

REACTIONS OF MERCAPTANS,

By

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INTRODUCTION

This thesis deals with three reactions of mercaptans: ionization, air oxidation, and the reaction with disulfides. In order to place the more detailed discussions which follow in the proper relation to one another and to the thesis as a whole, they will be discussed briefly in turn. Comprehensive reviews have been compiled by Malisoff (1) and by Reid (2).

The ionization of mercaptans is important in living organisms, as the reaction of mercapto groups in glutathione and in proteins depends in part on the extent of ionization. The reaction is also important in petroleum refining as extraction with aqueous alkali can be used to remove the mercaptans present in crude oil. The extent to which a mercaptan is removed depends on its solubility and on its ionization constant.

The ionization constants of organic acids and bases are usually determined by potentiometric measurements in mixed aqueous-organic solvents because of their limited solubility in water. This procedure is very convenient, and has certainly given significant and interesting results; however, the exact interpretation and comparison of acidity scales in different solvents presents serious fundamental difficulties. It cannot be doubted that water would be a convenient standard solvent for purposes of comparison if the solubility limitations could be circumvented.

The ionization constant of sparingly soluble compounds can be determined from measurements of partition coefficients (3) or of solubility,

the main requirement being a sufficiently sensitive analytical method of determination. One purpose of this research was to illustrate the determination of ionization constants from solubility measurements. Hexanethiol was chosen as the subject of study, first, because its properties are representative of those suitable for application of the method, and secondly, because previous determinations of the constant seemed open to doubt.

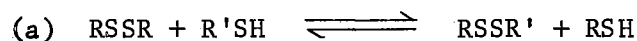
The second part of this thesis deals with another important reaction of mercaptans, their oxidation by molecular oxygen. There have been numerous patents issued for the oxidation of alkanethiols to disulfides in petroleum refining;¹ however, there have been few quantitative studies of the reaction. It has been shown that alkanethiols are oxidized beyond the disulfide stage by oxygen in concentrated (2.7M) alkali, but the products were not identified (4). The possibility that mercaptans might be oxidized with air to sulfonic acids seemed worth investigating further. In the present study the effect of various metal ions on the oxidation of alkanethiols in alkaline solution was determined. The products of the oxidation in concentrated (3.0M) alkali have been identified and isolated. A mechanism has been proposed for the oxidation.

The third and final part of this thesis deals with a reaction of mercaptans which has recently become important in connection with radiation protection, i.e. the reaction with symmetrical disulfides to form mixed disulfides.

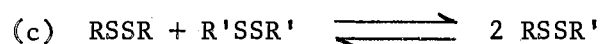
An unsymmetrical disulfide results from the reaction of a symmetrical disulfide with a mercaptan, according to equation (a); the reaction

¹Original literature references not referenced in this section may be found in reference (2), page 118.

may then proceed further, according to equation (b):



Unsymmetrical disulfides may also result from the reaction of two symmetrical disulfides according to equation (c):



The equilibrium constant for equation (c) is given by expression (d):

$$(d) \quad K_1 = \frac{(\text{RSSR}')^2}{(\text{RSSR})(\text{R'SSR}')};$$

Those for equations (a) and (b) by expressions (e) and (f), respectively:

$$(e) \quad K_2 = \frac{(\text{RSSR}')(\text{RSH})}{(\text{RSSR})(\text{R'SH})}$$

$$(f) \quad K_3 = \frac{(\text{R'SSR}')(\text{RSH})}{(\text{RSSR}')(\text{R'SH})}.$$

The following relation exists between these constants:

$$K_1 = \frac{K_2}{K_3}.$$

On the basis of statistical probability, the values for the constants should be: $K_1 = 4$, $K_2 = 2$, $K_3 = 0.5$, $K_4 = K_2 K_3 = \frac{(\text{R'SSR}')(\text{RSH})^2}{(\text{RSSR})(\text{R'SH})^2} = 1$.

In the present investigation, the values of the various constants have been determined for four mercaptan-disulfide systems and the deviation from statistical behavior has been correlated with chemical structure.

PART I

IONIZATION CONSTANT OF HEXANETHIOL FROM
SOLUBILITY MEASUREMENTS

CHAPTER I

HISTORICAL

Even though mercaptans have been known for a long time, little work has been done on the ionization constants of these compounds. This is probably due to their rather offensive odor, and also because they are not appreciably soluble in water. Mercaptans ionize according to the following general equation: $\text{RSH} + \text{M} \rightleftharpoons \text{RS}^- + \text{MH}^+$, where M is the solvent.

Ionization of Cysteine

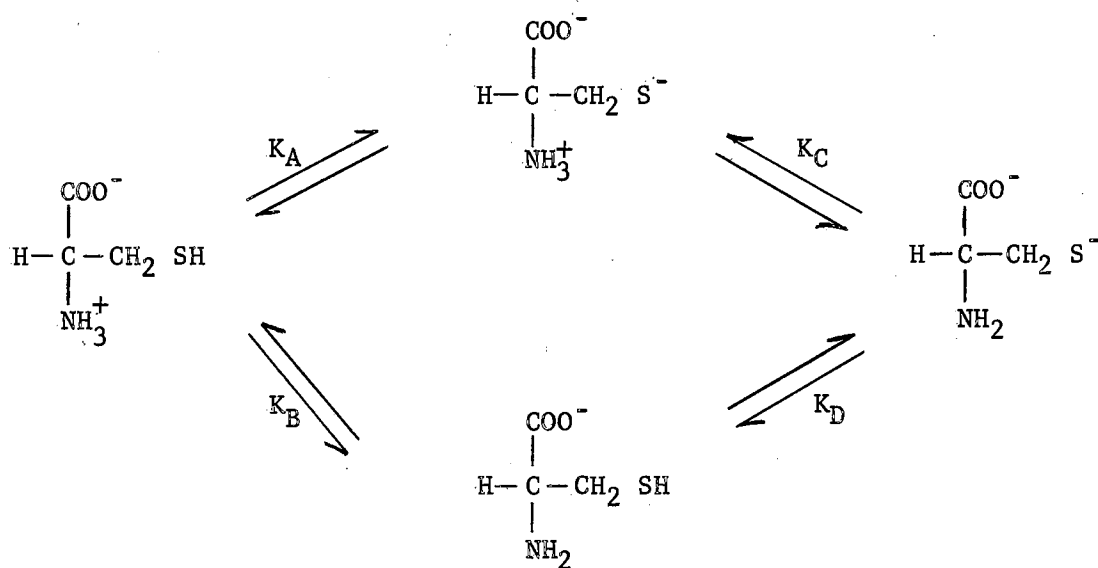
Cysteine was the first mercapto compound to be studied in respect to its ionization constants. This came about because of its biological importance. The ionic equilibria are, however, more complex than that of a simple mercaptan. Three hydrogens can ionize and the respective ionization constants will be denoted by appropriate subscripts; pK is the corresponding negative logarithm.

In 1927 Cannon and Knight (5) deduced the ionization constants of cysteine from hydrogen electrode titration curves. They obtained values of 1.90 for pK_1 , 8.14 for pK_2 , and 10.34 for pK_3 , and they associated these constants with the ionization of the carboxyl, mercapto, and ammonium groups respectively. In 1931 Cohn (6) found values of 1.96, 8.18, and 10.28 for pK_1 , pK_2 , and pK_3 ; he reversed the assignments of pK_2 and pK_3 to the ammonium and mercapto groups. The results of Borsook, Ellis, and

Huffman (7) agree fairly well with the values obtained by Cohn. Their values were estimated thermodynamic constants obtained by extrapolating observed values to zero ionic strength.

More recently, Calvin (8) suggested that the assignment of Cohn should be reversed and gave 8.3 for pK_2 and 10.8 for pK_3 . This was supported by Grafius and Neilands (9) who obtained 8.30 for pK_2 and 10.40 for pK_3 .

Edsall (10) was the first to suggest that the second and third dissociation constants of cysteine might be composite constants, describing the equilibria:



$$K_1 = K_A + K_B \quad \text{and} \quad 1/K_2 = 1/K_C + 1/K_D$$

The ultraviolet absorption of the mercaptide ion was utilized by Benesch and Benesch (11) to estimate that two-thirds of the mercapto group was ionized in the titration of the second proton. It was therefore concluded that the acid strength of the mercapto group is about twice as great as that of the ammonium group.

Gorin (12) found that a large increase in the ultraviolet absorption accompanies the ionization of the mercapto group of thioglycolic acid. He observed a similar increase in absorption during the titration of the second proton of cysteine hydrochloride. It was therefore concluded that the ion $^{-}\text{SCH}_2\text{CH}(\text{NH}_3^{+})\text{COO}^{-}$ is produced in this process. The value of pK_2 in 0.1M potassium chloride solution was found in these experiments equal to 8.27. The development of mercaptide ion absorbance during the dissociation of cysteine was also observed by DeDeken and his associates (13).

Recently, Gorin and Clary (14) studied the effects of ionic strength and dielectric constant on the relative ionizations of the mercapto and amino groups in cysteine and found that the amount of $^{-}\text{SCH}_2\text{CH}(\text{NH}_3^{+})\text{COO}^{-}$ compared to $\text{HSCH}_2\text{CH}(\text{NH}_2)\text{COO}^{-}$ is greatly diminished by adding ethanol, but is little affected by changes in ionic strength.

Ionization of Mercaptans

The dissociation constant of thiophenol has been studied by several investigators since 1933 (15). Electrometric titrations have given the following pK values in varying percentages of ethanol-water: 9.32 in 95 percent (16), 8.05 in 85 percent (17), 7.8 in 50 percent, 7.28 in 49.8 percent (16), and 7.76 in 48 percent (18). Fletcher (19) obtained a pK of 7.47 using the same method in 23 percent tert-butyl alcohol. The ionization constants of a great number of substituted thiophenols have also been determined (15, 16, 18, 20-22).

Schwarzenbach and Epprecht (23) measured the acidity constants of a series of aliphatic dithiols from methylene to tetramethylene dithiol.

When this investigation was begun, the only values for the ionization constants of alkanethiols in water had been reported by Yabroff (3). This

investigator examined the mercaptans from ethyl to butyl by potentiometric titration, and the mercaptans from ethyl to heptyl (excepting hexyl) by partitioning between isooctane and 0.5M sodium hydroxide. The data are shown in Table I. Fletcher (19) found 11.51 for butanethiol and 11.72 for octanethiol in 23 percent tert-butyl alcohol. Maurin and Paris (24) reported 12.0 for ethanethiol and 13.5 for hexanethiol. The last results are of uncertain significance, because they were estimated from the extent of reaction with indicators in aqueous ethanol, using the indicator constants determined in water. Furthermore, the difference reported between ethanethiol and hexanethiol seems excessively large.

Very recently the ionization constants of a series of substituted mercaptans have been determined by pH titration, spectrophotometrically, and by gas solubility methods (25, 26); the results are shown in Table I.

TABLE I
pK VALUES REPORTED FOR ALIPHATIC MERCAPTANS IN WATER

Compound	pK	Method	Reference
Ethanethiol	10.50	pH Titration	25
	10.89	Gas Solubility	26
	10.60	Extraction	3
	10.64	pH Titration	3
Propanethiol	10.65	Extraction	3
	10.82	pH Titration	3
Butanethiol	10.65	Extraction	3
	10.78	pH Titration	3
2-Methyl-2-propanethiol	11.05	Extraction	3
	11.14	pH Titration	3
Pentanethiol	10.70	Extraction	3
2-Methyl-2-butanethiol	11.21	Extraction	3
Heptanethiol	10.75	Extraction	3
Thioglycolic Acid	10.06	pH Titration	25
	10.40	Spectrophotometrically	25
	10.0	pH Titration	5
	10.32	Spectrophotometrically	11
Methyl Thioglycolate	7.68	pH Titration	25
Ethyl Thioglycolate	7.93	Spectrophotometrically	26
	7.95	pH Titration	26
Thiolactic Acid	10.3	pH Titration	5
	10.47	pH Titration	7
	10.35	Reaction	27
2-Mercaptopropionic Acid	10.27	pH Titration	25
	10.20	Spectrophotometrically	25
2-Mercaptoethanol	9.5		8
	9.58	pH Titration	25
	9.48	Spectrophotometrically	25
2-Ethoxyethanethiol	9.38	pH Titration	26
2,3-Dihydroxypropanethiol	9.51	pH Titration	26
2-Aminoethanethiol	8.17	pH Titration	28
	8.6	pH Titration	8
	8.10	pH Titration	25
	8.35	Spectrophotometrically	25
1-Thio-D-Sorbitol	9.50	Spectrophotometrically	25
Mercaptoacetone	7.86	pH Titration	26
Benzyl Mercaptan	9.43	Spectrophotometrically	26

CHAPTER II

EXPERIMENTAL

The method used to determine the ionization constant of hexanethiol in water depends upon the fact that the solubility will increase with increasing pH, due to the ionization of the mercaptan and the fact that the mercaptide ion (RS^-) formed is completely soluble in water.

The solubility of hexanethiol was determined in solutions containing 0.10, 0.30, and 0.50M potassium chloride, as well as in buffer solutions containing these concentrations of potassium chloride and 0.02M bicarbonate-carbonate.

The ionization constant of hexanethiol was also determined by titration in 44.4 percent aqueous ethanol. The ionization constant of ethanethiol was determined in water and in 44.4 percent aqueous ethanol by the same method.

Reagents

Hexanethiol (I) used in the solubility measurements was an American Petroleum Institute standard sample obtained from the Chemical and Petroleum Research Laboratories, Carnegie Institute of Technology, Pittsburgh, Pennsylvania, and certified to contain less than 0.1 mole percent impurities. It was transferred to a number of smaller bulbs in the following way: The bulbs, of about 0.5 ml. capacity with long

capillary necks, were placed in a vacuum desiccator, which was first evacuated and then filled with nitrogen; the bulbs were then placed neck down in the opened ampule of hexanethiol, the whole was put in the vacuum desiccator, and the procedure repeated. The pressure of nitrogen forced the hexanethiol into the bulbs, the capillary ends of which were then sealed.

Hexanethiol (II) used in the titrations was an Eastman Kodak white-label product which was redistilled under nitrogen; the middle one-third, boiling at $133-135^{\circ}$ and 740 mm., was stored in small bulbs as described above. Iodimetric titration (29) indicated a purity of 88 percent.

Ethanethiol was an Eastman Kodak technical-grade product; it was redistilled and the fraction collected that boiled at $30-1^{\circ}$ and 741 mm. The purity was 94 percent. It was stored like hexanethiol (II).

Nitrogen was a commercial product, passed through three successive gas washing bottles containing vanadous ion to remove oxygen (30) and one bottle containing ascarite to remove any acid vapors that could be carried over from the washing bottles.

The water used in the preparation of all solutions was doubly distilled, deaerated by boiling, and cooled with a stream of nitrogen bubbling through it. It was stored under nitrogen and dispensed with the aid of nitrogen under slight pressure.

Ethanol, 95 percent was diluted with an equal volume of water; such a mixture contains 44.4 percent ethanol by weight. It was deoxygenated by bubbling nitrogen through it, which had been passed through a solution of vanadous ion, ascarite, and a washing bottle containing 44.4 percent ethanol.

Attempted Determination of Hexanethiol by the Method of Kolthoff and Harris

Before solubility measurements could be made it was necessary to establish an analytical method for determining the amount of dissolved mercaptan in the water and the buffer solutions. The amperometric silver nitrate titration method of Kolthoff and Harris (31), which utilizes a rotating platinum indicator electrode seemed well suited for this purpose. However, the results obtained could not be repeated from day to day.

To determine if the electrode was functioning properly, a sample blank containing 25 ml. of water, 50 ml. of ethanol, and the appropriate electrolyte was titrated with silver nitrate before and after each titration of hexanethiol. The blanks titrated before the mercaptan samples gave a good line when the current was plotted against the volume of silver nitrate added. However, after six samples of hexanethiol were titrated, the blanks failed to give a linear relationship, and no reliable end-point could be determined. Apparently, the rotating platinum electrode becomes coated with silver mercaptide and, after a few titrations, becomes insensitive to changes in the silver ion concentration.

Determination of Hexanethiol by Ultraviolet Spectrophotometry

Due to the fact that the method of Kolthoff and Harris gave inconsistent results, it was decided to utilize the ultraviolet absorption of the mercaptide ion as an analytical method; mercaptide ions have an absorption peak in the ultraviolet at 240 m μ . In order to convert all the dissolved mercaptan to the mercaptide ion, all the samples were made

approximately 0.10M with sodium hydroxide before measuring the optical density at 240 m μ .

The molar absorbancy coefficient of the hexanethiolate ion was determined as follows: Approximately 0.1 g. of hexanethiol (I) was weighed accurately and dissolved in 250 ml. of 0.1M sodium hydroxide; this was diluted fifty times, giving about a $5 \times 10^{-5}\text{M}$ concentration of mercaptan. The absorbance was measured at 240 m μ . with a Beckman Model DU spectrophotometer in a 1-cm. silica cell; the blank cell was filled with 0.1M sodium hydroxide. Six determinations gave an average value of 5290 ± 50 . The optical density at 240 m μ . divided by the molar absorbancy coefficient gives the molar concentration of hexanethiol.

Solubility Measurements

An excess of hexanethiol (I) was added to the buffer solution in a glass-stoppered flask and the air was displaced by nitrogen. The mixture was shaken by hand for five minutes and put in a thermostat at $25 \pm .05$ C. for one-half hour. This procedure was repeated once. After shaking a third time, the mixture was allowed to stand in the thermostat for two to three hours. Most of the undissolved thiol came to the surface during this time, but some remained suspended in the aqueous layer. A 10 ml. sample was withdrawn from the bottom of the flask with a hypodermic syringe attached to a 6" #18 needle, transferred to two test tubes, and centrifuged for 4 minutes. An aliquot portion of the solution was withdrawn with another syringe from the middle of the test tubes, a suitable amount of the sample, measured with a rapid delivery pipette, was added to sodium hydroxide solution so the final hydroxyl ion concentration was about 0.1M , and the total thiol concentration about

$5 \times 10^{-5} \text{M}$. The solubility was then calculated from the optical density and the molar absorptancy coefficient at 240 μ .

The operations of transfer and dilution were performed in about six minutes, and loss of mercaptan by oxidation in this time was negligible. However, losses of 5 to 10 percent were observed if the operations were prolonged unduly.

The pH of the aqueous layer after equilibration with the mercaptan was measured with a Beckman Model G pH meter, with a type E-2 high pH glass indicator electrode, and a calomel reference electrode. It was standardized with borax buffer of pH 9.18.

Titration of Hexanethiol and Ethanethiol

The ion product of water in 44.4 percent aqueous ethanol

In order to calculate the ionization constant of hexanethiol in this solvent from potentiometric titration data, the ion product of water in this solvent must be known. In order to determine this, 50 ml. of the solvent was titrated with 0.1140N sodium hydroxide and the pH measured after each addition with a Beckman Model G pH meter using the type E-2 high pH glass electrode. The OH^- ion concentration was calculated from the amount of sodium hydroxide added and the H^+ ion concentration was measured with the pH meter. The value found at 25°C was $4.0 \pm .3 \times 10^{-15}$.

Titrations

A quantity of mercaptan was accurately weighed and dissolved in sufficient solvent to give a concentration between 2×10^{-2} and $2 \times 10^{-3} \text{M}$. This solution was then titrated in a thermostated beaker ($25 \pm .1^\circ \text{C}$.) with standard carbonate-free sodium hydroxide delivered from a micro-buret.

During the titration nitrogen was made to flow over the surface of the solution. The pH was measured at the midpoint in the titration, and the ionization constant was calculated from the equation:

$$K = \frac{(H^+) \left[(Na^+) - \frac{K_w}{(H^+)} \right]}{(RSH) - (Na^+) + \frac{K_w}{(H^+)}} .$$

The hydrogen ion activity, represented by the symbol (H^+) , was measured with the pH meter. The term $(Na^+) - \frac{K_w}{(H^+)}$ is equal to the mercaptide ion concentration, $\frac{K_w}{(H^+)}$ being the correction for the hydrolysis of the mercaptide ion, with (Na^+) determined from the amount of sodium hydroxide added. (RSH) is the original concentration of mercaptan. The results are shown in Table II.

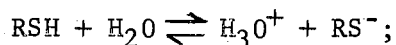
TABLE II
pK OF HEXANETHIOL AND ETHANETHIOL FROM pH TITRATIONS

Mercaptan	Solvent	pK
Hexanethiol	44.4% Aqueous Ethanol	9 Determinations 11.92 [±] .07
Ethanethiol	44.4% Aqueous Ethanol	6 Determinations 12.06 [±] .07
Ethanethiol	Water	10 Determinations 10.57 [±] .06

CHAPTER III

DISCUSSION

For the ionization of a mercaptan in water one can write the equation:



and the thermodynamic equilibrium constant is given by

$$K_t = \frac{[\text{H}_3\text{O}^+][\text{RS}^-]}{[\text{RSH}][\text{H}_2\text{O}]} = \frac{[\text{H}_3\text{O}^+](\text{RS}^-)\gamma_{\text{RS}^-}}{[\text{H}_2\text{O}](\text{RSH})\gamma_{\text{RSH}}}$$

where the quantities in square brackets represents the activities, those in parentheses the molal concentrations, and γ the activity coefficients of the chemical species involved.

In the experiments described, the solubility of hexanethiol was determined in solutions containing 0.1, 0.3, and 0.5M potassium chloride. In these solutions, the ionization of mercaptan can be neglected, and the experimental solubility \underline{s} set equal to (RSH). The solubility was then determined in buffer solutions containing the same concentrations of potassium chloride as well as 0.02M bicarbonate-carbonate buffers; in these cases, the experimental solubility $\underline{s} = (\text{RSH}) + (\text{RS}^-)$.

If one assumes (a) that the solubility of RSH is not affected by the presence of the buffer components and (b) that the experimental pH measurements correspond to the hydronium ion activity, one can calculate a "practical constant" \underline{K} by means of the equation

$$(a) \quad \underline{K} = \frac{[\text{H}_3\text{O}^+](\text{RS}^-)}{(\text{RSH})} = K_t \frac{\gamma_{\text{RSH}}}{\gamma_{\text{RS}^-}} [\text{H}_2\text{O}] .$$

At a given potassium chloride concentration, the activity of water and the activity coefficients of RS^- and RSH should be nearly constant, and K should also be constant.

The results are listed in Table III, and it can be seen that the values of pK determined at varying pH values differ by an amount greater than experimental error, which should be about 0.05 units. This indicates that the assumptions and approximations made are not strictly correct, but the differences are within 0.2 units, and the errors which attach to the use of equation (a) are therefore not large. As the concentration of potassium chloride is increased, it tends to "swamp" the other effects, and it is observed that the variation in pK is smallest for the 0.5M solution.

The activity coefficient of RSH is inversely proportional to its solubility (32), and hence it is seen that it increases by a factor of about 1.3 as the potassium chloride is increased from 0.1 to 0.5M. On the other hand, the activity coefficient of RS^- should decrease; the two changes partly compensate, and hence it is reasonable to expect that the pK values would not vary much in this range, as is observed. A reasonable estimate for γ_{RS^-} at 0.1 ionic strength is 0.83 (33) while γ_{RSH} and $[\text{H}_2\text{O}]$ are nearly 1; pK_t can be estimated on this basis to be 10.4 ± 0.1 .

It seemed of interest to compare the ionization constant in water determined as described above with that determined in a mixed solvent by the potentiometric titration method. Accordingly, hexanethiol of about $3 \times 10^{-3}\text{M}$ concentration in 44.4 percent ethanol was titrated with sodium hydroxide. The mercaptan is so weakly acidic that its reaction with sodium hydroxide cannot be considered quantitative, as in the case of stronger acids. In order to calculate the mercaptide concentration from

the electroneutrality expression

$$(\text{RS}^-) = (\text{Na}^+) - (\text{OH}^-)$$

(OH^-) must be known. In order to determine this, very dilute sodium hydroxide solutions of known concentrations were made up in the solvent medium, and the pH measured. At the midpoint in the titration, when $(\text{RS}^-) = (\text{RSH})$, equation (a) reduces to $\text{pH} = \text{pK}$, as is well known.

TABLE III
pK OF HEXANETHIOL FROM SOLUBILITY MEASUREMENTS

pH	Ionic Strength	Solubility $\times 10^4$ moles/liter	pK
7.00	0.00	4.02	-----
7.00	0.10	3.61	-----
9.98	0.10	5.72	10.21
10.25	0.10	6.72	10.31
10.54	0.10	9.24	10.35
7.00	0.30	3.03	-----
9.92	0.30	4.42	10.26
10.32	0.30	6.07	10.32
10.70	0.30	9.50	10.37
7.00	0.50	2.72	-----
9.95	0.50	3.89	10.32
10.40	0.50	5.25	10.33
10.80	0.50	9.91	10.38

The experimental value of the pH at the midpoint in the titration was 11.9. For many reasons, equation (a) is not exactly applicable in these circumstances and the difference of 1.5 pK units comprises not only the intrinsic difference between the acid strengths in water and 44 percent ethanol, but also the quantitative consequences of several corrections and approximations. In any case, the difference of 1.5 pK units may usefully be regarded as a correction factor by which the pK values determined in the mixed aqueous organic medium can be transposed to water. To check the applicability of the correction, ethanethiol was titrated both in water and in 44.4 percent alcohol, and the pK values found at the midpoint of the titration were 10.6 and 12.1; the difference is 1.5.

The pK value for ethanethiol in water accords well with that found by Yabroff (3) and Danehy (25). The value for hexanethiol is a little lower than that estimated from the data of Yabroff.

PART II

OXIDATION OF HEXANETHIOL IN ALKALINE
SOLUTION BY MOLECULAR
OXYGEN

CHAPTER I

HISTORICAL

There is voluminous literature on the oxidation of cysteine, glutathione, and thioglycolic acid both by air and by other oxidizing agents. The literature has been reviewed by Reid (2), Tarbell (34), and Pascal (35). This thesis will be concerned with the oxidation by air or oxygen, and the review of the literature which follows will not include the above-mentioned mercaptans, except in cases where they are oxidized beyond the disulfide stage.

Barron et al. (36,37) measured the rates of oxygen absorption for a series of dithiols in the absence and presence of catalysts. They found that copper and iron protoporphyrin were the most effective catalysts. No simple correlation of the observed rates with structure could be made. However, it was observed that the rate of oxidation depended on the pH of the solution, on the distance between the mercapto groups, and on the electronegativity of the substituents on the β -carbon atom; electron-withdrawing groups decreased the rate of the uncatalyzed reaction. In the presence of copper(II) all rates were increased and there was little difference among the various mercaptans. It was assumed that the insoluble product formed on oxidation was a simple disulfide. Philipson (38) followed the oxidation of 2,3-dimercaptopropanol by measuring the disappearance of the mercapto groups spectrophotometrically. He found that at pH 5.0 there was no oxidation and that the rate of oxidation increased with increasing pH above pH 6. Copper(II) had no effect on the

rate of disappearance of the mercapto groups. Philipson suggests the possibility that the oxygen consumption and the disappearance of mercapto groups measure different steps in the oxidation. The oxidation product was a polymeric disulfide of molecular weight 500-600.

Fruton and Clarke (39) found that the rate of autoxidation of ethanethiol was independent of pH above 7.5, and independent of the iron concentration in the range 0.01 to 0.0001M. Complete oxidation to the disulfide could not be attained in a reasonable time.

Meguerian (40) investigated the oxidation of hexanethiol by oxygen to the disulfide, catalyzed by a series of hydroquinones. The reaction was studied in 0.084 to 0.121M methanolic sodium hydroxide at 30.2° C. The rate was zero order in hexanethiol and proportional to the sodium hydroxide and hydroquinone concentrations. Wallace and Schriesheim (41) studied the effects of various solvents on the base-catalyzed oxidation of butanethiol to its disulfide with molecular oxygen. They found the rate was some 300 times faster in a dipolar-aprotic solvent (dimethyl formamide) than in methanol. The rate using cesium t-butoxide in t-butyl alcohol was about 20 times faster than with sodium t-butoxide. These results are explained on the basis of solvation of the metal ion by the solvent.

Rosenthal and Voegtlin (42) reported that one to three times the amount of oxygen necessary to oxidize cysteine to cystine was absorbed by cysteine solutions in aqueous phosphate buffer at pH 6.6 to 7.3 in the presence of copper(II). The amount of oxygen absorbed depended on the amount of copper(II) present and on the pH. In the presence of iron(II) or manganese(II) the oxidation stopped after oxidation to the disulfide. Pyrophosphate ion inhibited the reaction beyond the cystine stage. It

was shown in separate experiments that cystine was not oxidized in the presence of copper(II). Povoledo, DeMarco, and Cavallini (43) measured the oxygen absorption by cysteine, cystine, 2-aminoethanethiol, and bis(2-aminoethyl) disulfide, in alkaline solution with copper(II) ions present. They found that the reaction proceeded to the sulfinic acids, which were isolated by paper chromatography. Copper ion was a specific catalyst for the reaction, as many other metal ions were found to be completely inactive, as was copper(II) in the presence of ethylenediaminetetraacetic acid.

Klason (44) observed that dry sodium ethanethiolate was oxidized to sodium ethanesulfinate by atmospheric oxygen. Xan et al. (45) made a quantitative study of the rate of oxidation of representative mercaptans by oxygen in alkaline solution. They found that more oxygen was absorbed than could be accounted for by reaction to disulfide. In dilute (0.1M) alkali the excess amount of oxygen absorbed was very small, but in 2.7M alkali up to 165 per cent of the theoretical amount of oxygen was consumed. The oxidation products were not identified. If the differing solubility of oxygen in the sodium hydroxide was taken into account, the rate of the reaction increased with increasing sodium hydroxide concentration. The relative rates were: n -propyl > n -butyl > n -amyl > benzyl > thiophenol. It was also observed that the mercaptan which reacted faster absorbed more oxygen.

Proell and Shoemaker (46) investigated the oxidation of alkanethiols by oxygen in the presence of nitrogen oxides as catalysts. By control of the reaction conditions they were able to produce sulfoxides, sulfones, sulfonic acids or a mixture of these products. Alkanesulfonic acids were produced in good yield by using equimolar amounts of the mercaptan and

dinitrogen tetroxide. The oxidation was accomplished by oxygen, as the dinitrogen tetroxide was recovered at the end of the reaction.

The rate of oxidation of mercaptans to disulfides follows the order $\text{ArSH} > \text{HOOCCH}_2\text{SH} > \text{RCH}_2\text{SH} > \text{RR}'\text{R}''\text{CSH}$ (47).

CHAPTER II

EXPERIMENTAL

Reagents

Hexanethiol was a Matheson Coleman and Bell product, used without further purification. Iodometric titration (2) indicated a purity of 98.0 percent. Dodecanol was a white label product of Eastman Organic Chemicals. All other reagents, except those whose syntheses are described below, were of analytical reagent grade.

n-Hexyl Disulfide

The synthesis and properties of n-hexyl disulfide have not previously been described in the literature (48). The method employed, however, follows straight forwardly from the methods described for the preparation of other disulfides. Iodine was added to 59.1 g. (0.50 moles) of hexanethiol in 200 ml. of chloroform and 100 ml. of water until a slight excess remained, indicated by the red-brown color. Sodium hydroxide (100 ml. of 0.1M) was added to remove some of the hydrogen iodide formed in the reaction. More iodine was added until a slight excess remained. The chloroform layer was separated and the aqueous layer was extracted with 50 ml. of chloroform. The chloroform extract was combined with the original chloroform layer and washed with two 50-ml. portions of 5 percent sodium bicarbonate and with 10 ml. of 0.1N sodium thiosulfate to remove

iodine and hydrogen iodide. The chloroform was then removed at reduced pressure and the product vacuum distilled at 0.3 mm. pressure. A yield of 44.5 g. (76%) was obtained with a boiling range of 108-110° C. A small fraction was collected for physical properties measurements, boiling at 109° C. The following properties were measured: boiling point at 0.3 mm. pressure, 109° C.; refractive index at 25°, 1.6756; density at 25°, 0.9052. The ultraviolet absorption spectrum in 95 percent ethanol showed a peak at 255 mμ with a molar extinction coefficient of 410.

Barium Hexanesulfonate

To 100 ml. of concentrated nitric acid was added dropwise 29.5 g. (0.25 mole.) of hexanethiol over a period of about two hours. The reaction temperature was kept below 50°C. with an ice bath. The solution was evaporated on a hot plate until the evolution of brown fumes ceased. About 5 ml. of water was then added and the solution evaporated again. The remainder, crude hexanesulfonic acid, was added to 10.3 g. of barium hydroxide suspended in 100 ml. of water until the solution was acidic. The barium hexanesulfonate which precipitated was washed with water, ether, and dried. It was then recrystallized once from water.

Analysis. Calculated for $C_{12}H_{26}O_6S_2$ Ba: C, 30.80%; H, 5.60%; S, 13.70%. Found; C, 31.01%; H, 5.60%; S, 13.54%.

Oxygen Absorption Measurements

The oxygen absorption was followed by the Warburg technique (49). The Warburg manometers and flasks were calibrated by the method of Lazarow (50). The following procedure was used for the measurements in 0.10M sodium hydroxide. About 0.12 g. of hexanethiol was accurately

weighed into 100 ml. of 0.15M sodium hydroxide, and shaken several minutes until dissolved. Then 2 ml. was placed in the main compartment of the Warburg flask. In the side arm of the flask there was put 1 ml. of catalyst solution. Catalyst solutions were prepared from the metal chloride salts so that 1 ml. contained 0.50 μ moles of the metal ion.. The flask was put on the Warburg apparatus and allowed to come to temperature equilibrium (25°C). The two solutions in the flask were mixed and the oxygen absorption was followed by the change in pressure at constant volume.

The effect of various metal ions on the rate of oxidation in 0.10M sodium hydroxide solution is shown in Figure 1. It is seen that copper(II) and manganese(II) are good catalysts for the reaction, while cobalt(II) and nickel(II) are less effective. Vanadium(II), chromium(III), iron(II), and tin(II) have no catalytic effect; to prevent crowding of the figure, only the data for iron(II) are shown. The amount of oxygen absorbed corresponds to the amount needed to oxidize the hexanethiol to the disulfide, or less.

Representative data for the oxygen absorption by hexanethiol in 3.0M sodium hydroxide are shown in Figure 2. In this case the amount of oxygen absorbed in the presence of copper(II) is about 0.34 moles of oxygen per mole of hexanethiol. This indicates that the oxidation has gone beyond the disulfide stage, which requires 0.25 moles of oxygen per mole of mercaptan. Oxidation to the next higher oxidation state, the sulfenic acid or the thiolsulfinate, requires 0.50 moles of oxygen. It appears that a mixture of products is formed, the disulfide plus some amount of higher oxidation products.

At 50°C., 0.25 moles of oxygen per mole of mercaptan were absorbed in one-half hour in 3.0M sodium hydroxide; the reaction was complete in

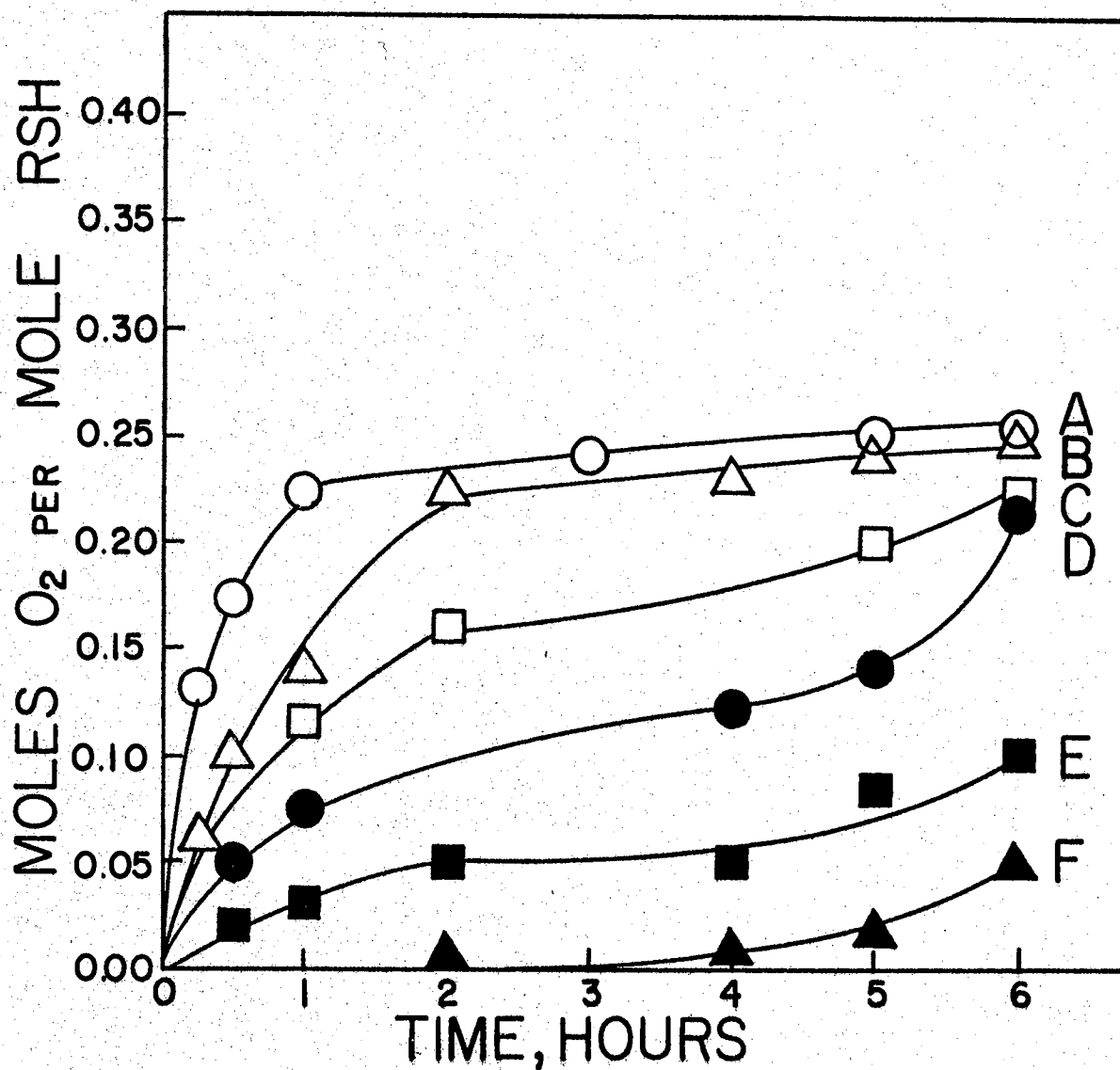


Figure 1. Oxygen absorption of hexanethiol in 0.10M sodium hydroxide in the presence of various metal ions. The amount of hexanethiol is 20-25 μ moles with 0.50 μ moles of metal ion in 3 ml. Temperature 25°C. Curve A, Mn(II); Curve B, Cu(II); Curve C, Co(II); Curve D, Ni(II); Curve E, NaOH only; Curve F, Fe(II).

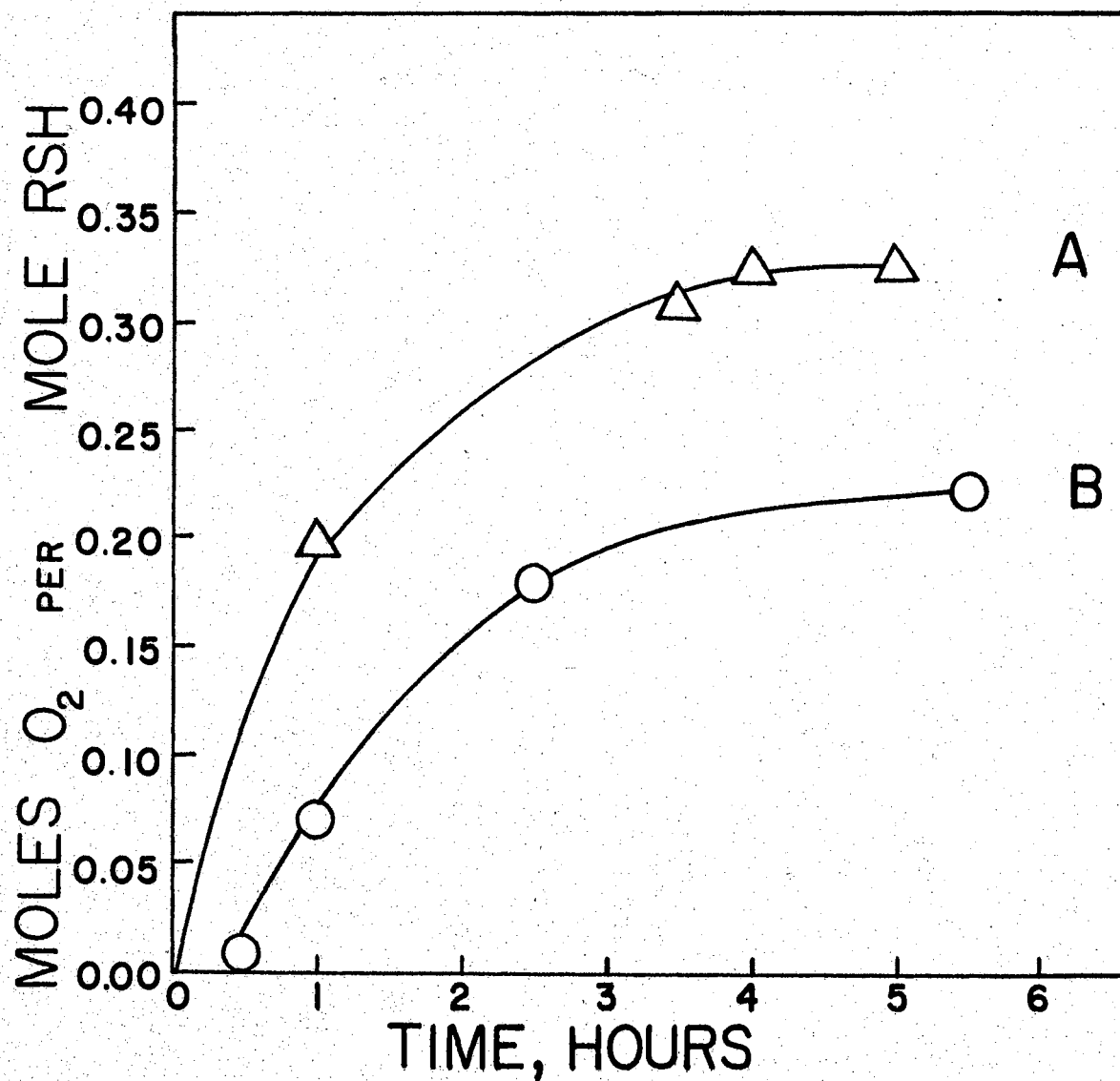


Figure 2. Oxygen absorption of hexanethiol in 3.0M sodium hydroxide: Curve A, with 2 mole per cent Cu(II); Curve B, NaOH only.

five hours, with about 0.37 moles of oxygen per mole of hexanethiol being absorbed. Copper(II) had no effect on the rate of oxidation or the extent of reaction at 50°C. These results are illustrated in Figure 3.

The oxygen absorption by hexanethiol in 3.0M sodium hydroxide in the presence of two mole per cent copper(II) was measured using varying concentrations of hexanethiol. In the range of concentrations from 1.5 to 17×10^{-3} M there was no measurable change in the extent of oxidation. This was the maximum concentration range which could be used in the Warburg apparatus.

The effect of copper(II) concentration was also studied. The results are shown in Figure 4. Two mole per cent copper(II) was the most effective concentration. When equivalent amounts of copper(II) and hexanethiol were used essentially no oxygen was absorbed, indicating that the copper(I) mercaptide was not oxidized under these conditions.

It was also found that the reaction was somewhat faster in pure oxygen than in air, but the oxidation did not proceed any further in oxygen. It was thought that perhaps copper(II) was a catalyst for the reaction to disulfide and not for the further oxidation. Therefore, in an attempt to complex and inactivate any metal ion impurities in the reagents, ethylenediaminetetraacetic acid was added and the oxygen absorption followed. However, there was no significant difference in the rate or extent of oxygen uptake in the presence or absence of ethylenediaminetetraacetic acid, at 25° C.

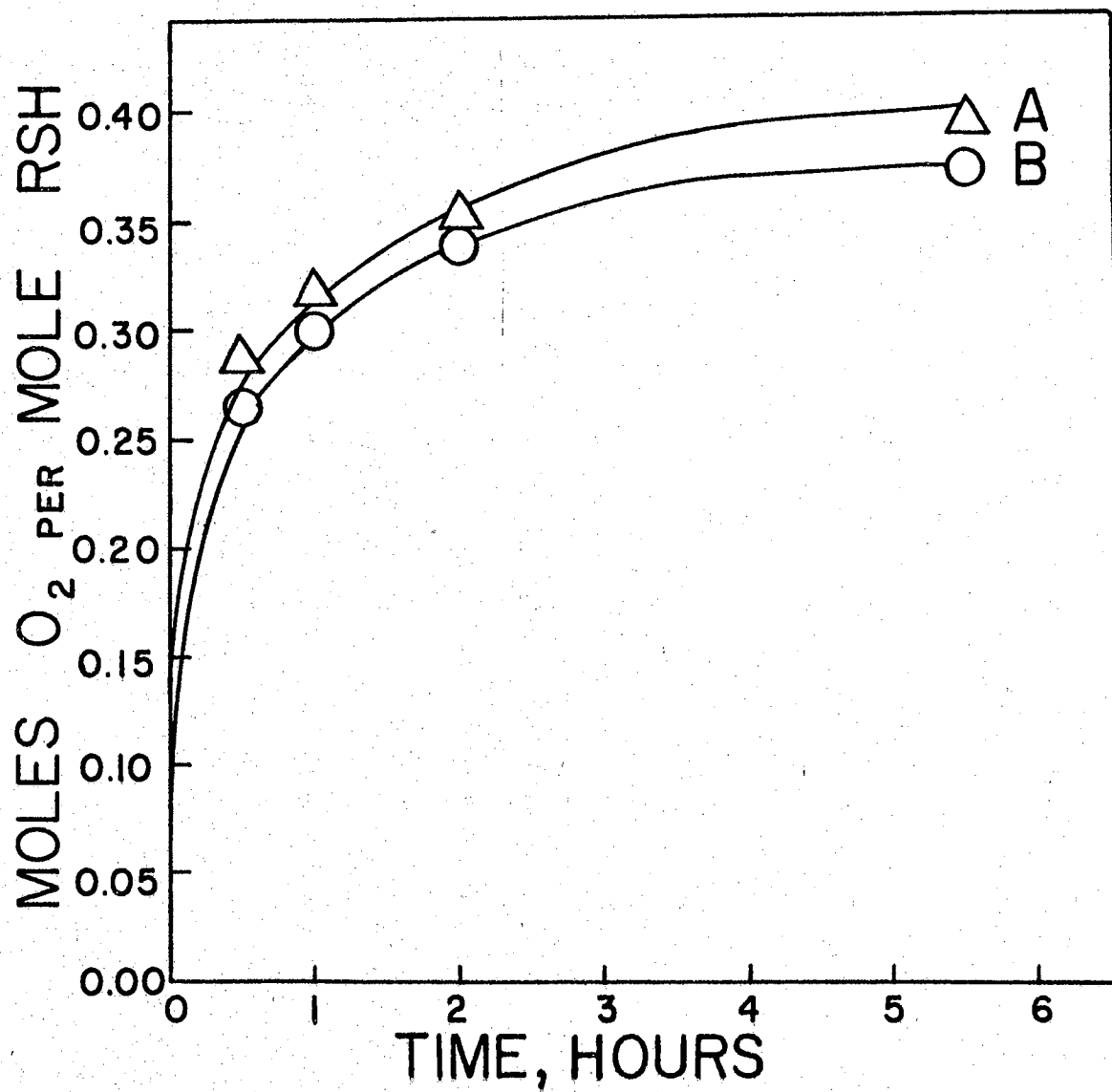


Figure 3. Oxygen absorption of hexanethiol at 50° C. Amount of hexanethiol is 21 μmoles in 3.0 ml. of 3.0M NaOH: Curve A, NaOH only; Curve B, with 0.5 μmoles of Cu(II).

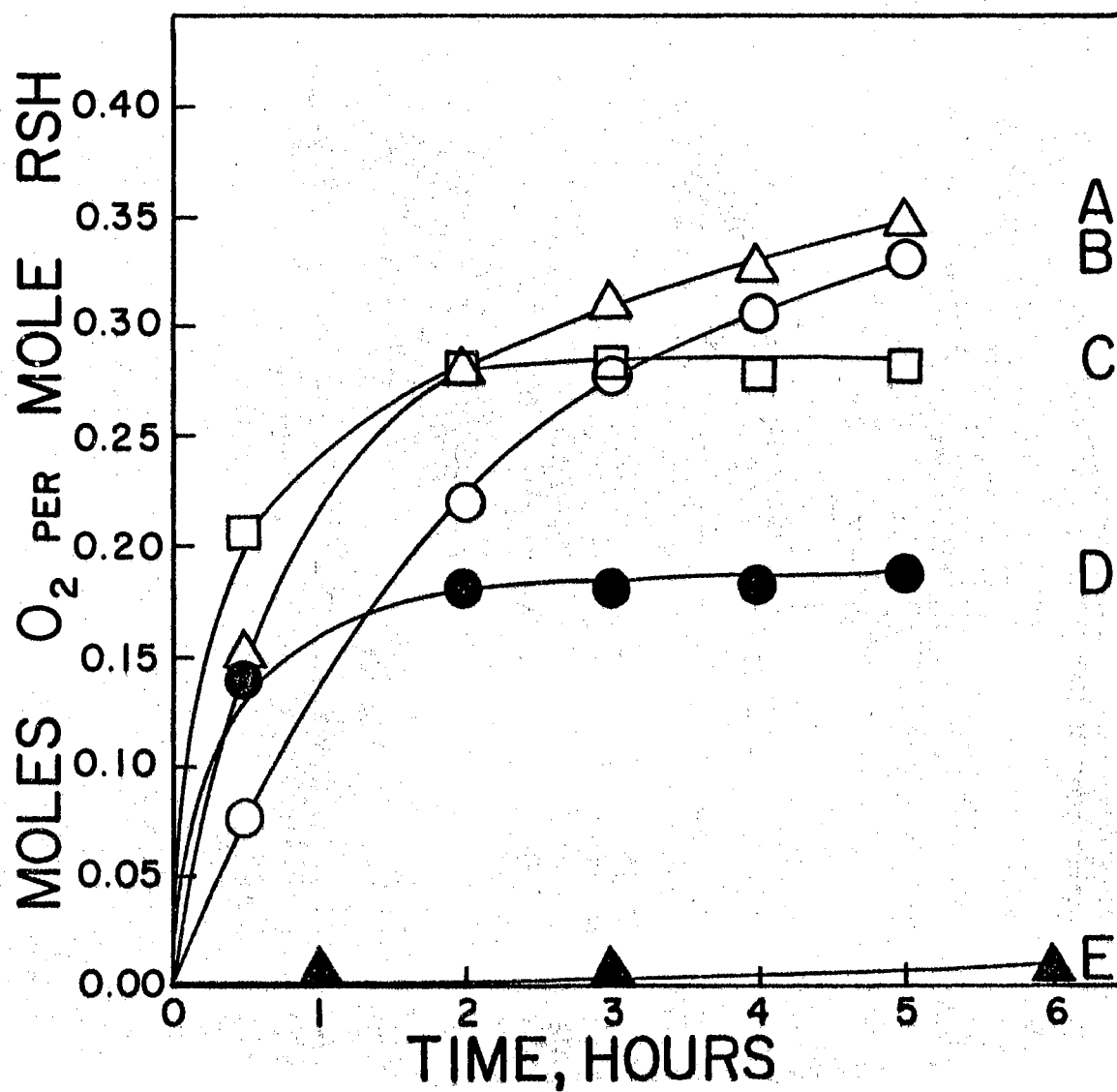


Figure 4. Effect of copper(II) concentration of the oxidation of hexanethiol with oxygen in 3.0M NaOH. The amount of hexanethiol is 23.5 μ moles in 3.0 ml. Temperature 25° C.: Curve A, 0.50 μ moles Cu(II); Curve B, 0.25 μ moles of Cu(II); Curve C, 1.0 μ mole Cu(II); Curve D, 5 μ moles Cu(II); Curve E, 12.5 μ moles Cu(II).

Products of the Reaction in Concentrated Sodium Hydroxide Solution

Identification of the Oxidation Products

Sulfenic acids, thiolsulfinates, thiolsulfonates, sulfinic acids, and sulfonic acids are possible products of the reaction. However, alkyl sulfenic acids have never been isolated; thiolsulfinates are decomposed by alkali, yielding the disulfide and sulfur dioxide (51); and the sulfinic acids are slowly oxidized in air to the sulfonic acids (52). Therefore the thiolsulfonate and the sulfonic acid are the only probable products. Attempts to isolate the higher oxidation products from the reaction mixtures in the Warburg apparatus failed. The reaction was then executed on a larger scale.

No evidence for the presence of thiolsulfonate was obtained by extracting the reaction mixture with carbon tetrachloride and examining its infra-red spectrum. Thiolsulfonates absorb in the range of 900-1200 wave numbers, and no peaks were observed in this range (53). A small amount of hexanesulfonic acid was isolated as the barium salt and identified by its infra-red spectrum, which showed a peak at 1070 and a doublet at 1160-1200 wave numbers. A known sample of barium hexanesulfonate, prepared as previously described, had a peak at 1065 and a doublet at 1150-1210 wave numbers. The literature value for the symmetric stretching frequency of the S-O bond in ionic sulfonates is 1050 wave numbers, and the asymmetric stretching frequency is at 1180 wave numbers (54). The 1180 band is sometimes split or at least much broader than the 1050 band (54). The broadening and the splitting were observed in this case.

The infra-red spectra were measured in potassium bromide pellets on a Beckman model IR-7 infra-red spectrophotometer with sodium chloride optics.

Attempted Oxidation of n-Hexyl Disulfide

Hexyl disulfide (1.82 g.) was added to 300 ml. of 2.0M sodium hydroxide and oxygen was bubbled through the rapidly stirred solution for five days. Stirring was fast enough to maintain the disulfide finely dispersed in the sodium hydroxide solution. The solution was extracted with three 5-ml. portions of ether and the ether extract was evaporated to about 20 ml. Dodecanol was added as an internal standard and the amount of unreacted hexyl disulfide determined by gas chromatography. The amount recovered was 1.71 g. (94%). The gas chromatograph used was an Aerograph model A-300 with a $\frac{1}{4}$ in. by 8 ft. aluminum column packed with 5 per cent SE-30 silicone rubber on 60-80 mesh acid washed Chromosorb-W. Helium was used as the carrier gas at a flow rate of 75 ml. per minute. The column temperature was 200° C. A more detailed description of the gas chromatographic method will be given in Part III. It was also found that no oxygen was absorbed by the disulfide in ten hours on the Warburg apparatus.

Quantitative Study of the Products of the Reaction

To 300 ml. of 2.0M sodium hydroxide was added 3.556 g. of hexanethiol. Oxygen was bubbled through the stirred solution at a rate of 50 ml. per minute for five days. The vapors carried over by the oxygen were trapped in a dry ice-acetone cold trap. The trapped material was extracted with carbon tetrachloride and an infra-red spectrum of the extract was obtained

to determine if any volatile sulfur compounds had been carried out of the reaction vessel. It was found that only water and hexanethiol were present in the trap; the amount of hexanethiol, determined by iodometric titration, was 0.078 g.

The reaction mixture was extracted with ether to remove the disulfide. Dodecanol (0.7420 g.), was added to the ether extract, as an internal standard and the mixture was analyzed by gas chromatography. The yield of disulfide was 91 percent.

The aqueous portion of the reaction mixture was passed through an ion exchange column to remove the sodium ions. The column was 5 x 70 cm., filled with Amberlite IR-120 cation exchange resin in the hydrogen form. The solution was passed through the column at a rate of 25-30 ml. per minute and eluted with 4 liters of water at the same flow rate. The solution was evaporated to about 2 ml. and neutralized with a saturated solution of barium hydroxide. The barium hexanesulfonate was removed by filtration and dried. The yield was 6 percent.

CHAPTER III

DISCUSSION

Many autoxidations are catalyzed by traces of metal salts. To be effective the salt should be derived from a metal having at least two readily accessible oxidation states differing by one unit, so the metal ion can be alternatively oxidized by oxygen and reduced by the compound being oxidized (55). In the present study copper(II), manganese(II), cobalt(II), and nickel(II) were found to catalyze the oxidation of hexanethiol in both dilute (0.1M) and concentrated (3.0M) alkali. However, iron(II), chromium(III), and vanadium(II) did not catalyze the reaction; no explanation of this can be offered. In dilute alkali, with the metal ions mentioned, the amount of oxygen absorbed corresponded to the amount required for oxidation to the disulfide, or less.

It was shown that in concentrated sodium hydroxide solution more oxygen was absorbed than can be accounted for by the oxidation to disulfide. The products of the air oxidation of hexanethiol are hexyl disulfide and hexanesulfonic acid. In a quantitative study of the products of the reaction it was found that 91 percent of the mercaptan goes to the disulfide and 6 percent to the sulfonic acid. The amount of hexanesulfonic acid formed in the reaction can also be calculated from the amount of oxygen absorbed, 0.35 moles per mole of mercaptan. Let

x = number of moles of RSH oxidized to RSSR

$1-x$ = number of moles of RSH oxidized to RSO_3H

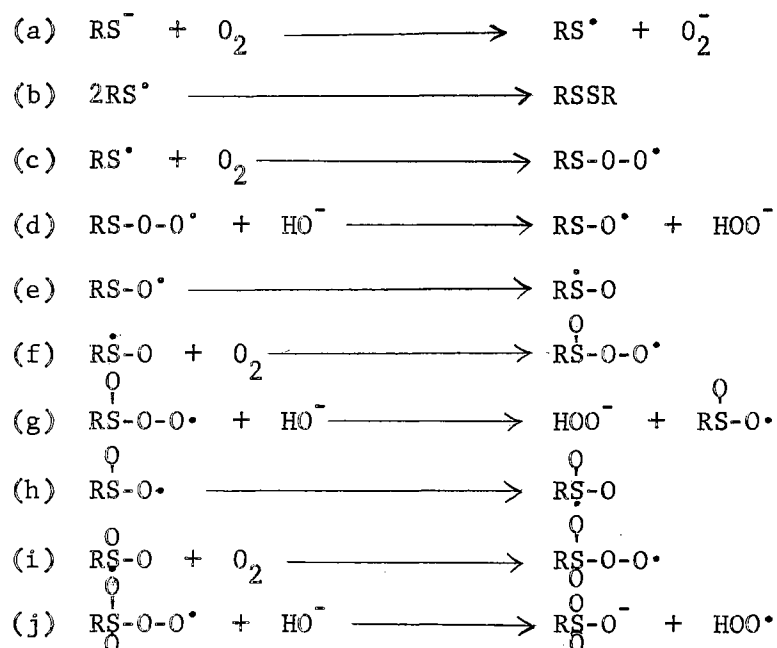
$\frac{1}{4}x$ = number of moles of oxygen used for $\text{RSH} \longrightarrow \text{RSSR}$

$\frac{3}{2}x$ = number of moles of oxygen used for $\text{RSH} \longrightarrow \text{RSO}_3\text{H}$

$$\frac{1}{4}x + \frac{3}{2}(1-x) = 0.35$$

$x = 0.92$; i.e. 92 percent of the mercaptan is oxidized to the disulfide. It was shown that the disulfide was not oxidized by oxygen in five days, under similar conditions. This proves that the disulfide is not an intermediate in the formation of the sulfonic acid. Therefore, there are two competing reactions involved in the oxidation of hexanethiol in 3.0M alkali, one of which yields the disulfide and the other the sulfonic acid.

From the present study it is not possible to formulate a unique mechanism for the oxidation which satisfies all the experimental facts. However, the following mechanism is proposed for the reaction.



Reactions (a) and (b) have been previously proposed for the oxidation of mercaptans to disulfides by molecular oxygen (41). The peroxide and hydroperoxide ions, formed in reactions (a) and (b) respectively, are probable products of the reaction; hydrogen peroxide has been detected as one of the products in the oxidation of cysteine by molecular oxygen (56). The mode of catalysis by certain metal ions in this reaction is not known.

PART III

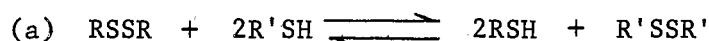
EQUILIBRIA IN MERCAPTAN-DISULFIDE INTERCHANGE REACTIONS

CHAPTER I

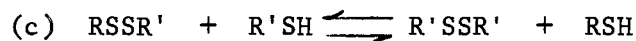
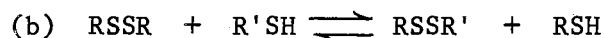
HISTORICAL

Mercaptan-Disulfide Exchange Reactions

The reaction between a disulfide and a mercaptan may take place as shown in equation (a).



It is also possible for a mixed disulfide to be formed, as indicated by equation (b), which can react further according to reaction (c).



Lecher (57) was the first to observe this. Wikberg (58) detected the mixed disulfide of glutathione and cysteinylglycine in a mixture of these mercaptans that had stood for a period of time. He also prepared the mixed disulfide of glutathione and cysteine by oxidizing a mixture of the mercaptans with hydrogen peroxide at pH 7.5. The same mixed disulfide has been prepared from glutathione and cysteine-S³⁵. The mixed disulfide was separated from the symmetrical disulfides by paper electrophoresis (59).

Gorin et al. (60) have shown that an exchange reaction also occurs between simple alkyl disulfides and mercaptans. When propyl disulfide and decanethiol were heated in a sealed tube, it was found that the total number of moles of mercaptan stayed constant but its molecular weight

decreased, indicating the formation of propanethiol. This product was isolated by distillation.

Bersin and Steudel (61) determined the equilibrium constants for the cystine-thioglycolic acid system by measuring the change in optical rotation of the system, however, they assumed that dithiodiglycolic acid and cystine do not form a mixed disulfide, and this assumption has been shown to be incorrect (62).

Barltrop et al. (63) measured the equilibrium constant for the reaction of trimethylene disulfide with 2-mercaptoethanol and benzyl mercaptan in aqueous ethanol. The reaction was followed spectrophotometrically, using the decrease in the absorption at 330 m μ due to the trimethylene disulfide. The equilibrium constant calculated on this basis was 3.3 for 2-mercaptoethanol and 13 for benzyl mercaptan.

Kolthoff et al. (62) studied the reaction of cystine with thioglycolic acid and glutathione. Their method of investigation depended on the fact that cystine was only slightly soluble in the pH range between 5 and 7 and the solubility was increased in the presence of freely soluble disulfides or mercaptans. The results were also substantiated by a polarographic study. Their results are shown in Table IV.

Fava and coworkers (64) determined reaction-rate constants for the exchange between S³⁵-labelled disulfides and the corresponding unlabelled mercaptans. The rates are comparable for n-butyl, n-hexyl, and phenyl, but t-butyl is 10⁶ times slower. They also calculated the equilibrium constants for the reaction of trimethylene disulfide with butanethiol and methyl thioglycolate, which were 7.5 and 3.8, respectively, at 25° C.

Eldjarn and Pihl (65-69) determined the equilibrium constants for the reaction of cystine, oxidized glutathione and cystamine with several

TABLE IV

EQUILIBRIUM VALUES REPORTED FOR THE MERCAPTAN-DISULFIDE REACTION

System	Reference	K_1	K_2	K_3	K_4
Cystine ----					
Glutathione	62	3.0	2.8	1.0	2.8
	69		12.4	0.17	
Thioglycolic Acid	62	5.1	0.8	4.1	3.3
	70	6.1	7.4	1.29	10.2
Cysteamine	69		4.76	0.75	
N-methylcysteamine	69		2.61	0.43	
N-dimethylcysteamine	69		2.30	0.36	
N-trimethylcysteamine	69		2.78	55.6	
N-diethylcysteamine	69		2.79	0.36	
2-Mercaptoethylpiperidine	69		2.81	0.31	
2-Mercaptoethylmorpholine	69		2.63	0.36	
2-Mercaptoethylguanidine	69		2.04	0.37	
N-benzylcysteamine	69		2.29	0.35	
N-acetylcysteamine	69		5.00	0.62	
Aletheine	69		2.94	0.66	
2-Mercaptoethanol	69		1.39	0.66	
Oxidized Glutathione ----					
Cysteamine	67		5.00	0.34	
N-acetylcysteamine	67		2.86	0.28	
N-dimethylcysteamine	67		1.56	0.32	
N-diethylcysteamine	67		1.92	0.29	
2-Mercaptoethylpiperidine	67		1.89	0.25	
4,4'-Dithiobis(benzenesulfonic acid) ---- Cysteine					
	72		1.2	1.0	
4,4'-Dithiobis(naphthalene-sulfonic acid) ---- Cysteine					
	72		0.03	0.56	
Trimethylene Disulfide ----					
Butanethiol	64		7.5		
Methyl Thioglycolate	64		3.8		
2-Mercaptoethanol	63		3.3		
Benzyl Mercaptan	63		13.0		
Ethyl Disulfide ----					
Methyl Disulfide	77	5.1			
<u>i</u> -Propyl Disulfide	77	4.1			
<u>t</u> -Butyl Disulfide	77	24.6			

radiation protective mercaptans. Their results are shown in Table IV. The procedure involved equilibrating a thiol with a disulfide, one of which was labelled with S^{35} ; the three labelled species were then separated by paper electrophoresis. From the amounts of the three radioactive species, the amounts of the other two components could be found and the equilibrium constant calculated.

Lamfrom and Nielsen (70) determined the rate and equilibrium constants for the reaction of cystine with thioglycolic acid by a spectrophotometric method. The equilibrium constants, shown in Table IV, were measured in aqueous solution at pH 6 and 25°C.

Parker and Kharasch (71) studied the equilibrium of unsymmetrical disulfides with mercaptans: $RSSR' + R''S^- \rightleftharpoons R'S^- + RSSR''$. When R' was either 2,4-dinitrophenyl or *o*-nitrophenyl and R'' was a simple aliphatic or unsubstituted aromatic, equilibrium was reached in less than five minutes in 95 percent ethanol at 20-22°C. The yield of $R'S^-$ was above 80 percent in each case.

Recently, Smith (72) reported equilibrium constants for the reaction of 4,4'-dithiobis(benzenesulfonic acid) (I) and 4,4'-dithiobis(1-naphthalene-sulfonic acid) (II) with cysteine. The equilibrium concentrations were measured spectrophotometrically using the absorption of the mercaptide ions of (I) and (II) and appropriate initial concentrations. The constants found are shown in Table IV.

The reaction of mercaptans with symmetrical disulfides has been used to prepare mixed disulfides¹. A high yield of the mixed disulfide can be

¹For references to patents on the preparation of unsymmetrical disulfides see references 48, 73 and 74.

obtained in some cases if the lower boiling mercaptan formed in the reaction is distilled off as it is formed (73). Birch et al. (74) distilled equilibrium mixtures of a mercaptan and a symmetrical disulfide to obtain the mixed disulfides in yields of 50-66 percent.

Disulfide Exchange Reactions

The disulfide exchange reaction has also been used for the synthesis of mixed disulfides (73,74).

Ryle and Sanger (75) studied the reaction of cystine with N,N'-bis(2,4-dinitrophenyl) cystine. The concentration of the unsymmetrical disulfide at equilibrium was determined spectrophotometrically after extraction of the symmetrical aromatic disulfide with ether.

Kolthoff, Stricks and Kapoor (62) measured the equilibrium constant for the reaction of cystine with dithiodiglycolic acid and with oxidized glutathione. The data are shown in Table IV.

Haraldson et al. (76) determined the equilibrium constants in three mixtures of simple aliphatic disulfides using gas chromatography as the method of determining the equilibrium concentrations of the components. The constants are shown in Table IV.

The mechanism of the disulfide and mercaptan-disulfide exchange reactions has been shown to be nucleophilic attack by mercaptide ion on the disulfide (61,62,64,65,77,78).

CHAPTER II

EXPERIMENTAL

Reagents

Hexanethiol, 2-mercaptoethanol, propyl disulfide, hexadecane, and 1-octanol of white label grade and t-butyl disulfide of practical grade were obtained from Eastman Organic Chemicals. Phenyl mercaptan, propane-thiol, decane, and isooctane, of the best quality available, and benzyl ether of practical grade were from Matheson Coleman and Bell. Phenyl disulfide and s-butyl disulfide were products of Columbia Organic Chemicals. 2-Hydroxyethyl disulfide was obtained from Aldrich Chemical Company. Octadecane and tetradecane were from Humphrey and Wilkenson. Hexyl disulfide was prepared by oxidation of hexanthiol with iodine as described in Part II. 2-Diethylaminoethanethiol hydrochloride was a gift from the Evans Chemetics Company. Lithium aluminum hydride was from Metal Hydrides Inc. and absolute ethanol was of reagent quality from U.S. Industrial Chemicals. All of the above compounds were used without further purification. All other chemicals were of reagent grade except those whose syntheses are described below.

2-Diethylaminoethanethiol

A solution of 48 g. (0.28 moles) of 2-diethylaminoethanethiol hydrochloride in 200 ml. of air-free absolute ethanol was mixed under

nitrogen with 150 ml. of air-free absolute ethanol containing 11 g. of sodium hydroxide. The sodium chloride formed in the reaction was removed by filtration and the solution distilled under reduced nitrogen pressure. The yield of diethylaminoethanethiol boiling at 62°C. and 15 mm. pressure was 15 g. Gas chromatography indicated the sample was essentially pure, and free of disulfide.

Bis(2-diethylaminoethyl)disulfide

To 200 ml. of methanol was added 26 g. (0.15 moles) of 2-diethylaminoethanethiol hydrochloride and 12 g. (0.30 moles) of sodium hydroxide. Air was bubbled through the solution for 24 hours. The sodium chloride was filtered off and the methanol removed at reduced pressure. The remaining liquid was filtered to remove sodium chloride and sodium hydroxide which had precipitated during the evaporation of the solvent. The liquid was then vacuum distilled. The yield was 5.8 g. boiling at 115-120°C and 0.4 mm. pressure.

s-Butyl mercaptan

s-Butyl mercaptan was prepared by the reduction of s-butyl disulfide with lithium aluminum hydride. A 500 ml., 3-necked reaction flask was fitted with a dropping funnel, a reflux condenser, and a mechanical stirrer. Lithium aluminum hydride (6.6 g.) in 250 ml. of dry ether was put in the reaction flask and 41 g. of s-butyl disulfide was added dropwise in about one hour. The solution was refluxed for 40 minutes. After cooling the flask in an ice bath, the excess lithium aluminum hydride was decomposed by the dropwise addition of water. The solution was acidified with 100 ml. of 15 percent sulfuric acid and stirred for 24

hours. The water layer was separated and extracted with ether. The ether portions were combined and washed with water. After the ether had been removed under reduced pressure, the solution was distilled at atmospheric pressure. About 20 g. of s-butyl mercaptan was obtained boiling at 83°C.

Attempted Preparation of t-Butyl Mercaptan

An attempt was made to prepare t-butyl mercaptan by reduction of t-butyl disulfide. One-half mole of t-butyl disulfide in 300 ml. of glacial acetic acid was refluxed with excess granular zinc for 10 hours. However, no mercaptan was obtained. It was attempted to reduce the disulfide with lithium aluminum hydride by the method described for the preparation of s-butyl mercaptan. After refluxing an ether solution of t-butyl disulfide with excess lithium aluminum hydride for 8 hours no mercaptan could be isolated and the disulfide was recovered unchanged.

Exchange Reactions

Apparatus

The gas chromatograph used in these determinations was an Aerograph Model A-300 from the Wilkens Instrument and Research Co. The chromatograph was equipped with a thermal conductivity detector which was operated at 200 ma. current. Helium was used as the carrier gas. The samples were injected into the chromatograph with a 10 μ l. "Microliter" syringe from the Hamilton Co. The areas under the chromatograph peaks were measured with an Ott compensating polar planimeter from the Fredrick Post Co. The measuring arm length was set so each division on the vernier scale was equal to four sq. mm.

Gas Chromatographic Columns

General Electric silicone SE-30 (1.65 g.) was dissolved in 200 ml. of methylene chloride. The solution was added, with stirring, to 30 g. of acid washed, 60-80 mesh Chromosorb-W, from the Johns-Manville Co. This mixture was stirred well and the solvent evaporated off on a hot plate with continuous stirring. An aluminum tube of $\frac{1}{4}$ in. outside diameter and 8 ft. long was bent in the shape of a "U" and filled with packing from both ends, while the column was vibrated with an electric hand vibrator. The column was then coiled to fit the Aerograph oven. It contained 16.2 g. of packing which was 5 percent by weight SE-30. A similar column, $\frac{1}{4}$ in. by $5\frac{1}{2}$ ft., was packed with this material by the same method. A $\frac{1}{4}$ in. by 8 ft. column was also prepared, in a similar manner, that contained 10 percent SE-30 silicone on acid washed Chromosorb-W.

Calibration

The gas chromatograph was calibrated with each component to be analyzed, except the mixed disulfide. Calibration was effected by the marker technique and gave a calibration constant which relates the area under the peak traced by the recorder to the amount of component present (79). The disulfide calibration was accomplished by chromatographing mixtures, of known composition, of the two symmetrical disulfides and a marker compound. The calibration constant for the unsymmetrical disulfide was taken as the mean of the constants for the two symmetrical ones. The concentration of the calibration samples extended over the range found in the equilibrium samples. A mixture of mercaptan and disulfide was chromatographed to determine the proper conditions for separation; no

reaction took place on the column, as evidenced by the absence of peaks for the mixed disulfide and the mercaptan derived from the disulfide.

Equilibrium Measurements

The mixtures of mercaptan and of a different symmetrical disulfide were prepared in absolute ethanol. The equilibrium point was approached from both directions; i.e. experiments were begun starting with RSSR and R'SH, and others were begun starting with R'SSR' and RSH. The initial mercaptan and disulfide concentrations were between 0.1 and 0.5M, whenever possible. A small amount (0.01 g./10 ml.) of catalyst, either sodium hydroxide or sodium methoxide, was added. The samples were then allowed to come to equilibrium in a constant temperature bath at $25 \pm 0.1^\circ\text{C}$. After equilibrium had been attained the catalyst was neutralized by the addition of concentrated hydrochloric acid. At equilibrium there are five components present, two mercaptans, two symmetrical disulfides and the unsymmetrical disulfide. The amount of each component was determined by gas chromatography.

Similarly, two different symmetrical disulfides were equilibrated in absolute ethanol. A small amount (0.02 g. in 10 ml.) of one of the corresponding mercaptans and base were added to catalyze the reaction. This was necessary to achieve equilibrium in a reasonable length of time.

Calculations

The equations used to calculate the equilibrium constants for the hexyl -- phenyl system will be shown in this section. The abbreviations used are listed below.

Capital letters	Subscripts
A = Peak area	h = Hexanethiol
C = Calibration constant	p = Phenyl mercaptan
M = Molecular weight	hh = Hexyl disulfide
W = Weight in grams	hp = Hexyl phenyl disulfide
N = Number of moles	pp = Phenyl disulfide
	m = Marker compound

No subscript indicates the quantity is for any component.

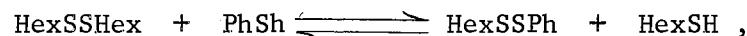
The relationship between the area of the sample peak and the weight of the sample, in the marker method, is given by the expression;

$$W = (W_m)(C) \frac{(A)}{(A_m)} .$$

The number of moles of the compound is given by the expression:

$$N = \frac{(A) (W_m) (C)}{(A_m) (M)} .$$

The equilibrium constant, K_2 , for the reaction,



$$\text{is } K_2 = \frac{(A_h) (C_h) (A_{hp}) (C_{hp}) (M_p) (M_{hh})}{(A_p) (C_p) (A_{hh}) (C_{hh}) (M_h) (M_{hp})} .$$

Likewise, K_3 for the reaction, $\text{HexSSPh} + \text{PhSH} \rightleftharpoons \text{PhSSPh} + \text{HexSH}$,

$$\text{is } K_3 = \frac{(A_h) (C_h) (A_{pp}) (C_{pp}) (M_p) (M_{hp})}{(A_p) (C_p) (A_{hp}) (C_{hp}) (M_h) (M_{pp})} .$$

For the reaction, $\text{HexSSH} + \text{PhSSPh} \rightleftharpoons 2 \text{HexSSPh}$,

$$K_1 = \frac{(A_{hp})^2 (C_{hp})^2 (M_{pp}) (M_{hh})}{(A_{pp}) (C_{pp}) (A_{hh}) (C_{hh}) (M_{hp})^2} .$$

The constant K_1 , can also be calculated from the relation $K_1 = \frac{K_2}{K_3}$.

Individual Equilibrium Systems

Hexyl -- Phenyl

The $\frac{1}{4}$ in. by 8 ft. column packed with 5 percent SE-30 on 60-80 mesh acid-washed Chromosorb-W was used for this separation. The helium flow rate was 90 ml./min. The injector temperature was 240°C. and the detector temperature was 280°C. The column temperature was maintained at 100° C. until the two mercaptans had emerged, then it was increased as rapidly as possible to 200° C. where it was held until the disulfides had been eluted. The column temperature was 200° C. for the disulfide equilibrium mixtures. The calibration data are shown in Table V. Benzyl ether was used as the marker compound for the disulfides and decane for the mercaptans.

The equilibrium constants for the reaction are shown in Table VI; The constants are calculated for the reaction where R = hexyl and R' = phenyl. A representative gas chromatogram of the disulfide equilibrium mixture is shown in Figure 5. Figure 6 is a representative gas chromatogram of the mercaptan-disulfide equilibrium mixture.

TABLE V
CALIBRATION CONSTANTS FOR THE HEXYL -- PHENYL SYSTEM

Compound	Molar Concentration	Calibration Constant
Hexyl Disulfide	0.04	0.93
	0.06	0.98
	0.08	0.96
	0.10	1.08
	0.12	0.94
	0.14	<u>1.01</u>
		Average = 0.98
Phenyl Disulfide	0.04	1.06
	0.06	1.23
	0.08	1.14
	0.10	1.25
	0.12	1.12
	0.14	<u>1.25</u>
		Average = 1.18
Hexyl Phenyl Disulfide		1.08
Hexanethiol	0.05	1.01
	0.08	1.03
	0.10	1.05
	0.12	1.06
	0.14	<u>1.07</u>
		Average = 1.05
Phenyl Mercaptan	0.05	1.19
	0.08	1.19
	0.10	1.23
	0.12	1.21
	0.14	<u>1.18</u>
		Average = 1.21

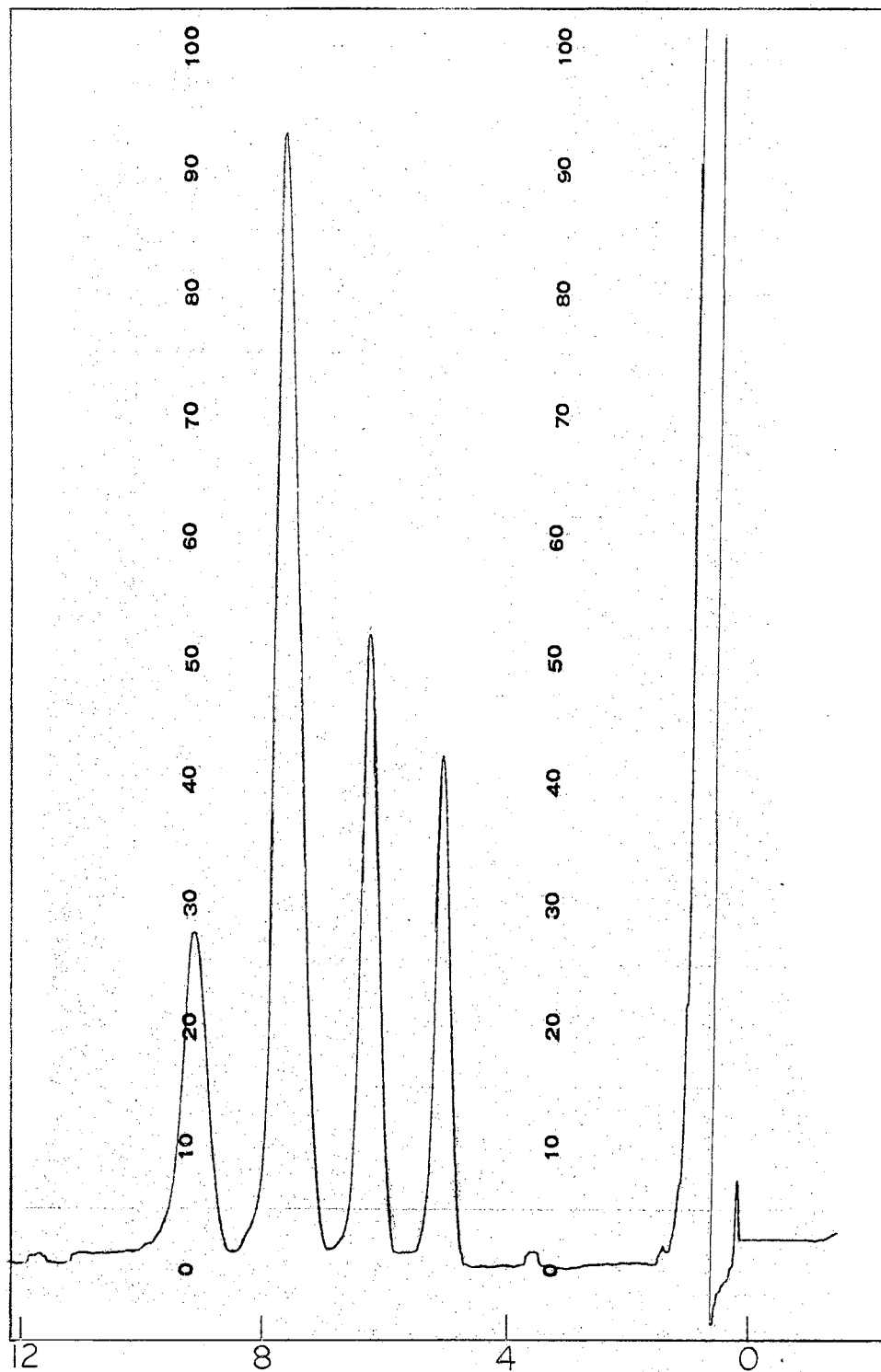


Figure 5. Gas chromatogram of a hexyl disulfide-phenyl disulfide equilibrium mixture. The peaks from left to right are phenyl disulfide, hexyl phenyl disulfide, hexyl disulfide, benzyl ether, and ethanol.

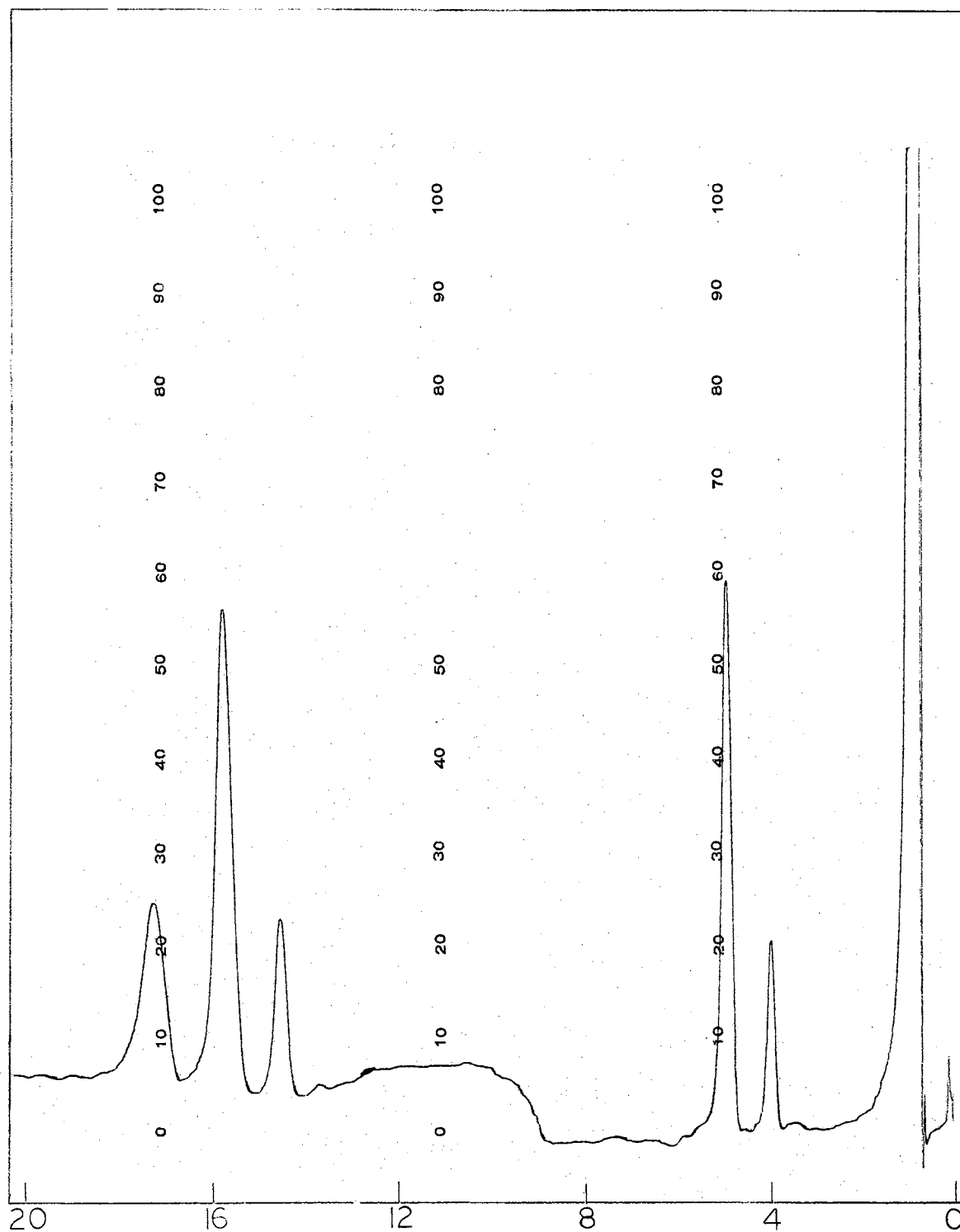


Figure 6. Gas chromatogram of a hexanethiol-phenyl disulfide equilibrium mixture. The peaks from left to right are phenyl disulfide hexyl phenyl disulfide, hexyl disulfide, phenyl mercaptan, hexanethiol, and ethanol.

TABLE VI

EQUILIBRIUM CONSTANTS FOR THE HEXYL -- PHENYL SYSTEM

Reactants	Initial Concentration	K ₁	K ₂	K ₃	K ₄
Phenyl Disulfide	0.2M	7.3	1.02	0.14	0.14
Hexanethiol	0.2M	7.6	1.03	0.14	0.14
Hexyl Disulfide	0.2M	7.7	1.16	0.15	0.17
Phenyl Mercaptan	0.4M	7.7	1.15	0.15	0.17
Hexyl Disulfide	0.2M	8.5			
Phenyl Disulfide	0.2M	8.2			
Hexyl Disulfide	0.15M				
Phenyl Disulfide	0.25M	8.0			
Hexyl Disulfide	0.25M				
Phenyl Disulfide	0.15M	7.7			
Averages =		7.8	1.09	0.15	0.16

Hexyl -- 2-Hydroxyethyl

The 2-hydroxyethyl disulfide was decomposed to some extent on the 8 ft., 5 percent SE-30 column. Therefore, a $\frac{1}{4}$ in. by $5\frac{1}{2}$ ft. column packed with 5 percent SE-30 on 60-80 mesh, acid washed Chromosorb-W was used for this separation. Even with this column the 2-mercaptoethanol and the 2-hydroxyethyl disulfide peaks showed a considerable amount of tailing; as a result the data for this system are somewhat less precise. The helium flow rate was 90 ml./min. The injector temperature was 220°C. and the detector temperature was 260°C. The column temperature was maintained at 80° C. until the two mercaptans were eluted and then increased as rapidly as possible to 180° C. where it was held until the

disulfides were eluted. The column temperature for the disulfide equilibrium samples was 180° C.

The calibration constants are shown in Table VII. Decane was used as the marker compound for the mercaptans and octadecane for the disulfides. Because of the wide variation of the calibration constants of 2-hydroxyethyl mercaptan and disulfide, the constants used in the calculation of the equilibrium constants were those measured at the same concentration as those found in the equilibrium mixture. The equilibrium constants for the reactions are shown in Table VIII. The constants are calculated for $R' = 2\text{-hydroxyethyl}$ and $R = \text{hexyl}$. A representative gas chromatogram of the disulfide equilibrium mixture is shown in Figure 7 and one for the mercaptan-disulfide equilibrium in Figure 8.

Propyl -- s-Butyl

The three disulfides in this system could not be separated on the 8 ft., 5 percent SE-30 column. Therefore, the $\frac{1}{4}$ in. by 8 ft., column packed with 10 percent SE-30 on 60-80 mesh, acid-washed Chromosorb-W was used. A suitable solvent could not be found; therefore, the mercaptan-disulfide equilibrium samples were prepared with only enough methanol to dissolve the sodium methoxide catalyst. The calibration samples were made up in toluene; 1-octanol was used as the marker for the disulfides and isooctane for the mercaptans. The injector temperature was 220° C. and the detector temperature was 260° C. The helium flow rate was 50 ml./min. The column temperature was 75° C. for the mercaptans and 150° C. for the disulfides.

The calibration data are shown in Table IX and the equilibrium constants in Table X. The constants are calculated for $R = \text{propyl}$ and

R' = s-butyl. A representative chromatogram of the disulfide equilibrium mixture is shown in Figure 9; one for the mercaptan-disulfide equilibrium in Figure 10.

TABLE VII
CALIBRATION CONSTANTS FOR THE HEXYL -- 2-HYDROXYETHYL SYSTEM

Compound	Molar Concentration	Calibration Constant
Hexyl Disulfide	0.04	1.06
	0.08	1.02
	0.12	1.10
	0.16	1.04
	0.19	1.09
		Average = 1.06
2-Hydroxyethyl Disulfide	0.08	2.21
	0.17	1.68
	0.25	1.76
	0.33	1.67
	0.41	1.63
		Average = 1.79
2-Hydroxyethyl Hexyl Disulfide		1.42
Hexanethiol	0.07	1.07
	0.15	1.07
	0.22	1.09
	0.29	1.06
	0.36	1.11
		Average = 1.08
2-Mercaptoethanol	0.15	3.48
	0.29	2.60
	0.43	2.35
	0.58	2.07
	0.71	2.24
		Average = 2.54

TABLE VIII
EQUILIBRIUM CONSTANTS FOR THE HEXYL -- 2-HYDROXYETHYL SYSTEM

Reactants	Initial Concentration	K_1	K_2	K_3	K_4
2-Hydroxyethyl Disulfide Hexanethiol	<u>0.2M</u> <u>0.2M</u>	3.8	0.95	0.25	0.24
2-Hydroxyethyl Disulfide Hexanethiol	<u>0.4M</u> <u>0.4M</u>	4.3	1.3	0.30	0.39
Hexyl Disulfide 2-Mercaptoethanol	<u>0.4M</u> <u>0.8M</u>	5.2	1.1	0.21	0.23
Hexyl Disulfide 2-Hydroxyethyl Disulfide	<u>0.2M</u> <u>0.3M</u>	4.9 5.1			
Hexyl Disulfide 2-Hydroxyethyl Disulfide	<u>0.2M</u> <u>0.4M</u>	4.9			
Averages =		4.7	1.1	0.25	0.29

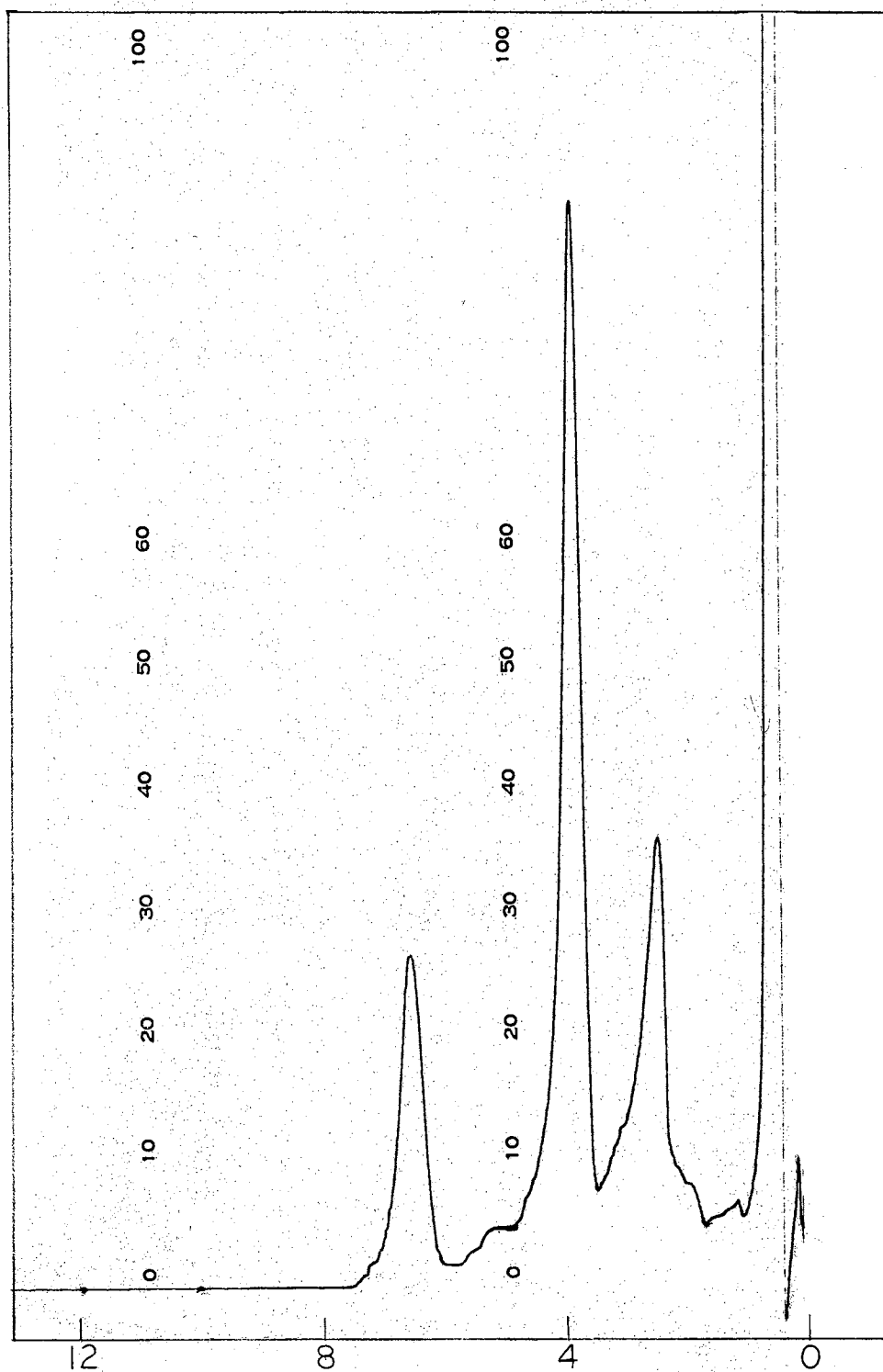


Figure 7. Gas chromatogram of a 2-hydroxyethyl disulfide-hexyl disulfide equilibrium mixture. The peaks from left to right are hexyl disulfide, 2-hydroxyethyl hexyl disulfide, 2-hydroxyethyl disulfide, and ethanol.

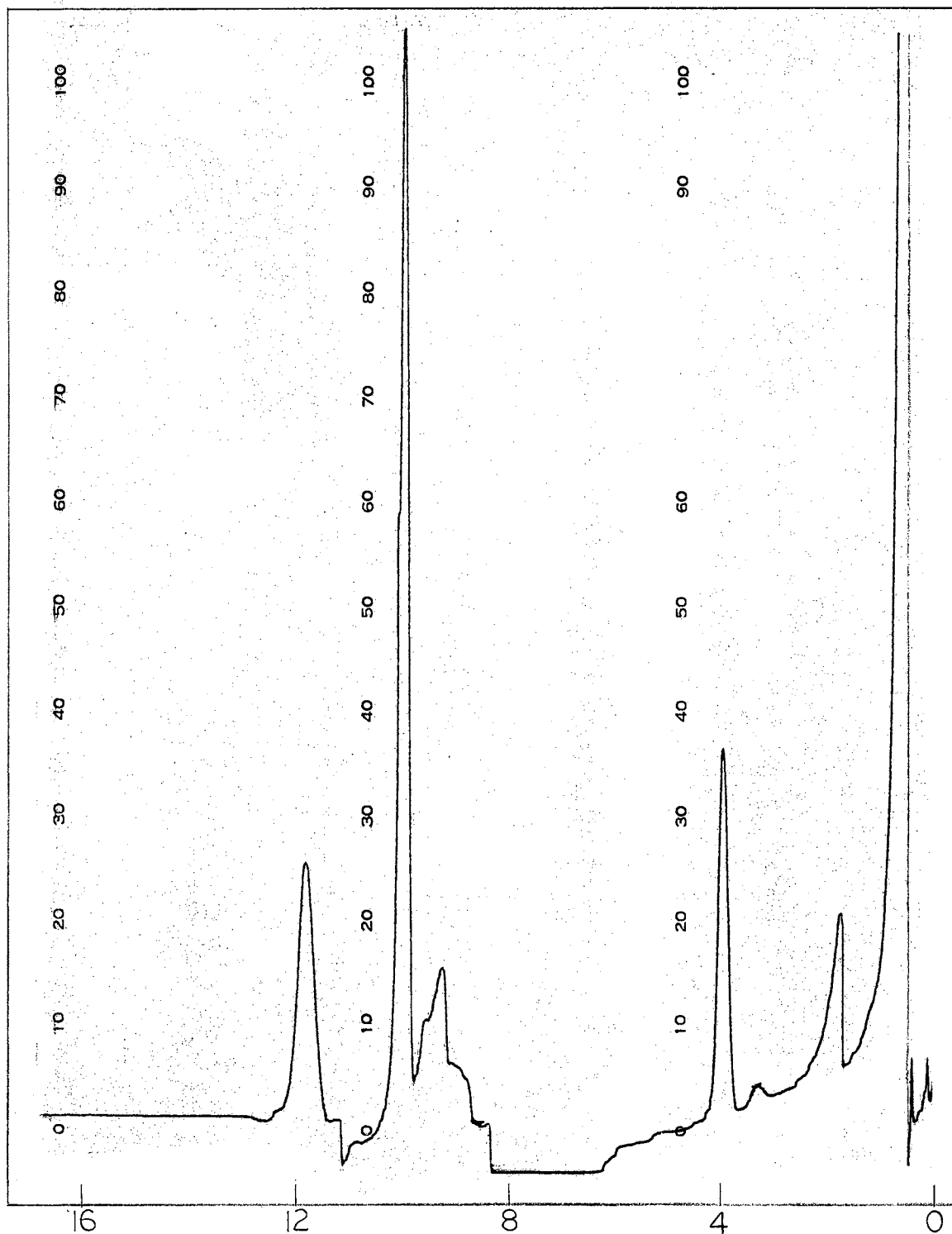


Figure 8. Gas chromatogram of a 2-hydroxyethyl disulfide-hexanethiol equilibrium mixture. The peaks from left to right are hexyl disulfide, 2-hydroxyethyl hexyl disulfide, 2-hydroxyethyl disulfide, hexanethiol, 2-mercaptoethanol, and ethanol.

TABLE IX
CALIBRATION CONSTANTS FOR THE PROPYL -- s-BUTYL SYSTEM

Compound	Molar Concentration	Calibration Constant
Propyl Disulfide	0.06	1.07
	0.08	1.07
	0.10	0.99
	0.12	1.10
	0.14	<u>1.10</u>
	Average =	1.09
<u>s</u> -Butyl Disulfide	0.06	1.19
	0.08	1.23
	0.10	1.21
	0.12	1.17
	0.14	<u>1.24</u>
	Average =	1.20
<u>s</u> -Butyl Propyl Disulfide		1.15
Propanethiol	0.04	1.12
	0.06	0.94
	0.08	1.07
	0.10	1.01
	0.12	1.03
	0.14	<u>0.99</u>
	Average =	1.03
<u>s</u> -Butyl Mercaptan	0.04	0.98
	0.06	1.05
	0.08	1.01
	0.10	1.14
	0.12	1.02
	0.14	<u>0.96</u>
	Average =	1.04

TABLE X
EQUILIBRIUM CONSTANT FOR THE PROPYL -- s-BUTYL SYSTEM

Reactants	Initial Concentration	K_1	K_2	K_3	K_4
Propyl Disulfide <u>s</u> -Butyl Mercaptan	0.002 moles 0.002 moles	4.27	2.17	0.51	1.11
Propyl Disulfide <u>s</u> -Butyl Mercaptan	0.002 moles 0.004 moles	4.25	1.95	0.46	0.90
<u>s</u> -Butyl Disulfide Propanethiol	0.003 moles 0.003 moles	4.00	1.87	0.47	0.88
<u>s</u> -Butyl Disulfide Propanethiol	0.002 moles 0.004 moles	3.93	2.12	0.54	1.15
<u>s</u> -Butyl Disulfide Propanethiol	0.002 moles 0.002 moles	4.25	1.91	0.45	0.86
<u>s</u> -Butyl Disulfide Propyl Disulfide	0.2M 0.2M	4.55 4.21			
<u>s</u> -Butyl Disulfide Propyl Disulfide	0.15M 0.15M	4.36 4.60			
Averages =		4.28	2.00	0.48	0.98

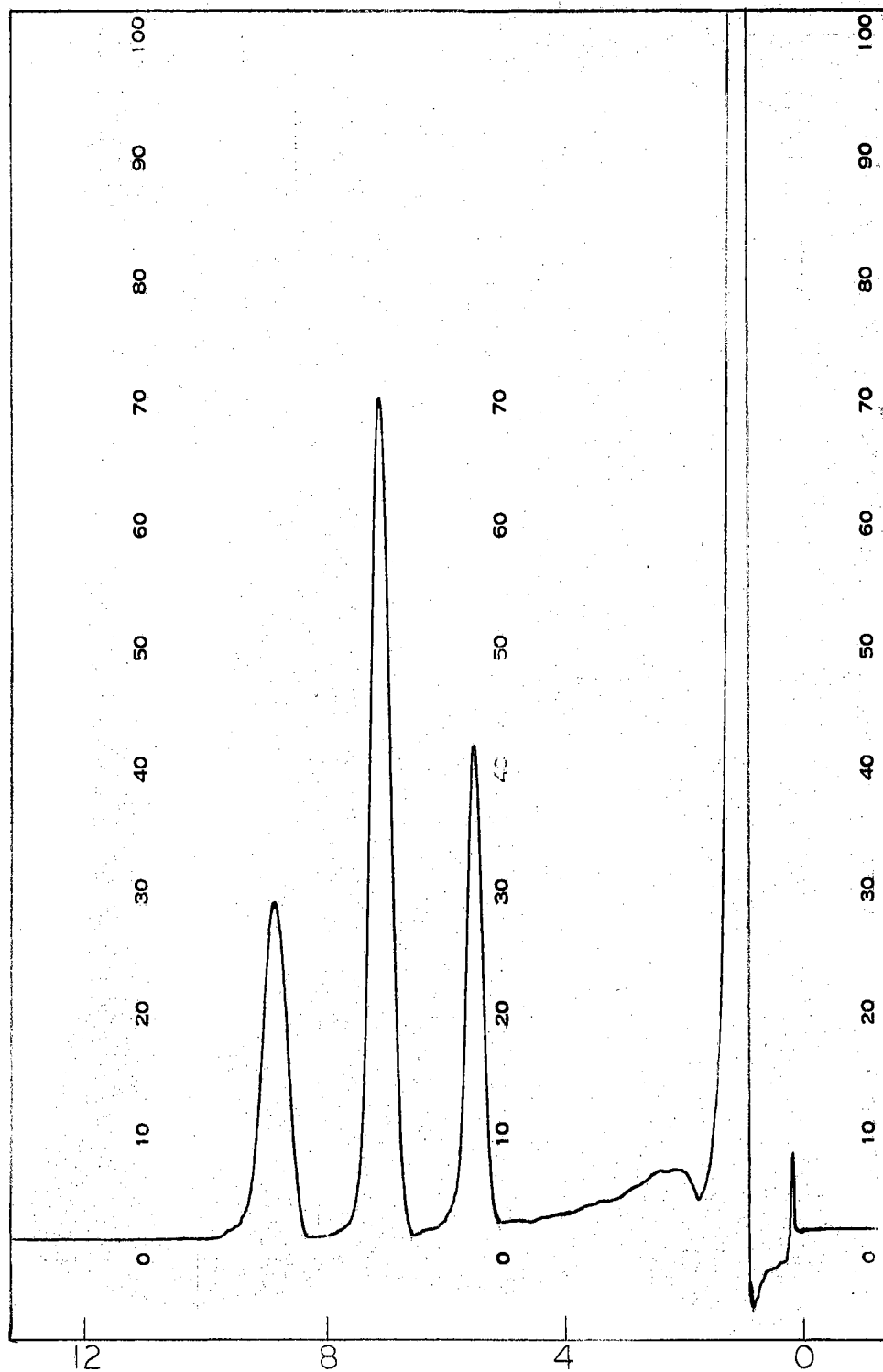


Figure 9. Gas chromatogram of a s-butyl disulfide-propyl disulfide equilibrium mixture. The peaks from left to right are s-butyl disulfide, s-butyl propyl disulfide, propyl disulfide, and ethanol.

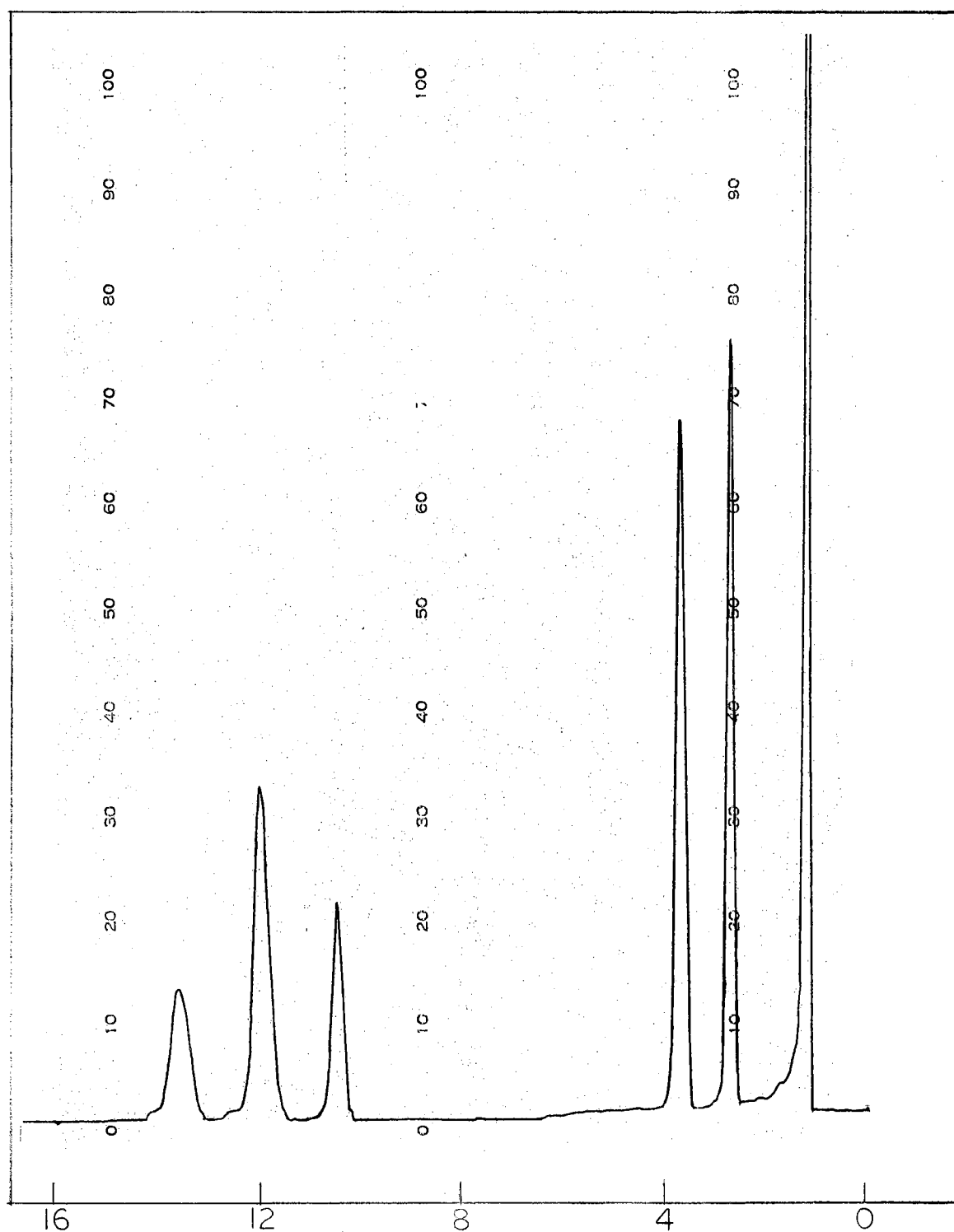


Figure 10. Gas chromatogram of a s-butyl disulfide-propanethiol equilibrium mixture. The peaks from left to right are s-butyl disulfide, s-butyl propyl disulfide, propyl disulfide, s-butyl mercaptan, propanethiol, and methanol.

Hexyl -- 2-Diethylaminoethyl

The disulfides were separated at 180° C. and the mercaptans at 100° C. on a $\frac{1}{4}$ in. by 5 ft., 5 percent Carbowax 20-M on Chromosorb-HMDS column. This column was purchased from the Wilkens Instrument and Research Co. The helium flow rate was 90 ml./min. The temperatures of the injector and detector were 220° C. and 260° C. respectively. The constants were calculated for R = hexyl and R' = 2-diethylaminoethyl.

The calibration constants are given in Table XI. Tetradecane and hexadecane were used as the marker compounds for the mercaptans and disulfides respectively. The equilibrium data are given in Table XII. Representative chromatographs are shown in Figures 11 and 12 for the disulfides and the mercaptan-disulfides respectively.

TABLE XI
CALIBRATION CONSTANTS FOR THE HEXYL -- 2-DIETHYLAMINOETHYL SYSTEM

Compound	Molar Concentration	Calibration Constant
Hexyl Disulfide	0.06	1.28
	0.07	1.32
	0.11	1.19
	Average =	<u>1.26</u>
Bis(diethylaminoethyl) Disulfide	0.06	1.53
	0.07	1.58
	0.08	1.51
	Average =	<u>1.54</u>
2-Diethylaminoethyl Hexyl Disulfide		1.40
Hexanethiol	0.10	0.86
	0.14	0.92
	0.16	0.89
	0.22	0.88
	0.29	0.89
	Average =	<u>0.89</u>
2-Diethylaminoethanethiol	0.10	1.10
	0.14	1.25
	0.16	1.13
	0.20	1.05
	0.27	1.06
	Average =	<u>1.12</u>

TABLE XII
EQUILIBRIUM CONSTANTS FOR THE HEXYL -- 2-DIETHYLAMINOETHYL SYSTEM

Reactants	Initial Concentration	K_1	K_2	K_3	K_4
Hexyl Disulfide 2-Diethylaminoethanethiol	0.4M 0.6M	5.25	1.31	0.25	0.33
Hexyl Disulfide 2-Diethylaminoethanethiol	0.3M 0.3M	4.48	1.30	0.29	0.38
Bis(2-Diethylaminoethyl) Disulfide Hexanethiol	0.3M 0.3M	6.62	1.26	0.19	0.24
Bis(2-Diethylaminoethyl) Disulfide Hexyl Disulfide	0.3M 0.3M	5.08 5.85			
Bis(2-Diethylaminoethyl) Disulfide Hexyl Disulfide	0.4M 0.4M	4.98 5.08			
Averages =		5.33	1.29	0.24	0.32

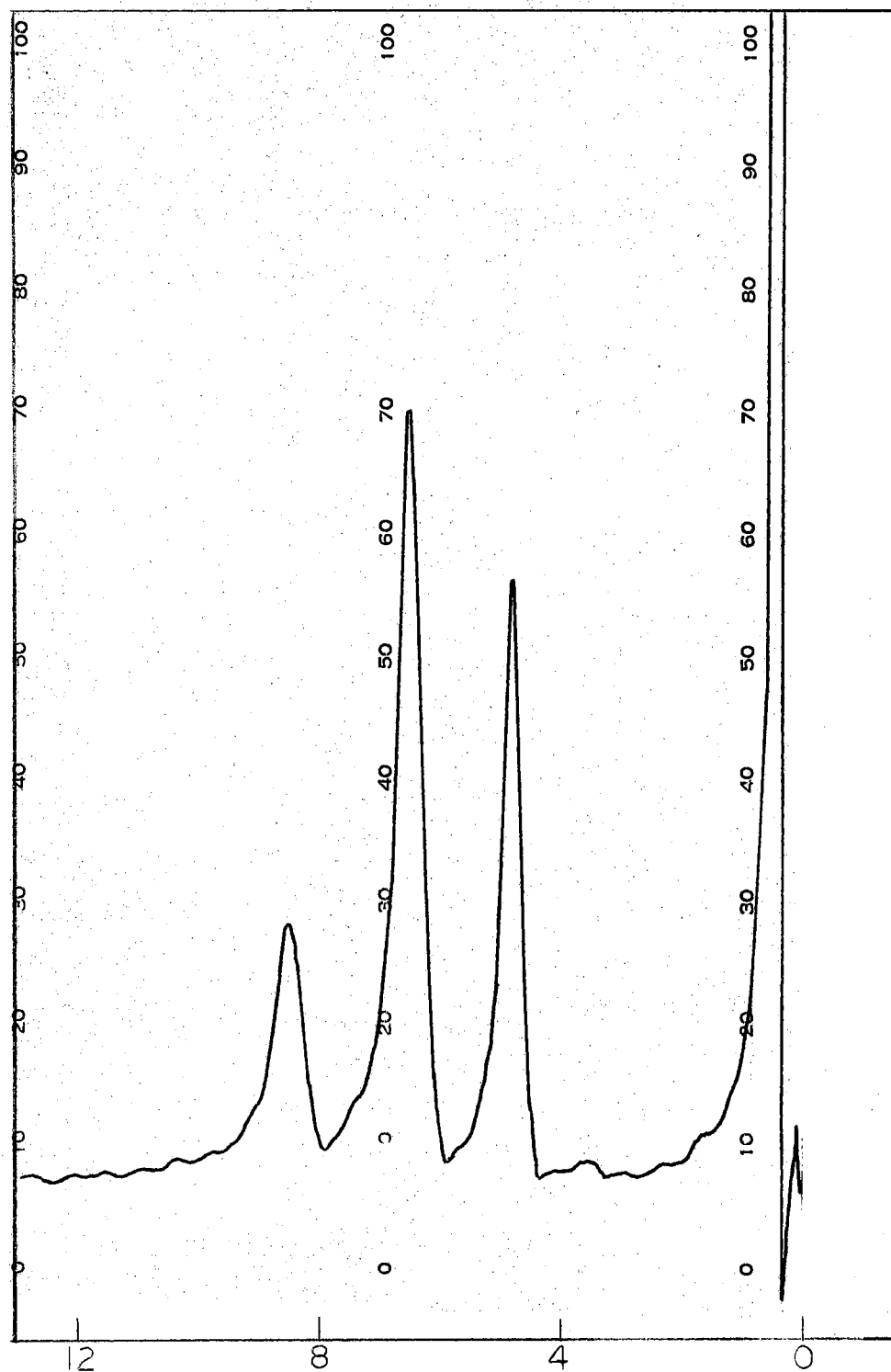


Figure 11. Gas chromatogram of a 2-diethylaminoethyl disulfide-hexyl disulfide equilibrium mixture: The peaks from left to right are bis(2-diethylaminoethyl) disulfide, 2-diethylaminoethyl hexyl disulfide, hexyl disulfide, and ethanol.

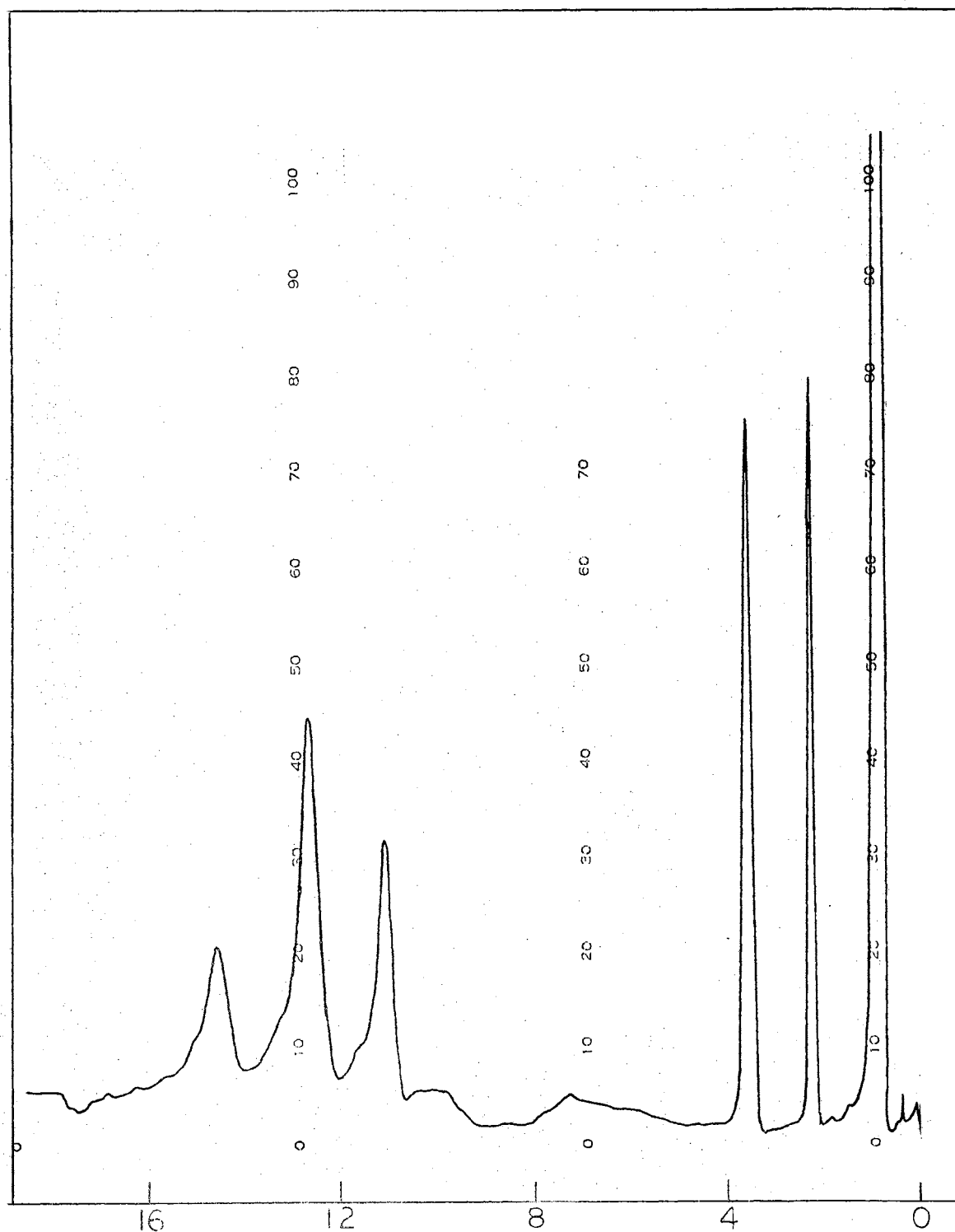


Figure 12. Gas chromatogram of a 2-diethylaminoethanethiol-hexyl disulfide equilibrium mixture. The peaks from left to right are bis(2-diethylaminoethyl) disulfide, 2-diethylaminoethyl hexyl disulfide, hexyl disulfide, 2-diethylaminoethanethiol, hexanethiol, and ethanol.

CHAPTER III

DISCUSSION

The equilibrium constant of the disulfide exchange reaction is influenced almost exclusively by steric factors. This was illustrated by the work of Haraldson (76), where a large deviation from the statistically expected value was found only in the case of the reaction between ethyl disulfide and t-butyl disulfide. In the present study it was found that the only value of K_1 that differed from the statistical value by a factor of two was that for the reaction of phenyl disulfide and hexyl disulfide. The value of K_1 was increased slightly for compounds containing electron-withdrawing substituents. It would appear that steric factors are the only influence.

The constant K_2 depends mainly on electronic effects; electron-withdrawing groups on R' will decrease K_2 . Electron-withdrawing substituents also increase the acid strength of the mercaptan involved. A semi-quantitative relationship between ΔpK , the ratio of the negative logarithm of the ionization constants of the two mercaptans, and ΔK_2 , the ratio of the observed equilibrium constant and the statistically expected one, was found in this study. The ΔpK for the phenyl -- hexyl system is 1.5 and ΔK_2 is 1.8.² The ΔpK for the hexyl -- 2-hydroxyethyl system is 1.2 and ΔK_2 is 1.8. In this case the

²For values of the ionization constants see part I.

correlation is not as good, probably because the equilibrium constants determined for this system are not too precise. In the hexyl -- 2-diethylaminoethyl system ΔpK is 1.5 and ΔK_2 is 1.5. The ΔK_3 for the phenyl -- hexyl system is 3.5 which is a much larger deviation from statistical than can be accounted for on the basis of the difference in the ionization constants of the mercaptans. This shows that K_3 is influenced both by electronic and steric factors as is expected. The ΔK_3 for the hexyl -- 2-hydroxyethyl system and the hexyl -- 2-diethylaminoethyl system is 2.1.

All the equilibrium constants for the propyl -- s-butyl system are very close to the statistically expected values because there are no large electronic or steric factors involved in these cases.

An attempt was made to study the hexyl -- t-butyl system, but equilibrium was not established in a reasonable length of time (20 days) at 25° C. This slow reaction of the t-butyl compound was also observed by others (64,76).

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