NO_2C_6H_4S\text{-})_2$ in 80% (v/v) aqueous 1,4-dioxane, and all carboxylic acids in water. [b] Optical density measurements ($p\text{-}NO_2C_6H_4S^-$ is deep red) made within 2 min of solution indicate that decomposition is complete. [c] Only 21.2% decomposed in 72 hr. [d] Only 27.5% decomposed in 120 hr; appears to be approaching equilibrium value. [e] In 48.9% aqueous EtOH.

The case of benzyl disulfide falls outside the pattern which has just been described. While the pK of benzyl mercaptan is 9.4, benzyl disulfide decomposes almost as fast as do disulfides corresponding to thiols whose pK's are between 6.5 and 7.0. But benzyl disulfide is the only member of the group which could possibly undergo an elimination reaction.

Scheme II exactly parallels the one which we have already found to correspond quantitatively to the alkaline decomposition of dithiodiacetic acid and, in part, to the alkaline decomposition of 2,2'-dithiodipropionic acid.[8] With the aid of a small-scale preparative run we have now established that the alkaline decomposition of benzyl disulfide does produce hydrogen sulfide and, after the aspiration of the latter from the acidified solution, the iodine consumption corresponds to the oxidation of the required amount of benzyl mercaptan to benzyl disulfide. We have not been able to identify or recover any benzoic acid, but there

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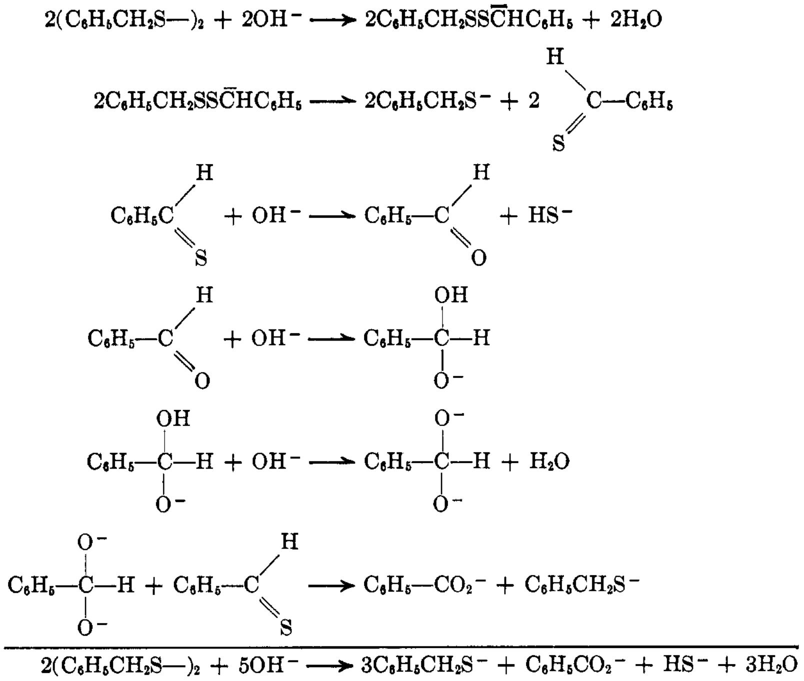
(7) A. J. Parker and N. Kharasch, *J. Am. Chem. Soc.*, **82**, 3071 (1960).

(8) J. P. Danehy and J. A. Kreuz, *ibid.*, **83**, 1109 (1961).

SCHEME II



is ample evidence for benzaldehyde. Clearly, then, benzyl disulfide appears to decompose by an α elimination.

Very remarkable, and quite unaccountable at present, is the case of 4,4′-dithiodiphenol. In aqueous 0.1 N NaOH at 35.2° it shows no sign of decomposition after 10 days. In aqueous 1 N NaOH, however, the results are as shown in Table II. The data, incidentally, were not obtained by the back-titration method since it was considered as a possibility that the phenolate anion might interfere with the phenolphthalein end point. We employed the phosphotungstic acid reagent of Folin[8] and as little as 0.1% decomposition of disulfide would easily have been detected.

TABLE II

DECOMPOSITION OF 4,4′-DITHIODIPHENOL IN 1.04 N AQUEOUS NAOH AT 35.2° [a]

Time, hr	Decompn, %
0	3.0
1.0	55.5
2.0	70.6
3.0	83.5
5.0	86.1
8.0	97.7

[a] No detectable decomposition in 0.109 N NaOH after 10 days at 35.2°.

These results are surprising for two reasons. First, the pK_{SH} of 4-mercaptophenol in 48.9% EtOH has been reported to be 8.33.[9] We would estimate that in water it would have a pK_{SH} of about 7.1. One would certainly expect, then, that it would decompose, although rather slowly, in 0.1 N NaOH. But it is even more surprising that a substance which is so resistant to 0.1 N NaOH decomposes so rapidly in 1 N NaOH.

While an attempt to correlate the sensitivity to alkaline decomposition of aliphatic disulfides with pK's of the displaced thiols is less impressive than in the case of aromatic disulfides, the generality of the principle is by no means invalidated. Corresponding to the 12 aliphatic disulfides which decompose by direct nucleophilic attack or not at all, there are only four thiols for which definite pK values are available and they are all within the range of 1 pH unit. But it is unmistakably clear that all of the aromatic disulfides which we examined, with two exceptions (2,2′-dithiodibenzoic acid and 4,4′-dithiodiphenol), are considerably more sensitive to alkali than the aliphatic ones which we found to undergo direct nucleophilic attack, with one exception (3,4-dithiahexane-1,6-bistrimethylammonium ion), and the thiols which are displaced from the aromatic disulfides have pK's which are 2.5–3.0 units lower than the thiols displaced from the aliphatic disulfides. Also, of the three aliphatic dithiodicarboxylic acids which do not decompose at all, even in 1 N NaOH, the pK's for the SH groups of the mercaptocarboxylic acids corresponding to two of them (dithiodiisobutyric acid and dithiodipivalic acid) must be near 10.5 and in two cases (dithiodiisobutyric acid and penicillamine disulfide) steric hindrance may make an appreciable contribution to the chemical inertness of the disulfide.

What, then, remains to be said about the earlier suggestion that attack by hydroxide ion on disulfide sulfur is inhibited by a negative charge, or accelerated by a positive charge, on the disulfide molecule? Inevitably, an aliphatic mercaptocarboxylic acid or mercaptosulfonic acid must have a high pK for the thiol group. But that does not mean that the negative charge repulsion is not an independently effective factor in determining reactivity, even though it may be difficult to distinguish it from the thiolate anion stabilizing factor (the pK effect). However, by considering another pair of cases available to us, it does seem possible to demonstrate that a positive charge, localized on the disulfide in the vicinity of a sulfur atom, accelerates the decomposition of the disulfide, independent of the pK effect. While the pK of 2-mercaptoethyltrimethylammonium ion ($HSCH_2CH_2NMe_3^+$) has not been reported, it is not likely to be very different from

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(9) G. Schwarzenbach and E. Rudin, *Helv. Chim. Acta*, **22**, 360 (1939).

TABLE III

ELEMENTAL ANALYSES

Compound	C, %		H, %		S, %		Cl, %	
	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
2-Sulfinobenzoic acid	45.15	45.12	3.25	3.57	17.22	17.38	...	...
3-Sulfinobenzoic acid	45.15	44.71	3.25	3.32	17.22	17.04	...	...
4-Chlorobenzenesulfinic acid	40.80	40.80	2.85	2.87	18.10	18.15	20.07	19.83
4,4'-Dithiodibenzoic acid	54.88	54.67	3.29	3.31	20.93	21.07	...	...

that of 2-mercaptoethylammonium ion ($HSCH_2CH_2NH_3^+$): in both cases the thiol proton must dissociate from a cationic species. When the disulfide corresponding to the first thiol is dissolved in aqueous alkali the positive charge persists, but when the disulfide corresponding to the second thiol is dissolved in alkali the positive charge completely disappears. The experimental fact that the first disulfide decomposes far more readily in alkali than the second one is fully in accord with the suggestion, Perhaps we should recognize that both charge repulsion or attraction, and the relative stability of the leaving group (p*K* effect), are factors which influence the sensitivity of disulfides to alkaline decomposition.

The stoichiometry for the alkaline decomposition of aromatic disulfides, originally suggested by Schiller and Otto and amply corroborated by the present investigation, has provided a basis for a novel scheme for the facile preparation of sulfinic acids from the corresponding aromatic disulfides (see Scheme III).

SCHEME III

$$4RSSR + 8OH^- \longrightarrow 6RS^- + 2RSO_2^- + 4H_2O$$

$$6RS^- + 1.5O_2 + 3H_2O \longrightarrow 3RSSR + 6OH^-$$

$$RSSR + 2OH^- + 1.5O_2 \longrightarrow 2RSO_2^- + H_2O$$

Using H_2O_2 rather than air

$$RSSR + 2OH^- + 3H_2O_2 \longrightarrow 2RSO_2 + 4H_2O$$

The latter are dissolved in a two- to fivefold excess of NaOH in an appropriate solvent and the calculated amount of aqueous hydrogen peroxide is added slowly and steadily over a 2-4-hr period. The solution is then diluted with water, acidified with hydrochloric acid, and flash evaporated, whereupon the sulfinic acid separates in crystalline form. So far, both 4-nitrosulfinic acid and 4-chlorosulfinic acid have been prepared in good yield by this procedure. Since the function of the hydrogen peroxide is simply to oxidize thiolate anion to disulfide, it should be clear that if more convenient, one may start with an alkaline solution of thiolate rather than of disulfide.

Experimental Section

Materials.—2,2'-Dithiodianiline, generously supplied by American Cyanamid Co., New York, N. Y., was dissolved in hot ethanol, decolorized by the addition of Darco activated carbon (Atlas Powder Co.), and recovered as bright yellow crystals, melting at 91-92°. Phenyl disulfide, melting at 60-61°, and 4,4'-dithiodianiline, melting at 74.5-75.5°, were purchased from Aldrich Chemical Co., Milwaukee, Wis., and used without further purification. Benzyl disulfide, melting at 70-72°, was obtained as EK 1602 from Distillation Products Industries, Rochester, N. Y., and used without further purification. 2,2'-Dithiodibenzoic acid, obtained as EK T 7441 from Distillation Products Industries, was dissolved in hot, anhydrous ethanol, decolorized by the addition of Darco activated carbon, diluted to approximately 70% by volume ethanol with water, and allowed to cool, whereupon a cream, microcrystalline powder was obtained, which melted at 291-293°.

3,3'-Dithiodibenzoic acid was prepared by the method of Smiles and Stewart;[4a] recrystallized from 90% by volume ethanol, it melted at 248-249°. 4-Mercaptobenzoic acid was prepared by the method of Smiles and Harrison.[4b] It was dissolved in water by the addition of 1 *N* NaOH to about pH 8.0, an exactly equivalent amount of aqueous hydrogen peroxide was added, and the solution kept at room temperature for 18 hr. 4,4'-Dithiodibenzoic acid was precipitated by the addition of aqueous hydrochloric acid. It was distinctly advantageous to wash the extremely bulky precipitate by decantation with water and to dry it by lyophilization. Elemental analyses are given in Table III.

4-Chlorophenyl disulfide, melting at 71-72°, *o*-tolyl disulfide, melting at 35-37°, and *p*-tolyl disulfide, melting at 46-47°, were prepared by adding the calculated amount of standardized 30% aqueous hydrogen peroxide to solutions of the corresponding thiols, EK products, in anhydrous ethanol. Almost quantitative yields of crystals separated, at room temperature in the first case and in the refrigerator in the second and third cases.

p-Nitrophenyl disulfide, prepared according to Price and Stacy,[10] recrystallized from hot acetic acid, melted at 181-182°.

4-(Methylthio)phenol (14 g, 0.1 mole), generously supplied by Crown Zellerbach Corp., Camas, Wash., was dissolved in 400 ml of anhydrous ammonia and small pieces of metallic sodium were added until the blue color persisted: 6.9 g of sodium required (0.3 g-atom). The blue color was discharged with a small amount of solid ammonium chloride and the solution was allowed to evaporate to dryness. The dry residue was dissolved in about 100 ml of water and acidified with HCl (which caused separation of dark oil), the mixture was extracted several times with ethyl ether, and the ether extract was washed with saturated NaCl, dried over magnesium sulfate, and evaporated to give 12.5 g (99% yield) of crude 4-mercaptophenol, which was redissolved in a small volume of about 40% by volume aqueous ethanol. The solution was adjusted to pH 7 with sodium bicarbonate and 1 *N* iodinein aqueous potassium iodide was added to the yellow end point. The precipitated 4,4'-dithiodiphenol was filtered, washed with water, and dried (yield, 12.1 g); recrystallized from aqueous ethanol, it melted at 148-150°.

Procedure for Alkaline Decompositions on an Analytical Scale.—Disulfide (0.25-0.50 mmole) was dissolved in sufficient organic solvent so that when the proper volume of relatively concentrated aqueous sodium hydroxide solution was added the concentration of disulfide would be 0.01 *M* and the other conditions as specified in Table I would be met. In the case of the dithiodibenzoic acids, the proper volume of water, rather than organic solvent, was added and sufficient extra alkali was added to neutralize the carboxyl groups, so that alkalinity would be effectively the same in these cases as in the others. Before addition of the alkali, however, the flask containing the solution, placed in the thermostat, was flushed with nitrogen. At suitable intervals flasks were removed from the thermostat, opened, alcoholic phenolphthalein added, and immediately titrated with 0.05 *N* HCl.

Procedure for Preparative Alkaline Decompositions.—Dithiodibenzoic acid (4.6 g) was dissolved in 100 ml of 1 *N* NaOH under nitrogen and held at 35.2° for 5 hr in the case of the 3,3' isomer and for 12 days in the case of the 2,2' isomer. The solutions were cooled and neutralized with HCl and the precipitated mercaptobenzoic acids were washed with water and dried by lyophilization. The acidic filtrates and aqueous washings were combined and passed through a cation-exchange column (Amberlite 120) in the H form. The effluent was evaporated to dryness under reduced pressure to give 65 and 33% yields, respectively, of 3-sulfinobenzoic acid, melting at 162-164°, and of 2-sulfinobenzoic acid, melting at 140-150° dec.

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[10] C. C. Price and G. W. Stacy, *J. Am. Chem. Soc.*, **68**, 498 (1946).

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.

Acknowledgment.—We are grateful to the National Institutes of Health for Grant GM-11836 under which this investigation has been carried out.

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

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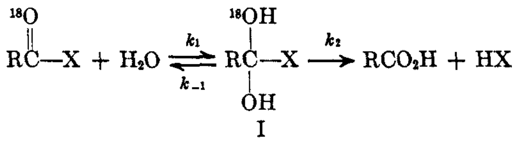
The alkaline hydrolyses of benzamide and N-methylbenzamide, but not of N,N-dimethylbenzamide, are accompanied by extensive oxygen exchange between water and the amide. The values of k_e/k_h for benzamide decrease with increasing hydroxide ion concentration and are greater in deuterium than in protium 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

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

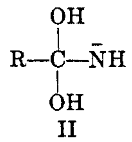


$$\mathrm{R}\overset{^{18}\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{{-}X + H_2O} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{R}\underset{\underset{\mathrm{OH}}{|}}{\overset{\overset{^{18}\mathrm{OH}}{|}}{\mathrm{C}}}\mathrm{{-}X} \xrightarrow{k_2} \mathrm{RCO_2H + HX}$$

I

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]



$$\mathrm{R{-}}\underset{\underset{\mathrm{OH}}{|}}{\overset{\overset{\mathrm{OH}}{|}}{\mathrm{C}}}\mathrm{{-}\bar{N}H}$$

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.

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(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).

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