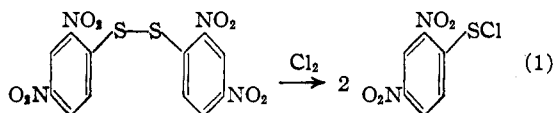[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

# Derivatives of Sulfenic Acids. III. The Catalytic Chlorinolysis of 2,4-Dinitrophenyl Disulfide[1]

## BY NORMAN KHARASCH, GEOFFREY I. GLEASON AND CHARLES M. BUESS

Prior to the present work, the chlorinolysis of 2,4-dinitrophenyl disulfide (equation 1) has been achieved only by resorting to elevated tempera-

tures of 120–130° and extended periods of reaction.[2,3]

Because the high-temperature chlorinolysis is attended by an explosion hazard, and in view of the potential importance of 2,4-dinitrobenzenesulfenyl chloride for analytic and synthetic purposes,[4,5,6] we have sought improved methods for the preparation of this sulfenyl chloride.

The present study demonstrates that the chlorinolysis of 2,4-dinitrophenyl disulfide, to yield 2,4-dinitrobenzenesulfenyl chloride, can be advantageously effected by using certain catalysts. Thus, in contrast to the rigorous conditions and the long periods of reaction which are required for the scission of the disulfide in the absence of catalysts, the catalytic chlorinolysis can be carried to completion in shorter periods of time and at much lower temperatures. The following substances have been shown to exert a positive catalytic effect when added to the reaction mixture: iron, ferric chloride, aluminum chloride, aluminum bromide, tin, antimony, iodine and sulfuric acid. In the experiments in which positive catalysis was observed by the addition of iron, tin, antimony and iodine, the effective catalysts are, undoubtedly, corresponding chlorides which are formed in situ.

Only small quantites of the catalysts need be used; but anhydrous conditions are necessary, and some precautions must be taken to insure the purity of the catalytic reagents. Thus, aluminum chloride taken directly from a previously opened bottle was not effective, but the freshly sublimed reagent gave excellent results. Although it is a simple matter to attain the conditions required for effective catalysis, it is worthy of mention that the use of fuming sulfuric acid as

the catalyst is particularly suitable. No precautions are necessary as regards the purity of the sulfuric acid; and, if added in slightly greater quantity than is needed for the catalytic action, it combines with the last traces of water and renders the system anhydrous. With fuming sulfuric acid as the catalyst, it was found that sym-tetrachloroethane, methylene chloride or carbon tetrachloride may be used as solvents for the catalytic chlorinolysis of 2,4-dinitrophenyl disulfide.

The actions of the catalysts are inhibited by various oxygen compounds. Thus, the catalytic effect of ferric chloride is voided by the presence of small amounts of water, ethyl ether or phenol. Nitrobenzene, however, does not retard the action of this catalyst. This inhibition of the catalytic action by substances which are stronger electron donors than is 2,4-dinitrophenyl disulfide is to be expected, for these preferentially coördinate the catalyst and thereby stop its action.[7]

We were also interested in determining whether the brominolysis of 2,4-dinitrophenyl disulfide can be similarly catalyzed. Our earlier studies[8] had shown that even under the most drastic conditions—in the absence of catalysts—the scission of the disulfide by bromine, to form the sulfenyl bromide, occurs only to a very slight extent. It has now been demonstrated, however, that the brominolysis of 2,4-dinitrophenyl disulfide can be readily effected at room temperature, employing aluminum bromide as the catalyst.

## Experimental[9]

The Use of Metallic Iron in the Preparation of 2,4-Dinitrobenzenesulfenyl Chloride.—Metallic iron was the first substance whose catalytic activity (via formation of ferric chloride in situ) was ascertained. The later runs with other catalysts were patterned on the one described in full for the case of iron below.

One hundred grams (0.25 mole) of 2,4-dinitrophenyl disulfide, prepared as cited in reference 5, and dried at 100° for two hours, was suspended in 250 ml. of ethylene chloride in a 500-ml. three-necked flask. This was equipped with a mercury-seal stirrer, a stopper, and a distillation head fitted with a thermometer and condenser. When a

(1) Presented before the Organic Division of the American Chemical Society, Atlantic City, September, 1949.

(2) J. H. Billman, J. Garrison, R. Anderson and B. Wolnak, THIS JOURNAL, **63**, 1920 (1941).

(3) N. Kharasch, H. L. Wehrmeister and H. Tigerman, ibid., **69**, 1612 (1947).

(4) The characterization of olefins with 2,4-dinitrobenzenesulfenyl chloride is described in a recent paper by N. Kharasch and C. M. Buess, THIS JOURNAL, **71**, 2724 (1949).

(5) Compare also references 4 and 5, and forthcoming papers of this series, for other uses of the reagent.

(6) This reagent is now available from the Hexagon Laboratories, Glendale 4, California.

(7) A study to establish the mechanism of the catalyzed chlorinolysis has been undertaken in our Laboratory, We have not as yet, however, obtained the requisite data to fully substantiate any one possible mechanism. The simplest over-all proposal which seems plausible is that coördination of the catalyst by the disulfide occurs, followed by chlorinolysis of the catalyst-disulfide complex to yield the sulfenyl chloride and regenerate the catalyst. If A represents a catalyst of the general acid type:

$$ArS—SAr + A \longrightarrow \overset{\displaystyle A}{\underset{\displaystyle \uparrow}{ArS—SAr}} \xrightarrow{Cl_2} 2\,ArSCl + A$$
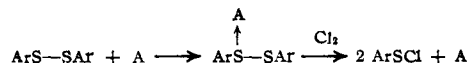
The elementary processes in the total reaction are, of course, subject to considerable further inquiry.

(8) N. Kharasch and S. I. Strashun, unpublished work.

(9) The melting point values reported are uncorrected.

smooth slurry was produced, the flask was heated in an oil-bath at 125°, and 30–40 ml. of the solvent was collected, at which time the distillate was clear (indicating adequate removal of any water present).

The mercury seal was replaced by one of ethylene chloride, and the stopper and distillation head were replaced with suitable gas inlet and exit tubes. The apparatus was protected with a drying tube of calcium chloride, and an alkali trap for the exit of chlorine gas was provided. Approximately 0.002 mole (0.15 g.) of Merck, "Iron by Hydrogen" powder was stirred into the suspension, and dry chlorine gas was then passed in, slowly at first, until a spontaneous warming and sudden absorption of the gas was noted. The flask was then surrounded by a water-bath at 20°, and the rate of introduction of chlorine was increased to the maximum which the reaction required, as noted by watching the trap. For best results, the addition of chlorine was carried out during about one hour. The suspended disulfide gradually disappeared, and after one to one and one-half hours, a clear amber-red solution resulted. The passage of chlorine was stopped, the gas inlet tube was removed, the flask was stoppered, and the mixture stirred for one hour longer, by which time the last of the disulfide particles had disappeared.

The solution was filtered through diatomaceous earth into a one-liter flask, and the flask was connected to the water pump to aspirate the excess chlorine. Anhydrous ether (400 ml.) was then thoroughly mixed with the remaining solution, and the flask was stoppered and placed into a water-bath at 20°. Within half an hour a sizable portion of product crystallized, and further crystallization was then achieved by immersing the flask in an ice–salt bath for three to four hours. The product was collected and the crystalline mass was broken up, dried on the suction filter plate, and washed with 100 ml. of cold ether. In several runs, the yield of brilliant yellow needles was in the range of 70 g. (60%). The product so obtained melted at 95–95.5°, and was entirely suitable for use without further purification. The ether was fractionated from the mother liquor and used in succeeding runs.

**Determination of the Catalytic Activities of Other Substances.**—Following the same general procedure as above, but using only one-tenth the quantities of reagents, various other substances were shown to be effective in the chlorinolysis of 2,4-dinitrophenyl disulfide. The complete disappearance of the disulfide was taken as indicative of completion of the reaction in each case. In these runs, maximum yields of 2,4-dinitrobenzenesulfenyl chloride were not sought, but in every case a substantial amount of excellent product was isolated. All of the runs were made at room temperatures under identical conditions. The figures listed directly after each catalyst, below, represent the amount of catalyst used for ten grams of the disulfide and the time recorded for complete solution of the disulfide: Fe (0.1 g.) 110 min.; FeCl₃ (0.04 g.) 45 min.; 30% fuming H₂SO₄ (1 drop) 30 min.; AlCl₃ (0.02 g.) 70 min.; concd. H₂SO₄ (3 drops) 80 min.; Sb (0.07 g.) 50 min.; AlBr₃ (0.15 g.) 15 min.; I₂ (0.08 g.) 50 min. The addition of metallic tin (0.4 g. of the metal to 10 g. of disulfide) failed to give completion of reaction in a four-hour period, but the reaction was effected after an overnight period of reaction was allowed.

**Yield Runs with Sulfuric Acid as Catalyst.**—The yields of pure 2,4-dinitrobenzenesulfenyl chloride obtainable by the methods described above, and also in the uncatalyzed chlorinolysis,[5] ranged from 60 to 70%. Since the major loss of product results from the solubility of the sulfenyl chloride in the mother liquor, and because high-quality successive crops of the product could not generally be obtained by further working up of the mother liquor, a batch process for increasing the over-all yield was preferred.

Table I shows the results of three successive preparative runs. The yield obtained from the first batch was only 71%; but by using the mother liquor from the first run as a partial charge for the second, the yield of sulfenyl chloride obtained (calculated on the new disulfide added) was 93%. On repeating the process a third time (using the mother liquor from the second batch and 50 g. of fresh disulfide), a 96% yield of product resulted. The over-all yield of nearly pure sulfenyl chloride obtained from the three runs was 152.5 g. (86%); and on recrystallization from carbon tetrachloride this yielded 141.7 g. (80%) of pure product, m. p. 96–97°.

## Table I

| Run number | 1 | 2 | 3 |
|---|---|---|---|
| Disulfide, g. | 50.0 | 50.0 | 50.0 |
| Catalyst (H₂SO₄SO₃), drops | 3 | 3 | 3 |
| Starting temperature, °C. | 25 | 27 | 26 |
| Time for completion, minutes | 30 | 35 | 30 |
| Wt. soln. (g.) after chlorinolysis | 230 | 249 | 248 |
| Wt. C₂H₄Cl₂, by difference, g. | 171 | 172 | 171 |
| Ml. ether to ppt. product | 200 | 200 | 200 |
| Product, g. | 40.5 | 55.0 | 56.5 |
| M. p. of crude product | 92–95 | 92–95 | 91–95 |
| Yield for run, % | 71 | 93 | 96 |

The over-all yield of sulfenyl chloride may be further increased, if desired, by continuing the batch process. In passing from one batch to the next, it is only necessary completely to remove the ether which is added in each run to precipitate the sulfenyl chloride as described in detail, above, for the case of catalysis by iron. This is easily done by distillation. At the same time, fresh ethylene chloride solvent is added to obtain a suitable solvent disulfide ratio, the new batch of disulfide is added, and the run is made in the usual manner. It will be noted in Table I that the weight of ethylene chloride used in each run is given by weight rather than by volume. This is because the actual amount of ethylene chloride used in each run was obtained by difference between the total weight of the solution obtained (after chlorinolysis and aspiration of excess chlorine), and the weight of solute contained therein, the assumption being made that all of the disulfide used was converted to sulfenyl chloride. A fresh sample of catalyst was also used for each run.

**Solvents.**—Using sulfuric acid catalysis, it was shown that the following solvents may be employed: ethylene chloride, methylene chloride, carbon tetrachloride or trichloroethylene. The reaction occurs much more slowly in the last solvent named. 2,4-Dinitrobenzenesulfenyl chloride is somewhat less soluble in carbon tetrachloride than in the other solvents mentioned. In some cases, employing carbon tetrachloride, it was observed that the large needles of the sulfenyl chloride began to precipitate before the micro-crystalline disulfide was completely converted. Gentle heating of the reaction mixture caused solution of the sulfenyl chloride and hastened the completion of the reaction.

**Inhibition of the Catalytic Effect of Ferric Chloride.**—Many of our early attempts to effect the catalytic function with iron were not successful. The failures were later traced to the presence of small quantities of water and alcohol (the latter being incurred from the preparation of the disulfide) in the systems. As stated above, careful drying of the disulfide, followed by azeotropic distillation of a fore-run of the reaction solvent, permitted the effective catalysis. Evidently, the nitro groups on the disulfide do not inhibit the catalysis. Added nitrobenzene (2 g. of nitrobenzene to 0.1 g. of ferric chloride, with 10 g. of the disulfide) also did not inhibit the catalysis. Phenol, however, was found to have a strong retarding effect on the catalytic action of ferric chloride.

**Catalytic Brominolysis of 2,4-Dinitrophenyl Disulfide.**—The use of aluminum bromide in ethylene chloride as solvent was found to exert a positive catalytic action on the brominolysis of the disulfide at room temperature. Thus, 5.0 g. of the disulfide, with 1.0 g. of aluminum bromide, and 9 g. of bromine was stirred for three hours. Addition of 50 ml. of ether to the reaction filtrate and working up of the resulting mixture led to 4.8 g. of the crude sulfenyl bromide, which melted at 97–102°. The melting point of this product approached the expected value (104.5–

105.5°) on recrystallization from carbon tetrachloride. The best conditions for employing this catalytic brominolysis are being developed in connection with another study in progress in our Laboratory.

**Acknowledgment.**—We are indebted to the Abbott Laboratories for a grant in partial support of this work.

### Summary

The chlorinolysis of 2,4-dinitrophenyl disulfide is catalyzed by various metal halide catalysts, as well as by sulfuric acid. The application of the catalytic action to the synthesis of 2,4-dinitrobenzenesulfenyl chloride is described. Oxygen-containing substances, such as water, ether or phenol, which preferentially coördinate the catalysts, inhibit the catalytic effects.

The brominolysis of 2,4-dinitrophenyl disulfide was also found to be catalyzed by aluminum bromide.
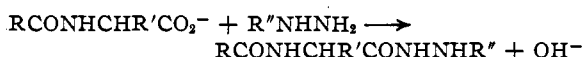
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# The Enzymatic Synthesis of N-Acyl-D- and L-Phenylalanylphenylhydrazides[1]

By Edward L. Bennett[2] and Carl Niemann

The papain catalyzed synthesis of acylated α-amino acid hydrazides,[3] conducted at approximately $pH$ 5, may be described in part by the equation

$$RCONHCHR'CO_2^- + R''NHNH_2 \longrightarrow$$
$$RCONHCHR'CONHNHR'' + OH^-$$

since amide or hydrazide formation has never been observed with amines which are substantially protonated at $pH$ 5[4] whereas all of the N-acylated-α-amino acids are almost completely ionized at this $pH$. With regard to the stereochemical aspect of the above reaction it has been assumed that only the N-acyl-L-amino acid amide or hydrazide is formed[3] though it has been suggested[5] that when R' is small, *i. e.*, a methyl group, there may be some loss in enzymatic stereochemical specificity.

The first indication that factors other than the configuration about the asymmetric α-carbon atom and possibly the size of the R' group in the N-acylated α-amino acid could influence the stereochemical course of the above reaction was obtained when it was observed[6] that N-carbobenzoxy-*o*-fluoro-DL-phenylalanine gave, in addition to the expected N-carbobenzoxy-o-fluoro-L-phenylalanylphenylhydrazide, significant quantities of N-carbobenzoxy-*o*-fluoro-D-phenylalanylphenylhydrazide. In continuing our studies along these lines we now wish to report some observations which clearly show that the nature of the acyl group, present in acylated DL-phenylalanines, may have a profound effect upon the stereochemi-

cal course of the papain catalyzed synthesis of the corresponding phenylhydrazides.

Five acylated DL-phenylalanines were incubated with activated papain, cysteine, and phenylhydrazine, at $pH$ 4.6 and 40°, with an initial mole ratio of phenylhydrazine to DL-acid of 0.5. The precipitated phenylhydrazides were collected, additional phenylhydrazine added to the solutions, and the process repeated until no more phenylhydrazide was obtained. The specific rotations of all of the phenylhydrazide fractions were determined and the amount of L- or D-isomer present in each fraction computed from the specific rotation of the component L- and D-phenylhydrazides obtained by fractional crystallization of the crude hydrazides. The data obtained from these experiments are given in Table I. In a second series of experiments the effect of increasing the enzyme concentration from 0.3 to 2.5% or of increasing the initial mole ratio of phenylhydrazine to DL-acid from 0.5 to 1.0 on the reaction of acetyl-DL-phenylalanine with phenylhydrazine was studied. In either case no evidence was obtained for the formation of acetyl-D-phenylalanylphenylhydrazide (*cf.* Table I).

The above data clearly show that for an acylated DL-phenylalanine, $RCONHCH(CH_2C_6H_5)\text{-}CO_2H$, when R = $CH_3-$ or $C_6H_5-$ the papain catalyzed synthesis of the phenylhydrazide proceeds with almost complete stereochemical specificity for the L-antipode. However, when R = $CH_3O-$, $C_2H_5O-$ or $C_6H_5CH_2O-$ this stereochemical specificity is lost to a striking degree and although the L-antipode is converted into the phenylhydrazide at the more rapid rate the rate of formation of the phenylhydrazide of the D-antipode is apparently of comparable magnitude. At present there are insufficient data to attempt to give a complete explanation of the above phenomena though it is now clear that a third factor must be added to the other two that previously had been believed to be sufficient to account for the stereochemical specificity of the proteolytic enzymes.

(1) Presented in part at the 115th meeting of the American Chemical Society at San Francisco, March, 1949.

(2) Procter and Gamble Fellow in Chemistry 1948-1949; present address, Radiation Laboratory, University of California, Berkeley, California.

(3) M. Bergmann and H. Fraenkel-Conrat, *J. Biol. Chem.*, **119**, 707 (1937).

(4) Unpublished experiments of Dr. P. L. Nichols.

(5) M. Bergmann, L. Zervas and J. S. Fruton, *J. Biol. Chem.*, **115**, 593 (1936).

(6) E. L. Bennett and C. Niemann, This Journal, **70**, 2610 (1948).