THE REACTIONS OF SULFUR TRIOXIDE, AND OF ITS ADDUCTS, WITH ORGANIC COMPOUNDS

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I. INTRODUCTION

Several events have occurred during recent decades which have led to increased interest in the reactions and derivatives of sulfur trioxide. It was, for the first time, made cheaply available in stabilized liquid form for use as a laboratory and commercial reagent, and it is now so marketed by several companies in various countries. Laboratory research and industrial practice have since established acceptable methods for its handling and use. Secondly, the discovery of its complex with dioxane has led to widespread research on this new approach to modifying the high reactivity of sulfur trioxide in reactions with a variety of organic compounds. Recent study of the older sulfur trioxide–pyridine complex likewise has shown new or broadened uses for it in sulfating dyes, carbohydrates, and sterols, and for sulfonating polycyclic compounds and acid-sensitive heterocyclics. In addition, greatly increased commercial production of certain sulfonates, especially surface-active agents and ion-exchange resins, has resulted in a corresponding increase in interest in the stronger, and possibly more efficient, reagents—particularly sulfur trioxide itself.

This review is intended to cover all pertinent reference to the reactions of sulfur trioxide, and its organic complexes—which in effect means principally those derived from dioxane and pyridine—with organic compounds through 1960. Not included are the reactions of sulfuric acid, or of sulfur trioxide as dissolved in it (oleum), or of the inorganic complexes of sulfur trioxide. The reactions most often encountered herein are these

Sulfonation (formation of a carbon-to-sulfur bond)

$$RH \xrightarrow{SO_3} RSO_3H$$

Sulfation (formation of an oxygen-to-sulfur bond)

$$ROH \xrightarrow{SO_3} ROSO_3H$$

Sulfamation (formation of a nitrogen-to-sulfur bond)

$$R_2NH \xrightarrow{SO_3} R_2NSO_3H$$

Sulfamation is sometimes termed "N-sulfonation." The above three reactions also apply to the sulfur trioxide complexes, since the complexing reagent can be regarded as simply modifying the degree of the reactivity of the sulfur trioxide. Reference is also made herein to cases in which organic compounds are oxidized, rather than sulfonated, by the reagents considered. As might be expected, the large size of the sulfonic acid group—about equal to that of *tert*-butyl (82)—is often an important factor in determining its degree of reactivity or place of reaction, and numerous references to steric factors are therefore made throughout.

Although this review is the only one known to be restricted to consideration of the reactions of sulfur trioxide and of its organic complexes, reference works (160, 196, 336, 373, 443, 453) and reviews (annually in *Industrial and Engineering Chemistry*, covering from 1941 to date) treat broadly the entire field of sulfonation (*i.e.*, the above reactions) as accomplished by other reagents (*i.e.*, sulfuric acid, oleum,

chlorosulfonic acid, and sulfamic acid), as well as by those considered herein. Nomenclature in this review follows *Chemical Abstracts*, or that used in the original publication.

II. PROPERTIES OF SULFUR TRIOXIDE

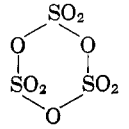
The chemistry of SO_3 is complicated and only partially known. It exists in the monomeric and in several polymeric forms. The vapor appears to be monomeric. Freshly distilled SO_3 is a water-white liquid, indicated by Raman spectral analysis to comprise approximately 90% of the trimeric, or γ-form (formula I), and 10% monomer (208), or, as reported by others (527) 20% trimer and 80% monomer. Some of the properties of liquid SO_3 are summarized in Table I (8, 331a).

TABLE I

PHYSICAL PROPERTIES OF LIQUID SULFUR TRIOXIDE

Boiling point (°C.)		44.8
Melting point (°C.)		16.8
Density (20°)		1.9224
Specific heat (cal./g., 25–35°):		0.77
Heat of dilution (cal./g.)		504
Heat of vaporization (cal./g.)		127.4
Viscosity (centipoises 30°)		1.590
Critical temperature (°C.)		218.3
Critical pressure (atm.)		83.8
Critical density		0.633
van der Waals constants	a =	2.105
	b =	0.964

If the freshly distilled liquid is exposed to even a trace of moisture, or is kept standing in a sealed ampoule at room temperature for a short time, it reverts to solid polymers of various possible chain lengths (formula II) and degrees of crosslinking and with correspondingly varied physical properties. Although solid SO_3 has been used to a minor extent in the laboratory for making complexes, and for conversion to SO_3 vapor by heating, it has not been considered a commercially practical compound because of its variability, difficulty in handling, and the high increase in vapor pressure occurring during vaporization (8).



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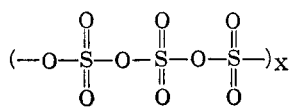


II

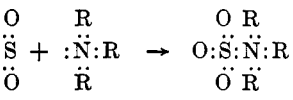
The discovery that liquid SO_3 could be stabilized satisfactorily against polymerization to solids by the addition of small quantity (as low as 0.1%) of various compounds—especially derivatives of boron, phosphorus, or sulfur—resulted in its commercial introduction in 1947 (70, 181).

For laboratory purposes, SO_3 in liquid form may involve use of the freshly distilled, or of the stabilized commercial, material. The vapor is available by distillation of the latter, or by heating oleum. On a commercial scale, the stabilized liquid can be employed directly in some cases, but more often it is vaporized and diluted with dry air before reaction with an organic compound. The vapor form is also obtained commercially by distillation from oleum, or from sulfuric acid plant converter gas, which contains 5 to 10% SO_3. Sulfur trioxide is miscible in all proportions with liquid SO_2 and with various chlorinated, and chlorinated-fluorinated, organic solvents. Their extensive use in organic reactions is cited in the review in the individual cases involved.

III. SULFUR TRIOXIDE COMPLEXES

Since these compounds are cited constantly throughout this review, their preparation and general properties are discussed separately in this section, with special reference to those in most common use.

Sulfur trioxide, being an electron acceptor or Lewis acid, combines with electron donors or Lewis bases, to form coördination compounds, also known as "adducts" or "complexes."



The bases employed may be tertiary amines—including those which are fairly strong (*i.e.*, trimethyl- or triethylamines), or considerably weaker (pyridine or dimethylaniline). Other even weaker bases used include tertiary amides, ethers and thioethers. The stability of the complex in general varies directly as the strength of the base used. Correspondingly, the reactivity of the complex varies inversely as the strength of the base used. Basic strengths of several amines used for preparing SO_3 complexes are given in Table II (232). When the adduct is employed for sulfonating an organic compound, the SO_3 is released and the base forms the salt of the new sulfonic acid

$$RH + SO_3 \cdot Base \rightarrow RSO_3H \cdot Base$$

Even the weakest complex is a much milder reagent than free SO_3. It is possible to moderate the reactivity of SO_3 to any desired degree by the correct choice of a complexing basic material.

TABLE II

BASIC STRENGTHS OF SOME AMINES USED FOR SO_3 COMPLEXES

Amine	pK_a, H_2O
Trimethylamine	10.72
Triethylamine	10.74
Dimethylaniline	5.06
Diethylaniline	6.56
Pyridine	5.22
2-Methylpyridine	5.96
2,6-Dimethylpyridine	6.72
N-Ethylmorpholine	7.70

Basic strength is not the only factor determining the reactivity of an SO_3 complex, however. Trimethylamine, although equal in basic strength to triethylamine yields a complex which is more stable and less reactive

(11). Likewise, an increasing degree of methylation in the 2 and 6 positions of pyridine does not greatly affect basic strength, but does markedly increase product yields in certain sulfamation reactions (440), as is discussed subsequently in more detail.

A. SULFUR TRIOXIDE–PYRIDINE

This complex often has been prepared by direct reaction of SO_3 with the base. A 90% yield was noted by adding pyridine to solid SO_3 suspended in carbon tetrachloride (46, 53). A quantitative yield of the theoretical assay was obtained with chloroform as solvent (458). Addition of pyridine in 1,2-dichloroethane at 0° to SO_3 dissolved in the same solvent gave a 95% yield (413). The Soviet investigator, A. P. Terent'ev, who has worked extensively with this adduct, adds equivalent dry pyridine, with cooling and stirring, to SO_3 in 1,2-dichloroethane; the product is filtered and dried rapidly at 100° (464). A 97% yield assaying 93 to 96% resulted from the addition of liquid SO_3 to SO_2–pyridine dissolved in liquid SO_2 (198); these reaction conditions are extremely mild. Addition of liquid SO_3 to pyridine gives a product of 87% purity (374). Sulfur trioxide can be vaporized into pyridine (102). The complex also has been prepared by bringing together the two components in equivalent quantities without a solvent, either in a heavy-duty mixer below 20° (459), or as finely divided mists or vapors entrained in dry air (61, 62).

Reaction of pyridine with $ClSO_3H$ immediately yields SO_3-pyridine and a mole of pyridinium chloride (46, 420, 525)

$$ClSO_3H + 2C_5H_5N \rightarrow SO_3 \cdot C_5H_5N + C_5H_5N \cdot HCl$$

With chloroform as reaction solvent at 0° (420, 458) a 62% yield is obtained; the complex separates and can be filtered while the pyridinium chloride remains dissolved in the filtrate. A common sulfating mixture for carbohydrates, sterols, and other sensitive compounds, is $ClSO_3H$ added to excess pyridine, no effort being made to remove the pyridinium chloride. It has been suggested, however, that the pyridinium chloride, at least in one case, has a detrimental effect if present during sulfation (326). Sulfur trioxide and $ClSO_3H$ are reported to form adducts of the same purity (about 92%) and melting point (97 to 100°) (380). Heating dry sodium pyrosulfate with pyridine for 30 minutes at 95° also yields the complex (37). Potassium pyrosulfate, either anhydrous at 115° (39), or in cold aqueous solution (51), can also be used. Ethyl chlorosulfonate forms the adduct (46, 525)

$$2C_5H_5N + C_2H_5OSO_2Cl \rightarrow SO_3 \cdot C_5H_5N + C_5H_5N \cdot ClC_2H_5$$

It has also been made by adding ice to a mixture of pyridine and sulfuryl chloride (48)

$$3C_5H_5N + SO_2Cl_2 + H_2O \rightarrow SO_3 \cdot C_5H_5N + 2C_5H_5N \cdot HCl$$

Sulfur trioxide–pyridine is available commercially (7).

The pyridine complex is a white solid variously reported to melt at 97 to 100 (380), 121 (458), 137 (331), 155 (525), and at 175° (46). These data all refer to various preparations of crude product, since no method for purifying SO_3–pyridine has as yet been suggested, aside from trituration with ice water to remove pyridinium sulfate (46). The lack of purification methods is explainable by its salt-like character, with its consequent low volatility and low solubility in nearly all common solvents, as mentioned below.

It is quite stable to, and insoluble in, cold water and cold aqueous alkali, but rapidly decomposes completely upon warming in both media (46). It is insoluble (*i.e.*, less than 1% by weight) in pyridine, nitrobenzene, cyclohexane, methylcyclohexane, *n*-hexane, chloroform, carbon tetrachloride, dioxane, ethyl ether, *n*-butyl benzenesulfonate, and acetone at 25° (374). It is soluble in dimethylformamide (9), and forms at least a 20 weight % solution in liquid SO_2 at −10° (9). The complex also dissolves in concentrated sulfuric, perchloric, and hydrochloric acids (49), from all of which it can be precipitated unchanged by dilution with cold water.

Sulfur trioxide–pyridine has been used extensively as a laboratory reagent for sulfating alcohols, sterols, and carbohydrates, for sulfamating amines and proteins, and for sulfonating acid-sensitive heterocyclic compounds and alkadienes; these reactions are run at moderate temperatures, usually below 120° in the presence of excess pyridine or a solvent such as 1,2-dichloroethane. It has been used for sulfating on a semimicro scale (177). Even upon prolonged heating at 150°, this complex does not react with paraffins, cycloparaffins, non-terminal olefins, benzene and its homologs, stilbene, anthracene, fluorene, or triphenylethylene (464). Slow reaction occurs with terminal olefins, resulting in a poor yield of sulfonate. At 170°, it sulfonates naphthalene, phenol, and aniline (47), but these reactions can be effected more rapidly with other cheaper reagents. It has been used somewhat commercially for sulfating oleyl alcohol and the leuco forms of vat dyestuffs.

Pyridine also forms a complex with two moles of SO_3. It has been prepared by the addition of SO_3 to pyridine dissolved in liquid SO_2 (198), or by the addition of SO_3 to SO_3–pyridine suspended in 1,2-dichloroethane (475). It melts at 83–85° (475). The second mole of sulfur trioxide is much more reactive than the first. Work with this adduct has been very limited; the Soviet group headed by A. P. Terent'ev has employed it for sulfonating heterocyclic compounds. The complex is designated herein as "2 SO_3-pyridine."

B. SULFUR TRIOXIDE–DIOXANE

Dioxane can react with one or two moles of SO_3

$$O(CH_2CH_2)_2O \xrightarrow{SO_3} SO_3O(CH_2CH_2)_2O \xrightarrow{SO_3} SO_3O(CH_2CH_2)_2OSO_3$$

Nearly all of the fairly extensive work with this complex has been with the 1-to-1 product and it is this product which is referred to herein as "SO_3–dioxane."

Although early work (449) indicated that the two adducts have similar properties and reactivity, there is some evidence that the SO_3-to-dioxane ratio may play a role, at least in sulfonating aromatic hydrocarbons. The 2-to-1 adduct sulfonates benzene at room temperature in one day (444, 449); however, in the presence of a large excess of dioxane, it did not react in 72 hours, even at elevated temperature (374). The 2-to-1 complex sulfonates polystyrene rapidly and completely at 5° (35), but if more than two moles of dioxane are used per mole of SO_3, the reaction is extremely slow and incomplete. As is pointed out below, the complex with bis(2-chloroethyl) ether behaves similarly.

Liquid SO_3 can be added carefully with cooling to undiluted dioxane (207, 374), or to a mixture of dioxane (207, 374), or to a mixture of dioxane and 1,2-dichloroethane (35, 422). Sulfur trioxide vapor can be passed into a mixture of dioxane and 1,2-dichloroethane (420, 449) or carbon tetrachloride (444); the solid adduct crystallizes and can be filtered. With $ClSO_3H$ below 20° dioxane does not form a solid adduct, but yields a liquid miscible in all proportions with 1,2-dichloroethane (450); at 20° hydrogen chloride is evolved, and SO_3-dioxane apparently is formed.

Sulfur trioxide–dioxane, being unstable, usually is prepared immediately before use. The solid adduct can decompose violently on standing for some time at room temperature (420); upon heating, it decomposes at 75° (449). At 0° in solution it has been found to decompose to the extent of 9% in 0.5 hour, and 13% in 20 hours (81). Upon contact with water, the complex is immediately converted to dioxane and sulfuric acid (449). It is therefore considerably more reactive than SO_3-pyridine.

Since its discovery in 1938, SO_3-dioxane has been employed extensively in the laboratory, mainly for sulfonating alkenes and for sulfating alcohols.

Like dioxane, 1,4-benzodioxane complexes with one or with two moles of SO_3 (373).

C. SULFUR TRIOXIDE–TRIMETHYLAMINE

This complex has been prepared by direct vapor phase interaction of SO_3 and trimethylamine without (103) a solvent. However, reaction solvents, such as chloroform (339) or liquid SO_2 (198), usually have been employed. Use of the latter entails exceptionally mild conditions, since the reaction is run at −10° with the solvent functioning as a refluxing autorefrigerant, and the heat of reaction is reduced by first forming the SO_2-amine complex. Alternative preparative methods have involved reaction of the amine with $ClSO_3H$ (237) using chlorobenzene as solvent at 10° or with cold aqueous SO_3–pyridine (47). It also has been made by treating dimethyl sulfate with tetramethylsulfamide (301) or by simply heating methyl dimethylsulfamate (503). This complex has been (11), and is (7), available on a semi-commercial scale.

Sulfur trioxide–trimethylamine is a stable solid melting with decomposition at 239° (103). It has generally low solubility in organic solvents with which it does not react; 3 g. dissolves in 100 ml. of acetone at 56° (11). However, it is soluble in dimethylformamide (9, 545), and liquid SO_2 gives an 18.5 weight % solution at 0° (103). At 25°, 1.5 g. dissolves in 100 ml. of water; at 50°, 10.8 g. dissolves (11). It dissolves in perchloric acid (49).

This SO_3 complex is the most stable of those studied to date, considerably more so than that derived from pyridine. The stability follows from the greater basic strength of trimethylamine compared with that of pyridine, as shown in Table I. This high degree of stability permits its use in aqueous systems. At 50° in the presence of 25 weight % water, it is 6.4% hydrolyzed in 24 hours (11). Stability in aqueous sodium hydroxide is given in Table II (11).

TABLE III

HYDROLYSIS OF SO_3-TRIMETHYLAMINE IN AQUEOUS SODIUM HYDROXIDE

0.18 g. per g. of water for 24 hours at room temperature

% NaOH	% Hydrolyzed
0.93	10.3
0.93	10.3
4.5	46.4
8.6	88.4

Usually, loss of this reagent by hydrolysis is minor since the compound being sulfated in aqueous medium reacts more easily.

The trimethylamine complex has been used in the laboratory for sulfating alcohols, starch, leuco vat dyestuffs and phenols, and for sulfamating aromatic amines and proteins. Many of these reactions, which are discussed in more detail in later sections, can be conducted in aqueous medium, which is commercially advantageous. A potential disadvantage in some cases is the persistent and unpleasant odor of small residual quantities of the free amine.

D. SULFUR TRIOXIDE–TRIETHYLAMINE

This complex has been prepared by the interaction of SO_3 vapor with that of the amine (64), by adding liquid SO_3 to the amine dissolved in carbon tetrachloride (331, 339), or by adding $ClSO_3H$ to the amine in chlorobenzene at 10° (237).

In general, the chemical behavior of this complex is similar to that of trimethylamine (11). Although the

two bases have nearly the same strength, as shown in Table II, the adduct from triethylamine is, somewhat surprisingly, less stable and more reactive. The triethylamine complex melts at 93.0°, but it has been recommended that it be stored under refrigeration (11). It is fairly soluble in acetone and in 1,2-dichloroethane, therein differing from the trimethylamine complex. At 25°, 2.7 g. dissolves in 100 ml. of water, which is double the solubility of the other adduct. Both complexes are sufficiently stable to be used in aqueous medium. The adduct sulfates polysaccharides in dimethylformamide solution even at 0°, an interesting technique which may find wider application where extremely mild conditions are required (545). The triethylamine adduct has a high oral toxicity (11). It has been (11) and is (270a) available in research quantities.

E. SULFUR TRIOXIDE–DIMETHYLANILINE

Direct reaction of the base with SO_3 yields the complex (547), which also is formed by adding the SO_3 to the base predissolved in liquid SO_2 (198). However, two investigators report difficulty in preparing the adduct using SO_3, even when employing a solvent (102, 374). The base also reacts with a half-molar proportion of $ClSO_3H$ using as reaction solvents carbon disulfide (102), or chloroform at 0° (420, 547): this procedure gives a 62% yield. Ethyl chlorosulfonate (547) and potassium pyrosulfate (102) likewise give the complex.

This complex is reported to melt at 85 to 90° (331). Upon heating at 60°, however, it rearranges to the para-sulfonic acid (547). The complex has been studied to a limited extent for sulfating alcohols, phenols and leuco dyes, and for sulfamating alkyl aryl amines. It resembles SO_3–pyridine in general reactivity, since—as shown in Table II—the two bases have about the same strength. However, the dimethylaniline complex decomposes above 60°, while SO_3-pyridine has been used even at 170°.

F. SULFUR TRIOXIDE–THIOXANE

This complex (340, 341) is formed by the reaction of thioxane with either SO_3 or $ClSO_3H$ in carbon tetrachloride or 1,2-dichloroethane as solvent. The 1-to-1 adduct is a solid melting with decomposition at 124°. It is slightly soluble in carbon tetrachloride, chloroform, 1,2-dichloroethane, and ethers, but is easily soluble in thioxane itself, from which it may be recrystallized. Like dioxane, thioxane also forms a 1-to-2 adduct which melts at 99° with evolution of SO_3; its solubility behavior resembles that of the 1-to-1 complex, to which it is converted by contact with thioxane. Limited study of the 1-to-1 complex has shown (340, 341) that, like the dioxane analog, it sulfonates alkenes and sulfates alcohols. It may, therefore, have no advantages over the dioxane complex. Thioxane itself has a higher boiling point and lower solubility in water than dioxane, but it is more expensive.

G. SULFUR TRIOXIDE–BIS(2-CHLOROETHYL) ETHER

This complex, made by adding SO_3 to the ether (34, 448), has been used for sulfating higher secondary alcohols (298) at −10°, and for sulfonating polystyrene at −2° using 1,2-dichloroethane as solvent (34). In the latter case, the reaction is too violent if less than 1.5 moles is used per mole SO_3, and too slow and incomplete with more than 3.

H. SULFUR TRIOXIDE–2-METHYLPYRIDINE

Chloroform has been used as solvent for preparing this complex, made by adding liquid SO_3 at 10 to 20° (458). The complex also has been prepared from $ClSO_3H$ and excess base (440) below 30°, the by-product pyridinium chloride not being removed in this case. The adduct, and the 2,6-dimethyl analog, are stated to give considerably higher yields than SO_3–pyridine in sulfamating certain aromatic amines (440).

Mixed methylpyridines react with SO_3 without a solvent in a heavy duty mixer at 0 to 40° (459).

I. SULFUR TRIOXIDE–QUINOLINE

This complex has been prepared by the addition of liquid SO_3 to quinoline dissolved in 1,2-dichloroethane (374), or by heating the base with an alkali metal pyrosulfate (38). The former procedure gave a product of 84 to 88% purity, which was found (374) to be insoluble in hot or cold *o*-dichlorobenzene, *n*-butyl benzenesulfonate, *n*-hexane, methylcyclohexane, ethyl ether, dioxane, tetrachloroethylene, acetone or amyl acetate. In dimethylformamide it is slightly soluble cold, but very soluble hot; in acetic acid, it is very soluble, either hot or cold. It does not sulfonate benzene or xylene, but dissolves readily in monoethanolamine, probably with reaction.

J. SULFUR TRIOXIDE–DIMETHYLFORMAMIDE

Addition of liquid (124, 374, 550) or vaporized (277) SO_3 to excess liquid amide, with stirring and cooling, is the usual procedure for preparing this complex. In one case (185), two pounds of SO_3 was added dropwise to eleven liters of amide in 4 to 5 hours at 0 to 5°. The adduct also can be made from the amide and methyl chlorosulfonate (125). The excess amide functions as an excellent solvent, not only for the adduct itself, but for an exceptionally wide variety of organic compounds. A 2.5 *N* solution is completely stable for two months at −40°; at −5° 3% decomposes in one month (120). Another report (185) states that its efficiency is

unimpaired after 4 months at 0°, even though it turns yellow and finally orange. The stability of this complex, and the fact that it can be pipetted conveniently (277, 550) are unusual advantages, since the common amine complexes are only slightly soluble in organic solvents, and the dioxane adduct has poor stability. Since dimethylformamide is a very weak base, this adduct is highly reactive, even below room temperature. It has not been isolated and characterized, although it separates as a white solid from concentrated solutions. Comparatively little work has as yet been done with this unusual adduct. It has been shown to sulfamate amino groups and to sulfate hydroxyl groups in chitosan (550), to sulfate leuco dyes (388), and to form acyl sulfates from peptides (120, 276, 277) and from lysergic acid (185).

K. MISCELLANEOUS COMPLEXES

Reaction of SO_3 with the base has been employed to prepare adducts from tri-*n*-propylamine (318), tri-*n*-butylamine (331), and from N-alkylated morpholines (methyl, ethyl and *n*-butyl) (234, 304, 459). The reaction of pentamethylguanidine, a strong base, with SO_3–triethylamine takes place in preference to that with free SO_3 (239); the complex dissolves in water to give a stable, non-acid solution.

Amide adducts include those made from N-methylacetanilide, N,N-diethyl-4-toluenesulfonamide, tetramethylurea, N,N-dimethylurethane, formylmorpholide, tetramethyladipamide, N,N-dimethylbenzamide (124), N-alkyl ethylene carbamates (424, 425), and dimethylcyanamide (235).

N-Propyl-, N-isoamyl-, and N-benzylpiperidine oxides are stated to form the SO_3 complexes by reaction with SO_2 (23). However, another report (302) states that the amine oxide–SO_2 complexes are different from the amine–SO_3 adducts. Triethylamine oxide was converted to an SO_3 adduct (302) by reaction with SO_3–triethylamine. The pyridine oxide adduct was prepared by treating the oxide hydrochloride with SO_3 (55). An SO_3–trimethylphosphine oxide complex was made from the oxide and SO_3 (104).

Adducts were made by direct reaction of SO_3 with tetrahydrofuran (374) and with diethyl sulfide (168). Acetone is stated to form a complex at −20° in the presence of an inert solvent (74); low temperature is essential, since acetone sulfonates easily. Anthraquinone forms 1:1 and 1:2 complexes (130). Similarly, polycyclic mono- and diketones (benzanthrone, benzonaphthone and similar compounds) give adducts (315) with one mole of SO_3 complexing with each carbonyl group. A second mole of SO_3 will add, but it is much more loosely bound.

2,6-Dimethyl-γ-pyrone forms an SO_3 complex (336), but none of its properties was reported.

L. ACYL SULFATES

The reactivity of SO_3 also can be moderated by treating it with organic acids.

Sulfur trioxide reacts with acetic acid below 0° to form "acetyl sulfate" (365), which probably comprises a mixture of several species resulting from the equilibria

$$2CH_3COOH + SO_3 \rightleftarrows CH_3COOSO_3H + CH_3COOH \rightleftarrows (CH_3CO)_2O + H_2SO_4$$

A mixture of similar reactivity is made from acetic anhydride and sulfuric acid (365, 401). Acetyl sulfate readily sulfonates aromatic hydrocarbons, alicyclic ketones and olefinic compounds—the last forming acetoxysulfonates

$$RCH{=}CHR' + CH_3COOSO_3H \rightarrow CH_3COOCHRCHR'SO_3H$$

Alcohols are sulfated by acetyl sulfate, but amines and phenols are acetylated (365). Cellulose can be simultaneously acetylated and sulfated (132). Reduction in sulfone formation during sulfonation of aromatic hydrocarbons with SO_3 in the presence of acetic acid is attributed to intermediate formation of acetyl sulfate, as discussed in a later section.

n-Butyric acid also forms a sulfate with SO_3 at low temperature (366), which likewise sulfonates benzene and sulfates alcohols. In the latter case, however, it differs from acetyl sulfate in also forming some butyrate.

Benzoic acid similarly is converted to benzoyl sulfate in ethylene dichloride solvent at room temperature (322). This sulfate is used to sulfonate polystyrene, with subsequent recovery and reuse of the benzoic acid.

IV. REACTIONS WITH ALIPHATIC AND ALICYCLIC COMPOUNDS

A. SATURATED COMPOUNDS

1. Hydrocarbons

The meager data available indicate that SO_3 reacts with saturated aliphatic hydrocarbons, but not in a clean-cut manner. Dehydrogenation and oxidation accompany sulfonation, giving complex mixtures containing hydroxy and carbonyl compounds, carboxylic acids, and unsaturated compounds, as well as their derived sulfates, sulfonic acids, sulfones, sultones and sulfonate esters. Methane (427) at 260°, using $HgSO_4$ catalyst, gives methanesulfonic acid, methane-disulfonic acid and methyl methanesulfonate. Propane, *n*-butane and isobutane (454), in the range 60 to 300°, form polyhydroxy sulfonic acids with the hydroxyl groups partially sulfated. Hexane, heptane, and octane, all of unknown structure, were sulfonated at reflux with SO_3 vapor (553); they gave "disulfonic acids," together with much oxidation. An "isohexane" of uncertain structure was sulfonated to the extent of

50% with SO_3 dissolved in liquid SO_2 at $-10°$ (263); *n*-dodecane did not react under the same conditions. Polyethylene undergoes surface oxidation and sulfonation upon treatment with a dilute solution of SO_3 in tetrachloroethylene at room temperature (197). Decahydronaphthalene (decalin) forms an unidentified sulfonate upon treatment with SO_3 vapor for 2 hours at 193° (121), as does 12-methylperhydroretene ("abietane") at 0° in 3 hours in tetrachloroethane as reaction solvent (542). The reaction of SO_3 with alkanes and cycloalkanes has never been of preparative interest, but it is of practical importance as one factor in the formation of by-product sludge in the sulfonation of petroleum fractions (202).

Although alkanes will react with SO_3 and are not miscible with it, they can be employed satisfactorily as sulfonation solvents for other compounds which react more easily, especially at low temperatures. *n*-Butane (b.p. $-0.5°$) (75) and *n*-hexane (205) have been so used.

2. Halogenated Hydrocarbons

Many halogenated alkanes are miscible in all proportions with SO_3, and although they will react with it, as noted in Table IV, some of them can be employed quite satisfactorily as solvents for SO_3 reactions if care is taken to maintain a sufficiently low reaction temperature, and if the solvent reacts less easily with SO_3 than the compound being sulfonated. The presence of fluorine increases stability; fluorotrichloromethane is therefore a useful solvent, especially since it boils at 24° (9). 1,2-Dichloroethane also is used extensively as a solvent for SO_3 sulfonations. At room temperature, it reacts only to the extent of 3% in 4 days to form the products shown in Table IV. High boiling impurities in technical 1,2-dichloroethane react with SO_3, whereas the distilled material does not (374). Methylene chloride also is used as solvent in SO_3 sulfonations.

It is noted that all the halogenated alkanes react by replacement of one or more halogen atoms by oxygen. Hexachlorocyclopentadiene (195), hexachlorodifluorocyclopentene (112a), octachloroindene (155a), and decachloroindane react similarly by conversion of one or more CCl_2 groups to keto groups; dimerization also occurs in the first case. The reaction of carbon tetrachloride with SO_3 has been used for the practical preparation of both products indicated in Table IV. Phosgene evolution occurs upon gently warming a mixture of the two; distillation of the residue gives pyrosulfuryl chloride. Ethyl chloride resembles ethanol (97) in undergoing secondary sulfonation in the beta position.

Hexachlorocyclohexane ("benzene hexachloride") reacts with SO_3 at room temperature (9, 33)

$$\text{(A)}\quad C_6H_6Cl_6 + 4SO_3 \rightarrow C_6H_2Cl_3SO_3H + 3ClSO_3H$$

Apparently dehydrochlorination occurs to a mixture of trichlorobenzenes, which then undergoes sulfonation; the hydrogen chloride forms chlorosulfonic acid. At 220°, however, an 81% yield of hexachlorobenzene is formed in 5 hours (60). The authors propose the initial formation of a complex between one mole of halide and three moles of SO_3, which then decomposes directly to hexachlorobenzene by the abstraction of six protons. A more likely sequence may involve reaction A above, then reaction B, a known type

$$\text{(B)}\quad C_6H_2Cl_3SO_3H + 3ClSO_3H + 2SO_3 \rightarrow C_6Cl_6 + 3SO_2 + 3H_2SO_4$$

Hexabromocyclohexane reacts similarly, but with only 33% yield.

TABLE IV

HALOGENATED ALKANES AND CYCLOALKANES

Compound	Products	References
$CHCl_3$	CO, $ClSO_3H$, $S_2O_5Cl_2$	16
$CHBr_3$	CO, other products	16
CCl_4	$COCl_2$, $S_2O_5Cl_2$	16, 283, 350, 368, 409
C_2H_5Cl	$C_2H_5OSO_2Cl$, $HO_3SCH_2CH_2OSO_2Cl$	333, 351, 371
C_2H_5I	$C_2H_5OSO_3H$, HI, I_2	554
$ClCH_2CH_2Cl$	$ClCH_2CH_2OSO_2Cl$, $ClCH_2CH_2OSO_3H$	81
$BrCH_2CH_2Br$	$BrCH_2CH_2OSO_3H$	63, 554
CH_3CHCl_2	$CH_3CHClOSO_2Cl$	269
Cl_3CCCl_3	Cl_3CCOCl, $S_2O_5Cl_2$	17, 369
$C_6H_6Cl_6$	$C_6H_2Cl_3SO_3H$, $ClSO_3H$ (low temperature)	9, 33
$C_6H_6Cl_6$	C_6Cl_6, SO_2, H_2SO_4 (high temperature)	60
$C_6H_6Br_6$	C_6Br_6	60

3. Carboxylic Acids

Acetic acid reacts with SO_3 below 0° to form acetyl sulfate (364, 365)

$$CH_3COOH \rightarrow CH_3COOSO_3H$$

Acetyl sulfate is itself a sulfonating agent, as discussed elsewhere in this review. Metallic acetates, on the other hand, are converted to acetic anhydride (153), possibly *via* the salt of acetyl sulfate

$$2CH_3COONa \xrightarrow{2SO_3} 2CH_3COOSO_3Na \xrightarrow{\text{Heat}} (CH_3CO)_2O + Na_2SO_4$$

When acetic acid and SO_3 react at a temperature above 0°, or when acetyl sulfate is warmed, rearrangement and further reaction occur, yielding a mixture of compounds of which sulfoacetic acid, HO_3SCH_2COOH, is a constituent (364, 365). However, the yield is low and the procedure has not been recommended for preparative use. The anhydride of sulfoacetic acid is stated to form from ketene and SO_3-dioxane (422)

$$CH_2{=}C{=}O \xrightarrow{SO_3} \begin{matrix} CH_2{-}C{=}O \\ | \quad\quad | \\ SO_2{-}O \end{matrix}$$

This compound was not isolated as such, but as its aniline derivative. The reaction, involving the formation of a four-membered ring, is generally similar to that between alkenes and SO_3, as discussed subsequently.

Unlike acetic acid, monochloroacetic acid is sulfo-

nated smoothly with SO_3 vapor in 95% yield at 70 to 140° (432). Bromoacetic acid likewise gives a 70% yield (24) of sulfonic acid.

Propionic (29) and butyric (26, 366) acids similarly form the acyl sulfates below 0°. These also rearrange in poor yield to the alpha sulfo acids. However, with $2SO_3$-pyridine, butyric acid is said to be sulfonated quantitatively (497). 2-Chloro- and 2-bromopropionic acids (30) give 25 to 30% yields of the alpha-sulfonated acids upon treatment with SO_3 at 100 to 120°.

Long-chain fatty acids (C-9 and higher) can be alpha-sulfonated in good yields. Cheap availability of these acids has led to substantial industrial interest in this reaction, first in Germany, and more recently in the United States, as shown in a series of papers by A. J. Stirton and co-workers (72, 437, 438, 439, 533, 534, 535, 536, 537, 539, 540, 541), and by their commercial production (15). The molten acids, such as pelargonic (540) or palmitic (230), can be treated without a solvent with SO_3 vapor at 75 to 100°. This method gives colored by-products, which, however, can easily be removed (540) by recrystallization of the monosodium salts from water. Solvent procedures usually are preferred as yielding lighter colored products, however. Lauric acid has been sulfonated in refluxing butane (75), and stearic acid in liquid SO_2 (134, 332a). Tetrachloroethylene (438) and carbon tetrachloride (534, 535, 540) have been used for sulfonating pelargonic, lauric, myristic, palmitic, stearic and behenic acids in crude yields ranging from 60 to 97%. The SO_3 in these cases was added as liquid, although the vapor gives a lighter-colored product (540). The German industrial process for sulfonating a technical palmitic-stearic acid mixture, dissolved in five weights of carbon tetrachloride, involved addition of vaporized SO_3 at 25 to 30° (228), finally raising the temperature to 60° to complete reaction. The solvent could be recovered with a 5% loss, and the sodium salt—obtained in nearly quantitative yield as an almost white solid by bleaching—comprised 90% of the monosulfonate with the rest more highly sulfonated. A similar procedure has been used to sulfonate montanic acid (138), hardened palm kernel acid (260), and the C-7 to 9 fatty acids made by the oxidation of paraffin wax (261). A petroleum naphthenic acid has been sulfonated with SO_3 vapor in 66% yield (378).

Sulfur trioxide–dioxane, used at 60° for 0.5 to 1 hour, yields unusually light-colored alpha sulfonic acids from 9,10-dichloro- and 9,10-dihydroxystearic acids (540). In the second case, five moles of SO_3 was employed and the sulfated product was hydrolyzed to the desired dihydroxysulfostearic acid. Sulfur trioxide–pyridine does not sulfonate the long-chain acids (540), although $2SO_3$–pyridine quantitatively sulfonates butyric acid, as stated above.

The alpha sulfopalmitic and stearic acids have been converted to salts (536), ester-salts (72, 439, 533, 534), and amide-salts (539), all of which were evaluated as detergents (437, 537, 541). Sulfopelargonic esters are good wetting agents (540).

Sulfur trioxide–dioxane selectively sulfonates phenylalkanoic acids on the carbon adjacent to the carboxyl group, rather than on the aromatic ring, as is noted with other reagents such as sulfuric acid (510). Phenylacetic, 3-phenylpropanoic, 6-phenylcaproic and phenylstearic (540) acids give good yields. Diphenylacetic and cyclohexylacetic acids do not react, and 2-phenylbutanoic acid gives a poor yield; these observations are consistent with the large steric requirement of the entering sulfonic group. 4-Phenylbutanoic acid cyclizes to α-tetralone, which monosulfonates as expected on the carbon adjacent to the carbonyl group.

Aliphatic dicarboxylic acids are also sulfonated with SO_3. With one mole at 110–120°, succinic acid is simply dehydrated to its anhydride (31). With 2.5 to 4.0 moles, it yields mono- and disulfonic acids together with unsulfonated acid; more than 4.0 moles forms mono- and disulfonic acids together with some maleic anhydride formed by dehydrogenation. Succinic anhydride is left half unreacted by 0.9 mole SO_3 at 110°; the other half is converted to mono- and disulfonates. Methylsuccinic acid reacts with two moles to form the monosulfonic acid by replacement of the tertiary hydrogen atom (27); one mole is consumed in forming the acid anhydride. Propane-1,1,2-tricarboxylic acid sulfonates, and then decarboxylates (28)

$$CH_3CH(COOH)CH(COOH)_2 \xrightarrow{SO_3} CH_3CH(COOH)CH(SO_3H)(COOH) + CO_2$$

It is noteworthy that replacement occurs of the more reactive, but more sterically hindered, hydrogen atom. Some attack of the other hydrogen does occur, as indicated by the formation of disulfonate. Higher aliphatic dicarboxylic acids (glutaric, adipic, azelaic, and sebacic) have been sulfonated with SO_3 using trichloroacetic acid as solvent (193).

Lysergic acid is converted to acyl sulfate salts, either by treating the free acid with SO_3–dimethylformamide, or by treating potassium lysergate with SO_3 (184, 185). The acyl sulfate salts react with amines to form amides of lysergic acid. Similarly, SO_3-dimethylformamide forms the acyl sulfates of amino acids, which react with other amino acids to give peptides (120, 276, 277).

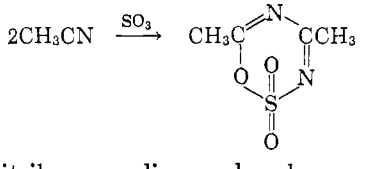
4. Esters

The sulfonation of three aliphatic ethyl esters (acetate, propionate, and butyrate) yielded only disulfonates (497) with three reagents. Sulfur trioxide gave 45, 48, and 15% yields. Use of $2SO_3$–pyridine resulted in 100% yields from the first two, while SO_2–dioxane gave

100% disulfonate from the first and last. Diethyl malonate, on the other hand, yielded 50% monosulfonate with SO_3–dioxane; a disulfonate would not be expected on steric grounds. The formation of di- rather than monosulfonates is a noteworthy difference from the free acids, which form only the mono compounds. Retention of the intact ester group is also striking, since there is some indication that cleavage can occur during sulfonation of esters with sulfur trioxide and subsequent workup (9). Thus methyl laurate, with SO_3 in liquid SO_2, forms alpha sulfolauric acid and dimethyl sulfate (332c). Gamma butyrolactone, also an ester, reacts with SO_3 in chloroform solution at 0° to form the monosulfonate (290). At 100°, without a solvent, however, it gave a disulfonate, therein resembling the ethyl esters mentioned above, and differing from the acids.

5. *Nitriles*

Aliphatic nitriles react with SO_3 and its complexes, but reports vary as to the products formed. Hydrogen cyanide (255) combines with SO_3 at a 7-to-3 molar ratio, but the composition of the product was not established. Acetonitrile reacts at a 2-to-1 ratio apparently as shown (159)



Aromatic nitriles, as discussed subsequently, react similarly. On the other hand, acetonitrile is reported (497) to form the nitrile alpha monosulfonate in 35, 28 and 70% yields with SO_3, $2SO_3$–pyridine, and SO_2–dioxane. In the light of these reports, the recommendations that acetonitrile be used as a sulfonation solvent (184, 243) should be accepted with reservation. Propionitrile gives 80% alpha sulfonated nitrile with $2SO_3$–pyridine, and 3-methylbutyronitrile 25% with SO_3–dioxane (497). Long-chain fatty nitriles (*e.g.*, lauric and palmitic) also are reported to form sulfonated nitriles upon treatment with SO_3 under mild conditions (245, 246) in solvents such as tetrachloroethylene, but no analytical data are presented which would exclude attack of the nitrile group. Benzyl cyanide and acrylonitrile are said not to react with SO_3–dioxane at room temperature in 3 minutes (485).

Cyanogen chloride reacts (14)

$$ClCN \xrightarrow{SO_3} ClSO_2NCO$$

This sulfonyl chloride–isocyanate is a highly reactive molecule which provides access to many derivatives not otherwise easily attainable.

6. *Ketones*

Like carboxylic acids, these compounds are sulfonated easily on the carbon adjacent to the carbonyl group

$$RCH_2COR' \xrightarrow{SO_3} RCH(SO_3H)COR'$$

Sulfur trioxide–dioxane has been the favored reagent in the range 5 to 50°, with 1,2-dichloroethane as reaction solvent. In some cases (512), the desired sulfonic acid can be isolated by simply cooling the reaction mixture. Acetyl sulfate also has been employed, especially with the diketones. Data are summarized in Table V.

TABLE V

SATURATED ALIPHATIC AND ALICYCLIC MONO- AND DIKETONES[a]

Compound	Monosulfonate yield, %	Reference
Monoketones		
Acetone	53, 70, 100[b]	494, 507
Di-(*n*-propyl) ketone	95, 100[b]	494
Di-(isopropyl) ketone	90	494
Pinacolone	70	507
Palmitone, *etc.*	—(SO_3 in CCl_4)	231
Coconut ketones	—(SO_3 in SO_2)	136
Acetophenone	70, 90, 93	488, 494, 507
4-Methylacetophenone	—	489
4-Ethylacetophenone	79	488
4-Isopropylacetophenone	87	488
4-Methoxyacetophenone	84	488
4-Ethoxyacetophenone	80	488
4-Chloroacetophenone	56	488
4-Bromoacetophenone	58	488
2,4-Dimethylacetophenone	80	489
2,4,6-Trimethylacetophenone	70	507
α-Chloroacetophenone	77	509
α-Fluoroacetophenone	46	509
Propiophenone	70	507
Isobutyrophenone	63, 70	507, 512
Pivalophenone	0	507
2-Acetonaphthone	Mixed mono- and disulfonates	507
2-Acetothienone	70	507
Camphor	—(AC)[a]	531
Fenchone	65(SO_3 vapor)	505
Fenchone	0(AC), —(AC)	292, 505
Cyclohexanone	70, 84	494, 507
1-Tetralone	70	510
1-Keto-1,2,3,4-tetrahydrophenanthrene	85(AC)	141
1-Keto-2-methyl-1,2,3,4-tetrahydrophenanthrene	71(AC)	141
Androsterone acetate	—(AC)	141
Isoandrosterone acetate	63(AC)	141
Estrone acetate	74(AC)	141
Coprostan-3-one	—(AC)	548, 549
Cholestan-3-one	—(AC)	548, 549
Progesterone	—(AC)	548
Diketones		
1,3-Indandione	Good, —(AC)[b]	223, 224, 225
Bis-(1,3-indandione)	—(AC)	224
2-Phenyl-1,3-indandione	—, —(AC)	223, 224
5,5-Dimethyl-1,3-cyclohexanedione	—, —(AC)	223, 224
5-Phenylcyclohexane-1,3-dione	—, —(AC)	223, 224
Perinaphthindan-1,3-dione	—, —(AC)	223, 224
Dibenzoylmethane	—, 0	223, 509
o-Diacetylbenzene	0	509
m-Diacetylbenzene	59[b]	509
p-Diacetylbenzene	53[b]	509
Cholestan-3,6-dione	—(AC)	549

[a] All sulfonations with SO_3-dioxane, except as otherwise indicated; AC = acetyl sulfate; — indicates yield not given. [b] Disulfonate yield at 2:1 molar ratio.

Pivalophenone did not react, as might be expected from the absence of hydrogen on a carbon adjacent to

carbonyl. Dibenzoylmethane did not react at 5° (509), but was found by others (223) to sulfonate at 25°. Among the ketones also containing carbocyclic rings, ring sulfonation was reported only for 2-acetonaphthone (507). The heterocyclic rings in 1- and 2-acetofurans and in 2-acetopyrrole do sulfonate to some extent, although 2-acetothienone did not (507).

Certain terpenic ketones behave abnormally. Camphor, even though it does have hydrogen atoms on a carbon adjacent to the carbonyl group, is sulfonated by acetyl sulfate preferably on a methyl group (531). Pulegone, as discussed under Unsaturated Ketones, behaves similarly in failing to react with acetyl sulfate on the adjacent carbon. Fenchone (isomeric with camphor) has no hydrogen atoms on the adjacent carbon, but it is sulfonated by acetyl sulfate on a methyl group located in the same position as in camphor (292). Another investigator (505) obtained the same sulfonate in 65% yield from fenchone with SO_3 vapor, but noted no reaction with acetyl sulfate. These anomalies cannot be attributed to the use of acetyl sulfate, since it sulfonates 1-keto-1,2,3,4-tetrahydrophenanthrene (141), and several steroidal ketones (141, 548, 549) normally on the adjacent carbon.

The sulfonation of unsaturated ketones is reviewed in a subsequent section.

7. *Aldehydes*

Saturated aldehydes resemble ketones and carboxylic acids in undergoing sulfonation with SO_3–dioxane on the carbon adjacent to the carbonyl group

$$RCH_2CHO \xrightarrow{SO_3} RCH(SO_3H)CHO$$

As indicated in Table VI, mono- or disulfonates can in some cases be obtained at will by a change in reactant ratio.

Aldehydes without hydrogen on the carbon adjacent to the carbonyl group can react through the carbonyl group. Formaldehyde yields "methylene sulfate" in 1,2-dichloroethane solvent at 10–35° (423).

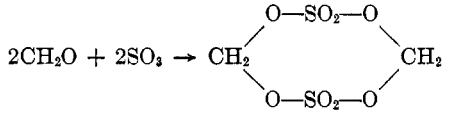


TABLE VI

SATURATED ALIPHATIC ALDEHYDES WITH SO_3–DIOXANE

Compound	Monosulfate yield, %	Reference
CH_3CHO	39, 80[a]	494
C_2H_5CHO	55	494
n-C_3H_7CHO	61, 78[a]	494
iso-C_3H_7CHO	75, —[a]	494, 507[a]
iso-C_4H_9CHO	78[a]	494[a]
$C_6H_{13}CHO$	65	494
$C_7H_{15}CHO$	60, —	494, 507
$C_9H_{19}CHO$	43, 34[a]	494
$C_6H_5CH_2CHO$	57, 41[a]	494, 507[a]

[a] Indicates yield of disulfonate at 2:1 molar ratio; — indicates yield not given.

Chloral forms a complex unidentified product containing ten carbon and three sulfur atoms (211), presumably also formed through the carbonyl group. Unsaturated aldehydes are reviewed in a later section.

8. *Alcohols*

Alcohols are converted to alkyl acid sulfates. Methanol has reacted with SO_3 vapor at −5° (325) or with liquid SO_3 in carbon tetrachloride solvent (429). Vacuum distillation on the acid sulfate yields dimethyl sulfate, a process once used commercially.

$$2CH_3OH \xrightarrow{SO_3} 2CH_3OSO_3H \rightarrow (CH_3O)_2SO_2 + H_2SO_4$$

The sulfation of absolute ethanol with SO_3 in liquid SO_2 solvent gives 74 to 86% ethyl acid sulfate, depending upon the length of time before analysis (97); the equilibrium

$$2C_2H_5OSO_3H \rightleftarrows (C_2H_5O)_2SO_2 + H_2SO_4$$

has been established experimentally from both directions. Treatment of absolute ethanol at 0° with SO_3 vapor (1 mole), then addition of a second mole at 50°, gives ethionic acid in good yield (97)

$$C_2H_5OH \xrightarrow{SO_3} C_2H_5OSO_3H \xrightarrow{SO_3} HO_3SCH_2CH_2OSO_3H$$

The same reaction has been run in liquid SO_2 (179).

The sulfated higher alcohols are important commercial surface-active agents.

A laboratory study of the comparative suitability of five reagents for sulfating a mixture of 1-dodecanol and 1-tetradecanol showed SO_3 vapor and SO_3 in liquid SO_2 to give comparatively high yields, low unreacted alcohol, and low inorganic salts, but somewhat darker colors (523). The passage of SO_3 vapor diluted with air into the undiluted liquid alcohol at 30 to 40° gives good results on a laboratory scale for the primary straight-chain alcohols derived from coconut oil (octyl, decyl, and lauryl) (207) and for the primary branched-chain C 10 and C 13 alcohols prepared by the Oxo process (167, 207). Lauryl alcohol has been sulfated in this way on a pilot plant (114) and a commercial scale (312). Cetyl and octadecyl alcohols have been sulfated similarly in the laboratory at 70 to 80°, since they are solids at room temperature (207).

The use of solvents has been suggested to facilitate the sulfation of higher alcohols with SO_3–especially of those compounds which are solid or excessively viscous at the reaction temperature. The organic sulfate product has been suggested (430) as the reaction solvent in a "dominant bath" procedure, but such an approach gives a product of poor quality since the sulfate is easily degraded by the strong reagent. Liquid sulfur dioxide has been proposed as solvent with decyl, lauryl and tetradecyl alcohols (179), and for C 12 and 13 Oxo alcohols (257). Tetrachloroethylene has been used for hydroabietyl alcohol (244).

Sulfur trioxide complexes also have been employed for alcohol sulfation. Ethanol (47) and 2-butanol (139) react with SO_3–pyridine at 25° in an hour or less to give good yields of the sulfates. Optically active 2-butanol also has been sulfated with the same reagent in 1 hour at 100° in 90% yield (109), with retention of optical purity and configuration; SO_3–dioxane gave similar results. Sulfur trioxide–pyridine sulfates benzyl alcohol in carbon disulfide (520). Primary and tertiary alcoholic derivatives of 1,4-naphthoquinone were sulfated on a semi-micro scale by heating for two minutes with SO_3-pyridine in excess pyridine at 100° (177). Monoethanolamides of long-chain fatty acids have reacted in a melt at 190° with SO_3-picoline (154). The trimethylamine adduct sulfates both 1- and 2-propanol (240); the former reacts first in a mixture of the two alcohols, thereby effecting separation. Ethanol has been sulfated with SO_3-trimethylphosphine oxide (104). Isoamyl alcohol is sulfated by acetyl sulfate without acetylation (365), but some acylation does occur when using *n*-butyryl sulfate (366).

Sulfur trioxide–dioxane quantitatively sulfates many alcohols, and this reaction has been used for their analytical determination (484, 485). With monohydric alcohols, the sulfation is complete at room temperature in three minutes, but polyhydric alcohols may require two hours. The procedure was found applicable to primary (ethanol, 1-butanol, 2-butanol, 1-nonanol, benzyl alcohol, and a phenylpropanol), secondary (1,1,1-trichloro-2-propanol, 2-octanol, cyclohexanol, and menthol), and tertiary (*tert*-butyl alcohol, 2-methyl-2-butanol, 2-methyl-2-hexanol, and 3-hydroxy-3-amyltetrahydrofuran) saturated alcohols. Polyhydric alcohols included 1,3- and 1,4-butanediols, pinacol, pentaerythritol, mannitol, glucose, galactose and fructose. Unsaturated alcohols (allyl, 2-methyl-4-penten-2-ol, and 1,4-butynediol) reacted only on the hydroxyl groups. However, others (450) report that at 0° SO_3–dioxane does not sulfate *tert*-butyl alcohol; only dehydration was noted, forming sulfuric acid. This discrepancy may be explained by differing reaction times, or by the instability of tertiary alkyl sulfates, which decompose rapidly in aqueous solution in the presence of either acids or bases (177). Sulfur trioxide–dioxane sulfates borneol and menthol (487).

Numerous complexes of SO_3 have been suggested in the patent literature for the sulfation of long-chain alcohols (411), but these have not been used commercially for the saturated compounds. Sulfur trioxide–dioxane has been proposed for lauryl (444) and for a C-17 Oxo alcohol (101), and SO_3–thioxane for C-15 to 19 secondary alcohols from ketones prepared by paraffin wax oxidation (340). Alcohols from oxidized petroleum fractions have been sulfated semi-commercially with SO_3–pyridine at 50 to 95° using a 30-minute reaction time (271). Stearyl alcohol has been sulfated with SO_3–dimethylaniline using chlorobenzene as solvent (431), and 7-ethyl-2-methyl-4-undecanol with SO_3-bis(2-chloroethyl) ether (298). Sulfur trioxide-N-methyl ethylene carbamate sulfates lauryl alcohol at 45° (425).

9. Sterols

The sulfation of steroids containing hydroxyl groups is of biological interest, since many of them are excreted from the body as the water-soluble sulfates. These steroids can be considered as high molecular weight polycyclic alcohols, except as mentioned below. Sulfur trioxide–pyridine always has been used with an organic solvent, usually chloroform. The reaction is commonly run at room temperature, but reaction times have varied widely. Cholesterol and cholestan-3β-ol took 2 hours (321), equilin (215) 24, and estradiol-3-monobenzoate (249) 68. The same system at reflux (61°) was employed for estrone (403), and for 7α- and 7β-hydroxycholesterols (13). Benzene with SO_3–pyridine at 55° was used with cholesterol, lanosterol, and γ-lanostadienol (71). A ternary solvent mixture (benzene, pyridine, and acetic anhydride) is reported to give quantitative sulfation using SO_3–pyridine at 50 to 60° in 20 minutes with cholesterol, ergosterol, and lanosterol (428); dibromocholesterol was sulfated similarly at 37°. Hydrocortisone was semisulfated in the 21-position (407). Sulfation on a semi-micro scale is effected by heating with SO_3–pyridine in excess pyridine for two minutes. This technique was applied to androsterone, isoandrosterone, and dehydroisoandrosterone (107), to three 3-hydroxy-20-oxopregnane isomers (557), and to one pregnene analog (557). In all of the sterols mentioned in this section the hydroxyl group is alcoholic, except in equilin, equilenin and estrone, where it is phenolic. Sulfation of sterols in aqueous medium has not been reported, possibly because of their low solubility in water.

10. Glycols, Polyether Glycols, and Polyether Alcohols

Glycols and polyether glycols have been sulfated by SO_3 in several forms, as noted in Table VII. Glycerol could be di- but not trisulfated with SO_3 vapor (216); trisulfation was, however, effected with oleum. The polyethylene glycols used varied in molecular weight from 200 to 6000.

TABLE VII
GLYCOLS AND POLYETHER GLYCOLS

Compound	Reagent	Solvent	Temp., °C.	Degree of sulfation	Ref.
Ethylene glycol	SO_3	SO_2	50	Di	179
Glycerol	SO_3 vapor	None	40	Di	216
Lauric monoglyceride	SO_3	SO_2	—	Mono	179
Polyethylene glycol	SO_3	SO_2	—	Partial	209
Polyethylene and polypropylene glycols	SO_3–amine	None	100	Mono	300
Hydroxylated polybutadiene	SO_3–pyridine	Benzene-pyridine	90	Partial	268
Poly-(vinyl alcohol)	SO_3-pyridine	None	110	Complete	172

TABLE VIII
POLYETHER ALCOHOLS (ETHYLENE OXIDE CONDENSATES)

Alcohol or phenol condensed	Moles ethylene oxide	Reagent	Reference
-Butyloctanol	3–5	SO_3 in liquid SO_2	285
Lauryl	3	SO_3 vapor	204
Tridecyl (Oxo)	3, 4	SO_3 vapor	21, 167, 204, 286
7-Ethyl-2-methylundecanol-4	5	SO_3 in liquid SO_2	284
Tallow (*n*-octadecanol)	4	SO_3 vapor	204
Octylphenol	3, 5, 12	SO_3 vapor	206
Nonylphenol	4, 9	SO_3 vapor	114, 206
Dodecylphenol	6	SO_3 vapor	206

Polyether alcohols, made by ethoxylation of long-chain alcohols and of alkylated phenols, are converted to sulfates which are commercial surface-active agents. In Table VIII are listed those, including the common commercial types, which have been sulfated with SO_3. This reagent, introduced as an air-diluted vapor into the organic compound at 30 to 40°, has been compared with chlorosulfonic acid (204), and with chlorosulfonic acid, sulfamic acid, and 20% oleum (167) for sulfating the alcohol-derived condensates; all reagents gave good yields of acceptable products. The alkylphenol-based materials have been similarly sulfated with SO_3 vapor on a laboratory (206) and on a pilot plant (114) scale, in the former case in comparison with sulfamic acid. The two reagents differ in that SO_3 gives some ring sulfonate, while sulfamic acid forms none. Products made from the two reagents give different test results in some performance tests (166), but not in others (206).

11. Carbohydrates and Nitrogenous Polysaccharides

Sulfur trioxide used as vapor, or (preferably) in carbon disulfide solution, was first reported in 1928 to sulfate three hydroxyl groups in each six-carbon unit of cellulose (501). Use of less than three moles of SO_3 gave the same trisulfate and unreacted cellulose. This sulfate was water-soluble, but did not form a viscous solution, an observation which, in the light of subsequent work, probably indicates degradation during sulfation. Heating with SO_3–pyridine at 100° introduced 2.78 to 2.9 sulfate groups. However, this product formed water solutions of higher viscosity and probably had a much higher molecular weight (186, 502). Starch similarly gave a material with two sulfate groups per unit (457).

This general technique has been used extensively since that time with only minor variations for sulfating many carbohydrates and related materials, mainly in attempts to duplicate synthetically the naturally-occurring anticoagulant heparin (65, 387). The usual procedure involves heating the organic compound from 1 to 8 hours in excess pyridine at from 60 to 100°. Occasionally, auxiliary or alternative solvents such as chloroform (156), benzene (266) or formamide (5) are employed. One to three sulfate groups are introduced per glucose unit in carbohydrates. The nitrogen-containing compounds are not only sulfated on free hydroxyl and thiol groups, but are also sulfamated on the amino groups. Other groups, if present, may react, as shown in Table IX. The formation of sulfamate, as well as sulfate, groups in the same molecule is not undesirable from the standpoint of preparing heparin analogs, since that compound has been shown (550) to contain both types of groups.

Compounds so sulfated include: adenosine (156), alginic acid (10, 65, 426), degraded alginic acid (309), anhydroglucose (153c), various aminoglucose derivatives (549a), cyclo-(heptaamylose) and cyclo-(hexaamylose) (66), cellulose (67, 267, 461), chitin (67, 266), chitosan (550), N-deacetylated chondroitin sulfate (551), dextramic acid (126), dextran (5, 363, 384, 386), degraded dextran (385), dextrin (387), galactose (363b), a D-galactose derivative (213), glucofuranosides (363a), glucose (153a, 363b, 432b), polymerized glucose (210, 313, 552), glycogen (67), gum arabic (67), various hexoses (513), various methylhexosides (153b), ovomucoid (395), pectic acid (65), degraded pectic acid (6), pectin (113), degraded pectin (281), polyuronic acids (65), riboflavin (157), saponins (396), starch (67, 267), sucrose (432a), tannin heterosides (396), degraded xylan (254, 272, 528), and yeast (67).

The use of excess pyridine has been thought to minimize degradation of the acid-sensitive polysaccharides during sulfation. Cellulose with 2.82 sulfate groups per glucose unit showed a degree of polymerization of 750 to 1000 units per mole (461). Since the latter figure is accepted as a possible minimum for unsulfated cellulose, degradation in this case may be minor. On the other hand, polygalacturonic acid methyl ester methyl glycoside was depolymerized to about half its original molecular weight during sulfation (65), indicating serious degradation.

Recent work has emphasized much lower sulfation temperatures in an effort to avoid such degradation, and the elimination of pyridinium chloride from the sulfation mixture, since it has been shown (326) that preparations of enhanced physiological activity result. Thus, SO_3–dimethylformamide has been used for sulfating chitosan at room temperature (550). The use of excess dimethylformamide as reaction solvent conveniently dissolves both the complex and the organic compound yielding a homogeneous system, while SO_3–pyridine is only slightly soluble in excess pyridine. However, SO_3–dimethylformamide caused some degradation, since chitosan (550) yielded a product with a degree of polymerization of 530 units per mole, while SO_3–pyridine gave 1280 units at 100°. Both products had one sulfate and one sulfamate group per monomer unit, but that prepared with dimethylformamide had superior use properties, since it was much less toxic with about equal physiological activity. Sulfur tri-

oxide in formamide has likewise been employed for sulfating alginic acid, xylan, pectin and methyl cellulose (370, 529).

A further, and possibly ultimate, move toward even milder sulfation conditions has involved the use of low temperature, a long reaction time, a powerful solvent, and an SO_3–amine complex considerably less reactive than SO_3-dimethylformamide. Sulfur trioxide–triethylamine, used with dimethylformamide solvent at 0° for 24 hours (545), was shown to introduce 0.5 to 1.0 sulfate group per monomer unit before degradation began. In a similar approach, laminarin reacted with SO_3–pyridine in formamide at −5° for 20 hours (352).

Other sulfation procedures have involved use of SO_3–bis(2-chloroethyl) ether at −5° for 1.5 hours for the sulfation of cellulose (247); 1,2-dichloroethane was employed as the reaction solvent. Chitosan reacted with SO_3 in liquid SO_2 for 10 to 24 hours at −10° (514); the same system has been used for chondroitin sulfuric acid (326), and for glucosamine (327). Sulfur trioxide–dioxane, used in excess, quantitatively sulfates all the hydroxyl groups in glucose and galactose and four of the hydroxyl groups in fructose at room temperature in 1 to 2 hours (485). Cellulose has been simultaneously sulfated and acetylated with acetyl sulfate (131, 132); the properties of the product, which is available commercially, have been described (155).

The low reactivity of the SO_3–amine complexes has permitted their use in a cold aqueous alkaline medium. Starch (339) is thus sulfated with the complexes of triethylamine, tributylamine, or N-methylmorpholine at room temperature in 16 to 24 hours. Reports vary regarding the activity of SO_3–pyridine in aqueous alkaline medium. One study (*cf.* Table IX) indicates that sulfation does not occur; with chitosan sulfamation was quantitative in 20 hours (530), but no sulfation was noted. However, starch is reported (339) to undergo sulfation under these conditions, although no data are presented.

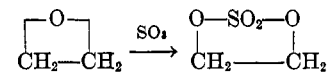
12. Ethers

Ethers, being "Lewis bases," form complexes with SO_3 of varying degrees of stability; most of these rearrange to dialkyl sulfates

$$R_2O \xrightarrow{SO_3} R_2O \cdot SO_3 \rightarrow (RO)_2SO_2$$

Dimethyl sulfate is manufactured in excellent yield and purity on a continuous basis from the ether and liquid SO_3 (196), a procedure said to be inapplicable to diethyl and other ethers. Monochloro- (250a, 265) and *sym* dichloromethyl (250a, 218) ethers form the sulfates with SO_3; in the latter case, a maximum 31% yield was obtained in an autoclave at 180° for 50 minutes. Ethyl ether forms diethyl sulfate if carefully treated in the cold with one mole of SO_3 (252); excess reagent causes sulfonation in the beta position, as with ethanol. Bis-(2-chloroethyl) ether, as discussed in a previous section, forms an SO_3 complex, which rearranges smoothly to bis-(2-chloroethyl) sulfate in 91% yield (448). A low yield of the analogous bromo sulfate was obtained similarly, but attempts to extend the reaction to di-*n*-propyl and to bis-(3-chloropropyl) ethers were unsuccessful. Dioxane, a diether, forms two complexes, as reviewed previously, but these have not been converted to sulfates.

Ethylene oxide, a cyclic ether, forms the sulfate in poor yield with SO_3–dioxane (233)



13. Amines, Amides, Amino Acids, and Proteins

Methylamine, ethylamine and diethylamine vapors react vigorously with undiluted SO_3 vapor to form the sulfamates (64), isolated as the barium salts

$$R_2NH \xrightarrow{SO_3} R_2NSO_3H$$

The same procedure monosulfamates urea (54)

$$NH_2CONH_2 \xrightarrow{SO_3} NH_2CONHSO_3H$$

However, the compounds considered in this section usually have been sulfated with SO_3–pyridine, either in cold aqueous alkaline medium or in hot (100°) anhydrous pyridine. As shown in Table IX, the two procedures give quite different results, with the anhydrous system being much more reactive than the aqueous. It is noteworthy that the anhydrous procedure fails with only two functional groups, and that one of these groups does react in the aqueous system.

TABLE IX
SULFATION OF PROTEIN FUNCTIONAL GROUPS WITH SO_3–PYRIDINE

Group	Medium[a]: Cold aqueous alkali	Medium[a]: Hot anhydrous pyridine
Amino NH_2	+	+
Amido NH_2	−	+
Imidazole NH	+	−
Indole NH	−	+
Imino NH	+	+
Amido NH (Peptide)	−	−
Guanidyl (*NH* and NH_2)	−	+
Alcoholic OH	−	+
Phenolic OH	+	+
Thiol	Not determined	+

[a] + indicates that reaction occurs; − indicates no reaction.

Aliphatic amines are easily sulfamated in aqueous alkaline solution at room temperature or below with SO_3–pyridine. Amines so reacting include methyl- and diethylamines (47, 52), and anabasine (355). Under the same conditions, amino alcohols (diethanolamine, 3-aminopropanol and DL-serine) sulfamate, but do not sulfate (530). Aqueous trimethylamine reacts with SO_3–pyridine forming SO_3–trimethylamine and pyri-

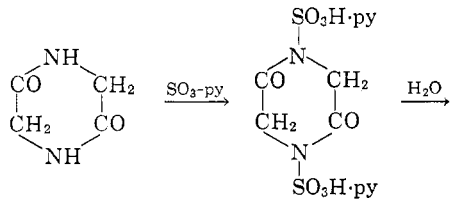
dine (47), a logical reaction in the light of the much greater basic strength of the former amine and the fair stability of both complexes in water. A series of twenty common amino acids and simple peptides was sulfated similarly, with the various groups reacting as shown in Table IX (58). Proteins (zein, casein, corn gluten) reacted with SO_3–trimethyl- and triethylamines in aqueous alkali at 45 to 60° in 2 hours or less (279).

Methylguanidine sulfate was monosulfamated by SO_3–pyridine in excess pyridine at 100° in 2.5 hours (380), and ethanolamine was both sulfamated and sulfated (380, 551). Benzylamine and glycine ethyl ester hydrochloride under the same conditions apparently underwent disulfamation; the unstable disulfamates rapidly hydrolyzed to monosulfamates in aqueous acid

$$RN(SO_3H)_2 \xrightarrow[H+]{H_2O} RNHSO_3H + H_2SO_4$$

The same procedure gave monosulfamation of heptamide and adipamide. A series of seventeen proteins and related compounds (379, 380) likewise reacted, with the various functional groups behaving as shown in Table IX. Insulin was progressively sulfated in a similar manner, but the products formed were all less active physiologically (421).

Amides also have been sulfamated by a special procedure involving fusion of the amide with solid SO_3–pyridine for a few minutes at 100 to 150°. Acetamide thus gave an 80% yield at 100° (57). Myristamide and stearamide, on the other hand, form the amide alpha sulfonic acids, among other products, with SO_3 in liquid SO_2 (332b). Urea was similarly monosulfamated at 120° with one mole of reagent, and disulfamated with 2.2 moles at 150° (56). Diketopiperazine was disulfamated by this melt technique (58); this is apparently the only known sulfamation of a secondary amide. The product then was hydrolyzed to the otherwise inaccessible disulfamated glycylglycine



$Py{\cdot}HO_3SNHCH_2CON(SO_3H{\cdot}py)CH_2COOH$

n-Butylamine was sulfamated in 70% yield with SO_3–dioxane (319). However, acetamide did not react with an excess of this reagent at room temperature in 3 minutes (485).

14. Oximes and Hydroxylamines

Acetoxime and acetophenone oxime sulfate quantitatively in a few minutes with SO_3–dioxane at room temperature (485). Benzoin oxime is similarly sulfated on both the alcoholic and the oximino groups. A series of four aldoximes, on the other hand, did not react completely. Quinone monoxime was sulfated with SO_3–pyridine using carbon tetrachloride solvent (105). Ethyl-, *n*-propyl, and isopropylhydroxylamines formed the *N*-hydroxysulfamic acids with solid SO_3 in chloroform suspension (402).

15. Miscellaneous Saturated Aliphatic and Alicyclic Compounds

Methanesulfonic acid reacts with SO_3 under mild conditions to form the pyrosulfonic acid and its solvate $CH_3SO_3SO_3H \cdot 2CH_3SO_3H$ (404a). Under more drastic conditions (3 hours at 145°) an 85% yield of disulfonate is obtained (135)

$$CH_3SO_3H \xrightarrow{SO_3} CH_2(SO_3H)_2$$

Nitromethane formed 15% sulfonate with SO_3, 4% with $2SO_3$–pyridine, and 6% with SO_3–dioxane (497); nitrocyclohexane correspondingly gave yields of 26, 22 and 20%. Sulfur trioxide–pyridine did not react with either compound.

Carbon disulfide is miscible with SO_3 in all proportions. Upon standing for a short time at room temperature, or immediately upon warming, the following reaction occurs (16, 17, 190)

$$SO_3 + CS_2 \rightarrow COS + SO_2 + S$$

Carbon disulfide has, however, been used as reaction solvent for the sulfation of cellulose with SO_3.

Trifluoromethyl hypofluorite forms the peroxyfluorosulfonate (515)

$$F_3COF \xrightarrow{SO_3} F_3COOSO_2F$$

As with the alkyl halides, the fluorine atom becomes bonded to sulfur.

B. UNSATURATED COMPOUNDS

All classes of unsaturated compounds sulfonate easily forming the various types of compounds shown in Fig. 1. Included are ethylene and acetylene derivatives containing a wide variety of other functional groups.

Most of the work on the sulfonation of unsaturated compounds has come from three sources. C. M. Suter, F. G. Bordwell, and collaborators in the United States have studied the sulfonation of alkyl and aryl ethylenes with SO_3–dioxane. Recent publications of the latter have begun a promising attack toward elucidating the mechanism and basic chemistry of these complicated reactions. A. P. Terent'ev and co-workers in the Soviet Union have employed SO_3–pyridine with cycloalkenes, alkadienes and alkene derivatives, the primary emphasis being preparative; some of his papers are available in English translation (12). Industrial chemists have

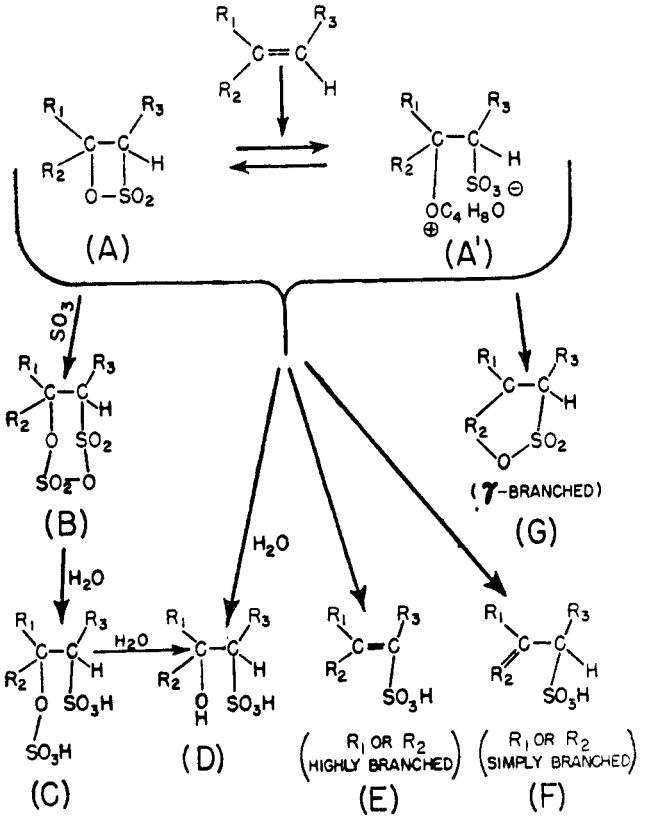


Fig. 1.—Alkene sulfonation products.

used free SO_3, generally with a solvent, to prepare surface-active agents from commercially available long-chain alkenes; this work has been largely empirical. A solvent widely employed in these studies is liquid SO_2, at its boiling point (−10°).

A β-sultone (formula A), or its dioxane solvated carbonium ion (formula A′), is now considered the primary alkene sulfonation product (79, 82, 83, 84, 85, 86), at least in many cases. This type of sultone was actually isolated from styrene (80, 86), and from a series of fourteen fluorinated ethylenes (Table XIII). These sultones are quite reactive and unstable and can form one or more of the several types of final products shown depending upon various factors, including reactant–reagent ratio (84), reaction temperature (389), method of product workup (84), and degree of polymerization or water content of the sulfur trioxide used (142, 165). In the case of branched-chain alkenes, the type and position of chain branching, with steric factors of primary influence, determine which of structures E, F, or G will be formed (79, 82); hetero-conjugation of doubly-bonded carbon with sulfonate and hyperconjugation of it with alkyl groups also play a role (82). With ring-halogenated styrenes, the type and position of the ring substituent determines what products are formed (115), as shown in Table X. Inductive effects of ring substituents appear to determine sulfate–sulfonate (type C) yields, since they become less as the fluorine atom is farther removed from the olefinic bond of the styrene. Furthermore, the yields of type C products from *meta* substituted styrenes decrease as the electronegativity of the *meta* substituent diminishes. Total electronic effect (inductive plus resonance) of the *meta* and *para* substituents (Hammett sigma values) appears to correlate with yields of olefinic (type E) sulfonates.

TABLE X

SULFONATE YIELDS FROM HALOGENATED STYRENES WITH SO_3–DIOXANE

Compound	Percentage yield: Sulfate–sulfonate (Type C)	Olefinic sulfonate (Type E)	Hydroxy sulfonate (Type D)
2-Fluorostyrene	58	30	12
3-Fluorostyrene	39	9	53
4-Fluorostyrene	15	68	18
2,4-Difluorostyrene	39	25	35
3-(Trifluoromethyl)-styrene	59	7	34
3-(Trifluoromethyl)-4-fluorostyrene	0	0	100
2-Chlorostyrene	10	5	85
3-Chlorostyrene	16 (15[a])	10 (18[a])	74 (67[a])
4-Chlorostyrene	0	38	60
2-Bromostyrene	0	6	94
3-Bromostyrene	0	8	92
4-Bromostyrene	2	33	65
3-Nitrostyrene	69[a]	4[a]	27[a]
4-Nitrostyrene	88[a]	6[a]	6[a]
Styrene	0	69	31

[a] Data from Reference (508).

Products of type B (sulfate–sulfonic anhydride or "carbyl sulfate") have been isolated only in the cases of ethylene and 1,1-difluoro-ethylene (with both of which no other products are formed), of trifluoroethylene and methallyl chloride (which give mixtures), and of tetrafluoroethylene and hexafluoropropylene, which give some product B with undistilled SO_3, but none with the freshly distilled material. However, this type of anhydride may be intermediate in many alkene sulfonations where the more stable compounds C or D actually are isolated as the final products.

The usual types of final products isolated after aqueous neutralization of the reaction mixture are alkenesulfonates (structures E or F), or a hydroxysulfonate (also called an "isethionate") of structure D, the last forming from sultone A by hydrolysis, either directly, or *via* compounds B and C. Compounds of type C (sulfate–sulfonates, or "ethionates") are unstable in aqueous medium and usually are isolated only with special precautions, as with cyclohexene (84), cyclopentene (84), methylenecyclohexane (464), halo- (115) or nitrostyrenes (115) (see Table X), and vinyl ethers (as discussed subsequently).

Steric factors, besides often determining sulfonate structure, can also prevent alkene sulfonation, as possibly with 1,1-diphenyl-2-methyl-1-propene (81). Polybutylene mixtures (9) sulfonate only to the extent of about 25%, the remainder apparently being too sterically hindered to react since the double bonds are

internally situated. Tetrachloroethylene does not sulfonate, possibly at least in part for similar reasons.

Hydroxysulfonates (type D) and olefinic sulfonates (type E) also result from the reaction of alkenes with acetyl sulfate, the primary product being an acetoxysulfonate

$$CH_3COOSO_3H + RCH{=}CHR' \rightarrow CH_3COOCH(R)CH(R')SO_3H \xrightarrow{H_2O} HOCH(R)CH(R')SO_3H + RCH{=}C(R')SO_3H + CH_3COOH$$

Cyclohexene forms (435) nearly equal quantities of both types.

1. *Alkyl and Aryl Ethylenes; Cycloalkenes*

This category includes compounds with only hydrogen or carbon atoms attached to the double-bonded carbons. Compounds studied, with main products formed, are listed in Table XI. All of these are hydrocarbons, except for a few compounds with halogen not on doubly-bonded carbon, and two ring-nitrated styrenes. It is noted that SO_3–dioxane has been the preferred reagent; SO_3–pyridine is much less reactive, requires higher temperatures, gives lower yields, and therefore has been employed much less often. Sulfur trioxide in liquid SO_2 has been used industrially, but product structures have not been determined. Acetyl sulfate was employed rarely.

TABLE XI
ALKYL AND ARYL ETHYLENES; CYCLOALKENES

Compound	Reagent[a]	Type major product(s)	Reference
C_2, Ethylene	VA	B	96
Ethylene	LI	B	178
C_3, Propylene	DI	D	449
Allyl chloride	LI	D	392
C_4, Isobutylene	PY	E, F (di)	470
Isobutylene	DI	E, F (di)	446, 450
Isobutylene	DI	F (mono)	19, 446
Methallyl chloride	DI	D	392
Methallyl chloride	DI	B, F	447
Methallyl chloride	TH	E or F	340
C_5, 2-Methyl-1-butene	DI	F	82
3-Methyl-1-butene	DI	G	79
2-Methyl-2-butene	DI	F	82
2-Methyl-2-butene	PY	E, F (di)	470
2-Pentene	DI	Not given	445
2-Pentene	TH	E or F	341
Cyclopentene	DI	C, D	84
C_6, 3,3-Dimethyl-1-butene	DI	G	79
4-Methyl-1-pentene	DI	E	82
4-Methyl-2-pentene	DI	G	79
1-Hexene	DI	C, D	83
1-Methylcyclopentene	DI	E	434
Methylenecyclopentene	DI	F	18
Cyclohexene	DI	C, D, E	84
Cyclohexene	DI	E	434
Cyclohexene	PY	C	462, 464
Cyclohexene	AC	D, E	435
C_7, 2,3,3-Trimethyl-1-butene	DI	G	79
4,4-Dimethyl-1-pentene	DI	E	82
4,4-Dimethyl-2-pentene	DI	G	79
Heptene (mixture)	LI	Not given	263
Methylenecyclohexane	PY	C	462, 464
Methylenecyclohexane	DI	F	19
C_8, 2,4,4-Trimethyl-1-pentene	DI	E	82
2,4,4-Trimethyl-2-pentene	DI	E	82
Diisobutylene	TH	E or F	340, 341
"Isooctene"	TH	E or F	340
Styrene	PY	E	462, 464, 472
Styrene	DI	D or E	87, 389
Styrene	DI	E	88
Styrene	DI	A	86
Styrene	DI	D	115
3-Chlorostyrene	DI	(Table X)	115, 508
1-, 2-, and 3-bromostyrenes	DI	(Table X)	115
1-, 2-, and 3-chlorostyrenes	DI	(Table X)	115
1-, 2-, and 3-fluorostyrenes	DI	(Table X)	115
2,4-Difluorostyrene	DI	(Table X)	115
3-Nitrostyrene	DI	(Table X)	508
4-Nitrostyrene	DI	(Table X)	508
C_9, 1-Nonene	DI	D	449
Propylene trimer	LI	E or F	398
1-Phenyl-1-propene	DI	E	452
2-Phenyl-1-propene	DI	E, F (di)	452
3-Phenyl-1-propene	DI	D	452
3-(Trifluoromethyl)-styrene	DI	(Table X)	115
3-(Trifluoromethyl-4-fluoro-styrene	DI	(Table X)	115
Indene	PY	E	462, 464
C_{10}, Camphene	PY	E	143, 462, 464
Camphene	AC	G	20a
1- and 6-nitrocamphenes	AC	G	20b
Diamylene	TH	E or F	340
2-Benzyl-1-propene	DI	F	89
C_{12}, 1-Dodecene	LI	Not given	148, 149
3,3-Dimethyl-2-phenyl-1-butene	DI	G	79
Triisobutylene	DI	E or F	446
Triisobutylene	TH	E or F	340
Propylene tetramer	LI	E or F	398
C_{14}, Tetradecene (normal)	LI	Not given	148, 149
1,1-Diphenylethylene	DI	E	85
C_{16}, 1-Hexadecene	DI	D	445, 449
Hexadecene	LI	D	178
Cetene	SO_3	E or F	294
1,1-Diphenyl-2-methyl-1-propene	DI	No reaction	81
Tetraisobutylene	LI	D	391
Tetraisobutylene	TH	E or F	340
Tetraisobutylene	DI	E or F	340
Diisoöctylene	AC	Not given	229a
C_{17}, 1-Heptadecene	DI	D	445, 449
Heptadecene	TH	Not given	340
2-Methyl-2-hexadecene	DI	E or F	446
C_{18}, Octadecene	AC	D	228
1-Chloro-9-octadecene	TH	E or F	340
1-Chloro-9-octadecene	AC	Not given	229a
C_{19}, Abietene	[b]	Not known	542
Miscellaneous			
C7 to 17 olefin fractions	LI	Not known	372
Cracked olefins (from carbon monoxide and hydrogen)	AC	D and, or E	262
Cracked olefin polymer (mol. wt. 1100)	VA	Not known	205
Diamylene polymer	TH	Not known	341
Polybutylene (mol. wt. 420)	VA	Not known	9
Polyisobutylene	TH	E or F	341
Polybutylene (C17 to 22)	AC	Not known	4

[a] Reagents are abbreviated as DI, SO_3–dioxane; PY, SO_3–pyridine; TH, SO_3–thioxane; VA, SO_3 vapor; LI, SO_3 in liquid SO_2; AC, acetyl sulfate. [b] SO_3 in tetrachloroethane.

2. *Halogenated Ethylenes*

All the compounds listed in Table XII sulfonate easily except tetrachloroethylene, which undergoes oxidation instead, but only slowly and at elevated temperature. Failure of this compound to sulfonate may be explained at least partially by the large steric requirements of the chlorine atoms. Because of its stability, complete miscibility with SO_3, and favorable boiling point (121°), tetrachloroethylene is a useful sulfonation solvent. One investigator has reported, however,

TABLE XII
CHLORINATED AND BROMINATED ETHYLENES

Compound	Reagent	Product	Reference
CH_2=CHCl	SO_3–pyridine	Acetaldehyde sulfonic acid	463
$(CH_3)_2C$=CHBr	SO_3–pyridine	Dimethylacetaldehyde sulfonic acid	463
ClCH=CHCl	Liquid SO_3	Monochloroacetaldehyde sulfonic acid	307
BrCH=CHBr	Liquid SO_3	Monobromoacetaldehyde sulfonic acid	390
Cl_2C=CHCl	Liquid SO_3	Trichloroethyl trichlorovinyl-sulfonate	192
Cl_2C=CCl_2	Liquid SO_3	Trichloroacetyl chloride	369
C_6H_5CH=CHBr	SO_3–dioxane	1-Bromo-2-phenylethene-1-sulfonic acid	511

that a solution of stabilized SO_3 in this solvent increases 37% in acid value on standing for twelve days at room temperature (374). Trichloroethylene, on the other hand, reacts so easily with SO_3 that it cannot be used as a solvent; it is noteworthy that with it sulfonation occurs on the carbon with only one chlorine. The four halides forming aldehydes sulfonate normally, since a halogen atom on the same carbon as a hydroxyl group in a product of structure D would be expected to generate an aldehyde group. The two monobrominated ethylenes sulfonate on different carbons, possibly for steric reasons.

Fluorinated ethylenes (Table XIII) present several factors of unusual interest. All of them, except F_2C=CH_2, form β-sultones, a type of compound isolated only recently in the one other case of styrene, as discussed above

TABLE XIII
SULTONES FROM FLUORINATED ETHYLENES

Compound	Yield, %	Reference
F_2C=CF_2	100	142, 165
F_2C=CFCl	86	142, 165, 264
F_2C=CCl_2	56	165
F_2C=CFH	60	142, 165
F_2C=CH_2	0	165
ClFC=CFCl	80	165, 264
F_2C=$CFCF_3$	85	142, 165, 264
F_2C=CFC_4H_9	Good	165
F_2C=$CF(CF_2)_6H$	Good	165
F_2C=$CF(CF_2CClF)_xCF_2Cl$ (x = 1 to 4)	72 to 82	264
F_2C=$CFCF_2CFCl_2$	73	264
F_3CCCl=$CClCF_3$	60	264

$$F_2C{=}CRR' \xrightarrow{SO_3} \overline{OF_2CCRR'SO_2}$$

The oxygen atom is always attached to the F_2C– group, except in the case of F_2C=CFCl, where the two possible sultones form in equal amounts (165, 264). With F_2C=CH_2, a quantitative yield of carbyl sulfate-type (structure B) product is formed; 34% was formed from F_2C=CFH. Only two other carbyl sulfates had been isolated previously. Two investigators (142, 165) have noted that the history of the SO_3 used affects the type of products formed. Tetrafluoroethylene and hexafluoropropylene form the sultones with freshly distilled SO_3, but undistilled material gives substantial carbyl sulfate in both cases. This difference may reflect a varying degree of polymerization of the SO_3, an effect not previously noted in alkene sulfonation. It may result also from the presence of a trace of moisture, since the addition of water to freshly distilled SO_3 produced the same effect.

3. *Vinyl Ethers and Esters*

These materials were sulfonated at 100° with SO_3–pyridine, forming the products shown in Table XIV.

TABLE XIV
VINYL ETHERS AND ESTERS WITH SO_3–PYRIDINE

Compound	Product isolated	Reference
Vinyl acetate	Acetaldehydesulfonic acid	482, 483
Vinyl butyl ether	Acetaldehydesulfonic acid; sulfate–sulfonate	462, 482, 490
Vinyl isoamyl ether	Acetaldehydesulfonic acid; sulfate–sulfonate	462, 490
Isobutenyl acetate	Dimethylacetaldehydesulfonic acid	482, 483
Isopropenyl acetate	Acetonesulfonic acid	482, 483

In all cases, the sulfur became attached to the carbon without oxygen. With the vinyl ethers, sulfate-sulfonates (formula C) were isolated; being typical formals, they were converted to the aldehydes with aqueous hydrochloric acid

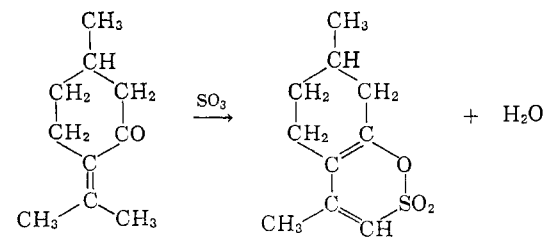
$$HO_3SCH_2CH(OR)OSO_3H \xrightarrow{H_2O} HO_3SCH_2CHO + ROH + H_2SO_4$$

Intermediates of type C were not isolated from the vinyl esters.

4. *Ketones and Aldehydes*

The limited work done with these compounds is summarized in Table XV. It appears that some of the unsaturated ketones, like the saturated analogs reviewed in an earlier section, sulfonate on a carbon adjacent to the carbonyl group, but that such may or may not occur on the double-bonded carbon. The saturated and unsaturated ketones are also similar in forming either mono- or disulfonates; with mesityl oxide, higher temperatures favor disulfonation.

Pulegone does not sulfonate as expected on the carbon adjacent to carbonyl, but reacts with acetyl sulfate (504) as shown



As stated earlier, camphor, which has a similar ring structure, also fails to sulfonate on the carbon adjacent to carbonyl. By the principle of vinylogy, the methyl group sulfonated in pulegone should, however, be as reactive as one attached directly to the carbonyl.

TABLE XV
UNSATURATED KETONES AND ALDEHYDES WITH SO_3–DIOXANE

Compound	Product	Temp., °C.	Yield, %	Reference
$(CH_3)_2C{=}CHCOCH_3$	$(CH_3)_2C{=}C(SO_3H)COCH_3$	0	50	144
$(CH_3)_2C{=}CHCOCH_3$	Mono- and disulfonates	35	—	144
$(CH_3)_2C{=}CHCOCH_3$	Disulfonate	70	50	144
$C_6H_5CH{=}CHCOCH_3$	$C_6H_5CH{=}CHCOCH_2SO_3H$	50	65	144
$(C_6H_5CH{=}CH)_2CO$	Mono- and disulfonates	50	73	144
$[(CH_3)_2C{=}CH]_2CO$	Monosulfonate	50	37	144
C15 to C57 Isophorones	Unidentified	40	—	317
Oleone[a]	Unidentified	—	—	231
Δ^4-Cholesten-3-one	6-Sulfonate	0	—	548
7-Ketocholestene[a]	4-Sulfonate	0	—	549
Pulegone[b]	A sultone (see text)	Cold	100	504
$CH_2{=}CHCHO$	$HO_3SCH{=}CHCHO$	0	98	144
$CH_3CH{=}CHCHO$	$CH_3C(SO_3H){=}CHCHO$	0	75	144
$C_6H_5CH{=}CHCHO$	Monosulfonate	60	12	144

[a] SO_3 in CCl_4 used. [b] Acetyl sulfate used.

The two sterols listed in Table XV also sulfonate under similar conditions with acetyl sulfate on carbon atoms separated from the keto group by vinyl groups, and in the case of cholesten-3-one this occurs, as with pulegone, in preference to reaction on an available adjacent carbon.

The two xyloquinones, as discussed later, resemble the unsaturated ketones both structurally and in manner of sulfonation. Benzoquinone and toluquinone, on the other hand, form hydroxysulfonates like alkenes.

The unsaturated aldehydes differ from their saturated analogs (as reviewed previously), and from both the saturated and unsaturated ketones, in sulfonating on the unsaturated carbon farther removed from the carbonyl group, although such could not have occurred in any case with the unsaturated ketones listed in Table XV, since that carbon atom either lacks hydrogen, or is attached to phenyl, which is sterically unfavorable to sulfonation.

Sulfur trioxide–pyridine is stated to be unsuitable for sulfonating unsaturated aldehydes (145).

5. *Alkenoic Acids, Esters and Glycerides*

Maleic anhydride gives an 85% yield of sulfomaleic anhydride upon heating at 50° with SO_3 (32); fumaric acid forms the same product. Crotonic acid at 50° yields 90% of a sulfonate of unstated structure (405). Both of these acids are resonance stabilized.

Alkenoic acids without resonance stabilization react at a lower temperature. In liquid SO_2 as solvent at −10°, undecylenic acid gave 80% unsaturated sulfonate, 10% hydroxysulfonate, and 10% sulfate–sulfonate (397, 405), all of unproved structure. Under similar conditions, oleic acid formed 54, 28 and 17% of the same three types of products. In both cases, 1 to 1.25 moles of SO_3 were used per mole of acid, and the total yield of sulfonate was 85 to 90%. Sulfoöleic acid, a commercial surface-active agent, has been manufactured by this type of process (460). Since this product has a carbon-to-sulfur bond, it is much more stable than the conventional type of "sulfonated" oleic acid made with concentrated H_2SO_4, which contains a relatively weak sulfate linkage. Oleic acid also has been sulfonated with two molar proportions of SO_3 at 5° using nitrobenzene as solvent (230); a hydroxysulfonate is stated to be the final product. Tetrachloroethylene also has been employed as solvent for this sulfonation (8); SO_3 (2 moles), dissolved in the solvent, was added dropwise at 10°. Another procedure involves the use of acetyl sulfate (68, 228, 256). The acetoxysulfonate presumably is formed; it hydrolyzes to the hydroxysulfonate upon treatment with water.

Oleic esters, on the other hand, react quite differently from the acid in liquid SO_2 (397, 405). At 1-to-1 molar ratio, half the ester remains unchanged, while the other half reacts with two moles of SO_3, presumably forming a product of type B, which hydrolyzes to types C and D during isolation. The ester groups are inferred to remain intact during sulfonation and workup. Sulfur trioxide requirements can therefore be halved in producing sulfoöleate esters, if the sulfoacid is esterified (397), rather than sulfonating the ester directly.

Oleic triglyceride (olive oil) has been sulfonated with SO_3–dioxane (444, 445) below room temperature, and with acetyl sulfate, made from SO_3 and glacial acetic acid at −20° (256). The latter reagent presumably yields an acetoxysulfonate similar to that formed from oleic acid. Pure oleic and linoleic monoglycerides are sulfated at 10° in 30 minutes with a large excess of SO_3–pyridine (73).

The "sulfonation" of castor oil [the triglyceride of ricinoleic (12-hydroxyoleic) acid] with concentrated sulfuric acid has long been practiced commercially on an entirely empirical basis for making leather- and textile-treating oils. The reagent is used in excess, and the products, being sulfates rather than sulfonates, are unstable. When an equal weight of SO_3 is used with petroleum ether as solvent, a product with considerably improved properties results (338), more so than when using lesser quantities of SO_3 or other reagents; this corresponds to approximately twelve moles of SO_3 per mole of castor oil. Patents describe treatment of castor oil with SO_3 in tetrachloroethylene (353), of acetylated castor oil with excess SO_3 in liquid SO_2 (220), of ricinoleic acid with SO_3 in carbon tetrachloride below 0° (270), and of ricinoleic acid amide with SO_3 in liquid SO_2 (229). Castor oil has reacted with acetyl sulfate at 30° (108), as has ricinoleic acid at low temperature (256). This treatment presumably sulfates the hydroxyl group and converts the olefinic group to acetoxy sulfonate. Castor oil also was treated with SO_3–pyridine at 35° (417), and with SO_3–N-methylethylene carbamate at 25° (424, 425); both of these adducts are said to sulfate the hydroxyl group but not to attack the double bond.

Dimerized linoleic acid and tall oil acids were sulfo-

nated with SO_3 in liquid SO_2 (397), and abietic acid (as gum rosin) was treated likewise in tetrachloroethane (542).

In nearly all of this work on fatty acids and their derivatives, no reaction products were identified; the work was empirical, with the objective of obtaining products with surface activity. Apparently none of these approaches is in commercial use, except in the case of oleic acid.

6. *Alkadienes and Cycloalkadienes*

1,3-Butadienes, as shown in Table XVI, give type E sulfonates with SO_3–pyridine in the four known cases.

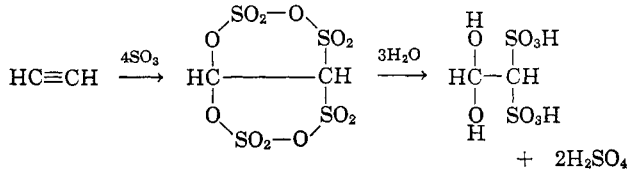
TABLE XVI
ALKADIENES AND CYCLOALKADIENES

Compound	Reagent	Product	Yield, %	Reference
Butadiene	SO_3–pyridine	Diene-1-sulfonate	50	462, 467, 469
2-Methylbutadiene	SO_3–pyridine	Diene-1-sulfonate	58	462, 467, 469
2,3-Dimethylbutadiene	SO_3–pyridine	Diene-1-sulfonate	57	467, 469
2,3-Dimethylbutadiene	SO_3-dioxane	2,3-Dimethyl-4-hydroxy-2-butene-1-sulfonic acid sultone	16	79
1,4-Dimethylbutadiene	SO_3–pyridine	2-Hydroxy-3-hexene-1-sulfonic acid (?)	—	462
1,1,4,4-Tetramethylbutadiene	SO_3–pyridine	A disulfonic acid	—	462
1,3-Cyclopentadiene	SO_3–pyridine	Diene-5-sulfonate	42	466
Guaiazulene	SO_3–dioxane	Cyclopentadiene ring sulfonates	—	506
1,3-Hexachlorocyclopentadiene	SO_3 liquid	$C_{10}Cl_{10}O$	85	195
Alloocimene dimer	SO_3 vapor	A sulfonate	—	400
Butadiene with isobutylene	SO_3 in liq. SO_2	Sulfonated copolymer	—	76
4-Phenylbutadiene	SO_3–pyridine	Diene-1-sulfonate	50	465, 468

Cyclopentadiene, on the other hand, forms a product of structure F, which can be explained by the unusually high reactivity of the methylene hydrogen atoms, or by the high degree of mobility of the ring unsaturation. Hexachlorocyclopentadiene resembles tetrachloroethylene in forming an oxygen-containing product rather than undergoing sulfonation.

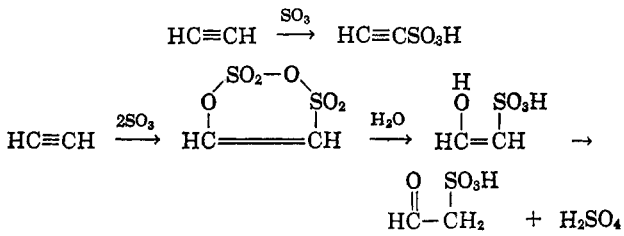
7. *Alkynes*

Acetylene reacts with SO_3 in liquid SO_2 at a 1 to 4 molar ratio, presumably forming a product of type B, which upon hydrolysis yields the expected acetaldehydedisulfonic acid (199, 200) as the monohydrate



The aldehyde group is highly reactive, and has been converted to numerous derivatives (200).

With SO_3–dioxane at 40°, acetylene reacts at lower ratios (146), to give a mixture of two products



1-Hexyne similarly yields 59% of the corresponding acetylenic sulfonate without forming any carbonyl derivative. Phenylacetylene, on the other hand, gave only the analogous sulfonated acetophenone or unidentified products (388a). Sodium phenylacetylide gave no definite products. This reaction deserves further study, since acetylenic sulfonates, with one doubtful exception (289), were previously unknown.

8. *Alkenols and Alkynols*

Sulfur trioxide–dioxane is stated to react with alcohol groups more rapidly than with unsaturated linkages, but to sulfonate the latter also when present in excess (443). However, allyl alcohol, 2-methyl-4-penten-2-ol, and 2-butyn-1,4-diol showed nearly quantitative sulfation of the hydroxyl groups in 3 minutes even using a large excess of reagent (485), indicating a longer time requirement for the other reaction.

Sulfur trioxide–pyridine, on the other hand, reacts almost exclusively with the hydroxyl group. It disulfates 2-butyne-1,4-diol (377) and sulfates propargyl (358), oleyl, and elaidyl alcohols (538) without attack of the unsaturated linkages, although SO_3–dioxane showed nearly the same selectivity with the last two alcohols (538). Sodium oleyl sulfate is an excellent detergent, and SO_3–pyridine has been employed commercially for preparing it (36). Oleyl alcohol has also been sulfated without double bond attack by SO_3–N-methylethylene carbamate at 35° (425). Geraniol (largely 2,6-dimethyl-2,6-octadiene-8-ol) similarly has reacted with SO_3–pyridine (520), as has also lomatiol (2-hydroxy-3-(3-methyl-4-hydroxy-2-buten-1-yl)-1,4-naphthoquinone) (177)—the latter on a semimicro scale at 100° in two minutes. An ethylene–allyl alcohol telomer, of molecular weight 246 with terminal unsaturation, was likewise sulfated with SO_3–pyridine using ethyl ether as solvent (310).

9. *Miscellaneous Unsaturated Aliphatic Compounds*

A series of twenty-one saturated fatty acid amides of methallylamine was sulfonated with acetyl sulfate (345) to give surface-active agents; the products were not analyzed. 2-Hydroxy-3-allyl-1,4-naphthoquinone, and the related compound lapachol, form cyclic sulfonates in good yields with acetyl sulfate (177); the expected type of hydroxysulfonate is hypothesized as intermediate in both cases.

V. REACTIONS WITH AROMATIC COMPOUNDS

A. BENZENE DERIVATIVES

1. Kinetics and Mechanism

Kinetic studies of sulfonation with SO_3 have been impeded by the extreme rapidity of the reaction in the initial stage and by the tendency of the SO_3 to form complexes with sulfonic acids during the final stage. Even with both reagents strongly diluted with 1,2-dichloroethane, benzene reacts with SO_3 in a fraction of a second (374), necessitating the use of a special continuous flow technique for making measurements. The initial stage only of the reaction was studied, since toward the end it becomes complex. A rate equation was thus derived for benzene

$$-dC_i/dt = 5.11C_{Hi}^{0.57}C_{Si}^{1.24}$$

where C_i is initial rate, C_{Hi} is initial concentration of benzene (g. moles per liter), and C_{Si} is initial concentration of SO_3 (g. moles per liter). Under the same conditions toluene was observed to react several times as fast as benzene, but no quantitative data were taken.

A series of aromatic compounds reacted with SO_3 in nitrobenzene solution (152, 521, 524), yielding the kinetic data summarized in Table XVII for the initial stage of the reaction. Some degree of correlation is noted for the three functions given for each compound, except for the dipole moment function in the case of nitroanisole.

TABLE XVII
REACTION RATES: ARYL SULFONATION WITH SO_3

	Velocity constant, liters/g. mole sec. k, 40°	Activation energy, cal./g. mole, E	Dipole moment functions $f(u)$
Benzene	48.8 (40.8)	4,800 (5,500)	0.00
Chlorobenzene	2.4	7,720	1.56
Bromobenzene	2.1	7,840	1.53
m-Dichlorobenzene	4.36×10^{-2}	9,220	3.12
Nitrobenzene	7.85×10^{-6}	11,400	3.97
p-Nitrotoluene	9.53×10^{-4}	11,025	3.56
p-Nitroanisole	6.29	4,320	5.13
1-Nitronaphthalene	3.27	7,900	—

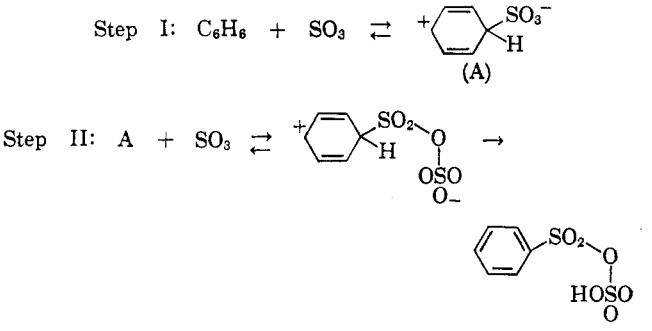
These data led to the rate expression

$$\text{Rate} \propto [\text{ArH}][SO_3]^2$$

In low strength oleum, on the other hand, the rate expression is (342, 527a)

$$\text{Rate} \propto [\text{ArH}][SO_3]$$

As the SO_3 content of the oleum is increased, the order with respect to SO_3 steadily increases, approaching 2 for pure SO_3 as shown above. This has led to the suggestion (152, 329, 521, 524) that dimeric SO_3 (S_2O_6) may be the effective species. However, the kinetic data can also correspond to successive reaction with two moles of monomeric SO_3—one attacking the ring, the other then protonating the incipient sulfonate group and also functioning as a base for removal of the proton, forming a pyrosulfonate



(The practical aspects of pyrosulfonate formation, with specific reference to benzene, are discussed subsequently.) Current thought favors monomeric SO_3 as the effective reacting species, not only when SO_3 itself is used, but also with sulfuric acid and oleum, as reviewed elsewhere (196, 342). Several other species have in the past been proposed for the last two reagents.

A kinetic study of the sulfonation of excess anisole with SO_3–dioxane in excess dioxane (527a), on the other hand, showed the reaction to be accurately pseudo-first order in SO_3 down to 95% completion. In this case, protonation of the incipient sulfonate group can be effected by sulfuric acid, hydrogen sulfate ion, anisolesulfonic acid or SO_3–dioxane, and the excess dioxane functions as the base for proton removal. The experimentally determined rate expression is

$$\text{Rate} \propto [\text{ArH}][SO_3][\text{HX}]$$

(HX represents the total concentration of all proton-supplying species, and is a constant for any given run.)

As indicated in Table XVII, the rates of reaction of various types of aromatic compounds with SO_3 vary widely. Substitution by halogen decreases the sulfonation rate considerably, but the nitro group is much more strongly inhibiting. Carbonyl and sulfonyl groups also slow sulfonation. On the other hand, substitution of the ring by alkyl, hydroxyl, alkoxy, or amino groups increases the ease of reaction. It is seen therefore that (aside from halogen, which is only mildly deactivating) *ortho-para*-directing groups facilitate reaction, while *meta*-directing groups hinder it.

Sulfur trioxide complexes have been of minor practical interest for ring sulfonation, since only the more active compounds (as hydrocarbons) react with the more active complexes (as SO_3–dioxane) at moderate temperatures. On the other hand, the complexes have proved highly useful for the sulfation of phenols and for the sulfamation of aromatic amines.

2. Hydrocarbons

(a) Benzene; Sulfone Formation.—Benzene reacts with SO_3 nearly instantaneously, as noted above.

At least three products always are formed—benzenemonosulfonic acid, diphenyl sulfone and sulfuric acid, and others may be formed—the proportions of each depending upon various factors. With both reagents in the vapor phase, a 50% yield of sulfone is obtained at 150–200° (116), and 30% at 70–80° (336). With excess SO_3 under the latter conditions, the product comprises 35% monosulfonic acid, 35% benzenedisulfonic acid, and 30% mono- and disulfonic acids of diphenylsulfone (336). At low temperature with excess SO_3, the sulfonic acid anhydride is a major product (9). Addition of SO_3, either as a liquid or vapor, to liquid benzene gives 15 to 18% sulfone, but addition of liquid benzene to liquid SO_3 yields 7.5% (207). Use of chloroform as reaction solvent reduces the sulfone to about 2% (130, 306). Liquid SO_2 has been studied most extensively as the solvent for this reaction, because of its favorable boiling point and cost, and because it dissolves both reagents and products (117, 118, 219, 306, 399). One of these studies (399) has led to several conclusions regarding the probable course of the reaction at 1-to-1 molar ratio, as well as the extent and possible mechanism of sulfone formation. The reaction is seen as occurring in two steps

$$\text{I}\quad C_6H_6 + 2SO_3 \rightarrow \underset{\text{(Benzenepyrosulfonic acid)}}{C_6H_5SO_2OSO_3H}$$

$$\text{II}\quad C_6H_5SO_2OSO_3H + C_6H_6 \begin{cases} \xrightarrow{A} C_6H_5SO_2C_6H_5 + H_2SO_4 \\ \xrightarrow{B} 2C_6H_5SO_3H \end{cases}$$

This scheme is felt (399) to explain several facts, for the reasons given: (a) the addition of hydrocarbon to the SO_3 gives about half as much sulfone as the reverse procedure (118, 207, 306, 399), because of mass action; (b) most of the total heat of reaction is evolved as the first half mole of SO_3 is added, since reactions IIa and B should be less exothermic than I; (c) the addition of 1 to 5 weight % acetic acid, or other organic acids, reduces sulfone formation from the 7 to 18% level to the 1 to 6% range (194, 399), since reactions III–IV are thought to predominate

$$\text{III}\quad C_6H_5SO_2OSO_3H + CH_3COOH \rightarrow C_6H_5SO_3H + CH_3COOSO_3H$$

$$\text{IV}\quad CH_3COOSO_3H + C_6H_6 \begin{cases} \xrightarrow{A} CH_3COC_6H_5 + H_2SO_4 \\ \xrightarrow{B} C_6H_5SO_3H + CH_3COOH \end{cases} \quad \text{(recycle to III)}$$

It is noted that only about half of the benzenesulfonic acid is formed by direct reaction of benzene with SO_3 (reaction I), the other half resulting from reaction IIB. In the presence of acetic acid, the second half is formed via acetyl sulfate (reaction IVB), since the acetic acid—present in only catalytic quantity—is thought to react cyclically. Reaction IVA, which would be analogous to sulfone formation as in reaction IIA, does occur, but only to a very slight extent (9). That reaction II largely controls the quantity of sulfone formed is shown by an increase in the yield of it from 6.5 to 18.3% as the temperature is raised from −9 to +75°, with reaction I being run at −9° in all cases (399).

This hypothesis has the weakness that the key intermediate, benzenepyrosulfonic acid, never has been isolated or characterized. Attempts to prepare it by treating one mole of benzene with two moles of SO_3 in liquid SO_2 have, on the other hand, given substantial yields of the sulfonic acid anhydride (9). When sulfonating dodecylbenzene, as is discussed in the next section, the anhydride forms even when using equimolar SO_3—yet sulfone formation is very low. Naphthalene also forms the sulfonic anhydride with excess SO_3, as discussed later. Definite evidence for the existence of pyrosulfonate does come, however, from a Raman spectral and freezing point study of mixtures of methanesulfonic acid and SO_3 (404a). Methanesulfonic anhydride also was identified after treating the reaction mixture with water. The author assumes that it was formed by interaction of the pyrosulfonate with water, but does not consider the more likely possibility that it may have been present in the original reaction mixture. It therefore appears that proposed mechanisms of aromatic sulfonation must account for anhydride formation as well as sulfone formation. Equilibria of the following types may be involved

$$2\ C_6H_5SO_2OSO_3H \rightleftarrows (C_6H_5SO_2)_2O + H_2SO_4 + SO_3$$

$$C_6H_5SO_2OSO_3H + C_6H_5SO_3H \rightleftarrows (C_6H_5SO_2)_2O + H_2SO_4$$

A mechanism similar to that outlined above, and also involving a pyrosulfonate intermediate, likewise has been suggested to explain sulfone formation in sulfonations with chlorosulfonic acid (314). The concept that pyro compounds, and related materials, may be key intermediates in sulfone formation may receive substantiation from the observation that methyl pyrosulfate, made from SO_3 and dimethyl sulfate, promotes sulfone formation between an aromatic sulfonic acid and a hydrocarbon (518)

$$RSO_3H + (CH_3OSO_2)_2O \rightarrow RSO_2OSO_2OCH_3 + HOSO_2OCH_3$$

$$RSO_2OSO_2OCH_3 + R'H \rightarrow RSO_2R' + HOSO_2OCH_3$$

Although direct continuous reaction of benzene with SO_3 is rapid and smooth, and therefore attractive industrially, high sulfone formation has been prohibitive to its commercial use. Aside from the work cited above, there has been no systematic study of the chemistry of sulfone formation. Empirically developed chemical "sulfone inhibitors," such as acetic acid already mentioned, and also including propionic and peracetic acids (194), acetic anhydride (194), sodium sulfate (456, 522), pyridine (99) and clay (98) are only partially effective. However, the addition of SO_3 to benzenesulfonic acid containing a large proportion of sodium sulfate, then the addition of benzene (522), is stated

to give low sulfone; most of the reaction product is then recycled. Another expedient involves reaction of the benzene with sulfuric acid, which gives no sulfone; the sulfuric acid, diluted by water of reaction, now is refortified by adding SO_3 and recycled. This type of operation, as exemplified by the Dennis–Bull and similar processes (196), has been used somewhat commercially, but the actual reagent is sulfuric acid rather than SO_3.

Benzene is not sulfonated by SO_3 complexes made from: thioxane, in 24 hr. at 40° (340); dimethylformamide (374); pyridine, at 150° (464); or dioxane, in 7.5 hours at 65°, or in 73 hours at 23° (374). However, $2SO_3$-dioxane is said to sulfonate benzene at room temperature in one day (449). These conflicting statements possibly may be explained by the presence of excess dioxane in the cases where no reaction occurred. It has long been known that benzene is sulfonated by acetyl sulfate (365), but only comparatively recently has this principle been applied to reduce sulfone formation as discussed above. *n*-Butyryl sulfate also sulfonates benzene (366).

(b) Toluene.—Toluene reacts several times as fast as benzene with SO_3 in a dilute solution of 1,2-dichloroethane (374). It also is disulfonated more easily, a reaction which can be reduced by adding SO_3 to the hydrocarbon, rather than *vice versa* (9, 399), even though this mode of addition gives more sulfone. Addition of liquid SO_3 to liquid toluene in the laboratory (207) gives about 5 weight % of disulfonate, but the milder SO_3 vapor forms less than 1% (9). Toluene also forms sulfone, but considerably less of it than benzene under comparable conditions (207, 399). Addition of liquid SO_3 gives about 11 weight % sulfone in the pilot plant (114), and 14% in the laboratory (207). Vaporized SO_3 is reported to give 22% (297). By using liquid SO_2 as reaction solvent, and especially by simultaneously adding the two reagents dissolved in SO_2 to the reactor (346, 399), sulfone formation can be reduced to 2%, and the product sulfonate is richer in *para* isomer (346) than when sulfuric acid is used. The toluene also can be added in two steps (555). Several American companies manufacture toluenesulfonic acid with SO_3 using this solvent. Sulfone formation can be further reduced, as with benzene, by adding acetic acid—either without (194) or with (347, 399) SO_2 as solvent. Malonic, azelaic and benzoic acids function similarly (399). When using SO_3 vapor, the addition of P_2O_5 is reported to raise the yield of *ortho* sulfonate and to eliminate the formation of the *meta* while holding that of sulfone constant; the addition of acetic anhydride is said to give the same yield of *ortho* sulfonate, while doubling that of sulfone and eliminating the *meta* (297). Another report (194), however, states that acetic anhydride functions like acetic acid in reducing sulfone formation during sulfonation of benzene. The addition of equivalent SO_3 to toluene dissolved in chloroform gives an excellent yield of monosulfonate (130). A saturated solution of SO_3–dimethylformamide in excess dimethylformamide sulfonates toluene very slowly at room temperature (374).

(c) The Xylenes; Other Short-Chain Alkylated Benzenes.—The addition of liquid SO_3 to *p*-xylene yields about 8 weight % of sulfone (194, 207), which is less than that formed from toluene; added acetic acid reduces the yield to about 3%. In liquid SO_2, the respective yields with mixed xylenes are 6 and 1.6% (399). *m*-Xylene is sulfonated immediately and quantitatively by $2SO_3$–dioxane (449), but not by SO_3-quinoline at 60° in 19 hours (374).

Ethylbenzene, sulfonated in liquid SO_2 with SO_3, formed sulfone to about the same degree as toluene (399). The same technique gives smooth sulfonation of the mixed isomers of diisopropylbenzene and of di-*sec*-amylbenzene (9). *tert*-Butylbenzene also reacts smoothly, but *p*-di-*tert*-butylbenzene, at 1-to-1 molar ratio, gives 0.5 mole of unreacted starting material and sulfonates apparently derived from isobutylene and from mono-*tert*-butylbenzene (9). This result is attributed to high steric hindrance of the *tert*-butyl group combined with its known ease of removal from the benzene ring under acid conditions.

Diphenylmethane was monosulfonated by SO_3–dioxane at room temperature (81).

(d) Long-Chain Alkylated Benzenes.—These sulfonates, commercially important as surface-active agents, are made from benzene alkylated with propylene tetramer. This process yields a mixture of alkylates with varying chain length, roughly separable by fractionation. A low boiling fraction, with average side chain about C-9, has been sulfonated with SO_3 vapor in one step (176) or in a two-stage process (127). The C-12 alkylated benzene fraction ("dodecylbenzene detergent alkylate") is of major commercial interest for making sulfonates widely used as surface-active agents. Sulfur trioxide vapor has been employed in the laboratory (207, 280), in the pilot plant (1, 114, 187), and on a commercial scale. The same procedure has been employed to sulfonate the high-boiling alkylate benzene fraction ("polydodecylbenzene") (203), and dodecyltoluene (182).

The presence of a long alkyl chain on the benzene ring leads to different behavior during sulfonation from that noted with benzene or toluene. Addition of liquid SO_3 to the undiluted liquid hydrocarbon gives unsatisfactory results with the long-chain compounds, apparently because of removal of the alkyl group by destructive dealkylation (203, 207). Unlike benzene or toluene, dodecylbenzene forms almost no sulfone, but it does give by-product sulfonic anhydride (201)

$$2RSO_3H + SO_3 \rightarrow (RSO_2)_2O + H_2SO_4$$

It is noteworthy that sulfones and anhydrides are both, in the over-all sense, formed by a dehydration process, which results differently depending upon the size of the substituting alkyl group. Steric factors also differ. Toluene yields considerable *ortho* sulfonate; this is also true of terminally-substituted long-chain benzenes, such as 1-phenyloctane or 1-phenyldodecane (217). However, as the phenyl group is moved toward the center of the chain, the yield of *ortho* isomer declines proportionately because of increasing hindrance of the two *ortho* positions on the ring. The extreme is reached with the *para* dialkylated benzenes in polydodecylbenzene; steric blockage is virtually complete and hardly any sulfonation occurs (203).

Liquid sulfur dioxide is an excellent solvent for sulfonating dodecylbenzene with SO_3 (59, 332, 354), and more than one American company has used this process commercially. Bis-(dodecylphenyl)-methane has reacted similarly (311). Laboratory and commercial equipment for using SO_3 in liquid SO_2 for sulfonating C-16 to 20 long-chain alkyl derivatives of benzene, cyclohexylbenzene, naphthalene, tetralin, biphenyl and phenol have been described (20); the sulfonates are stated to be of high purity.

(e) Petroleum Oils.—Petroleum lubricant raffinates are important raw materials for industrial sulfonates. Although the exact chemical composition of the derived sulfonates is not known, detailed study of the most important group—the so-called "mahogany" or oil-soluble materials—indicates (100) that they generally resemble the long-chain alkylated benzene sulfonates. Similar processes are applicable, including the use of SO_3 vapor, which has been employed in the laboratory (202) and on a commercial (273) scale, and the liquid SO_2 solvent approach (133, 248), which is also used commercially. The SO_2 solvent procedure entails no solvent cost, since it is produced by side reactions during sulfonation.

Although the reagents and reaction conditions for sulfonating lubricating oils can be similar to those used for dodecylbenzene, there are differences, since the latter is a relatively pure material, while the former is a mixture of hydrocarbons ranging from highly reactive to inert. Much of the art of petroleum sulfonate manufacture is concerned with the correct choice of the base stock and its method of refining, and with procedures for separation of the product sulfonate from sludge and unreacted oil. Petroleum hydrocarbons differ from dodecylbenzene in not forming sulfonic anhydrides during SO_3 sulfonation (202).

(f) Polystyrene.—Two types of sulfonated polystyrene are of commercial interest—one completely water soluble, prepared from styrene homopolymer, the other entirely insoluble in water and made from styrene–divinylbenzene copolymer. Both types of polymer are quite easy to sulfonate, therein resembling the nonpolymeric alkylated benzenes such as toluene or xylene. The polymeric nature of the hydrocarbons does, however, introduce certain unusual problems in their sulfonation.

In preparing the water-soluble product from styrene homopolymer, sulfone formation must be avoided, since over 0.1% gives an insoluble product (394). It is therefore somewhat surprising that a strong reagent like SO_3, which favors sulfone formation, can be used at all. Observance of the following conditions (394) makes this possible, using SO_3 either as vapor or liquid: (1) use of solvents (liquid SO_2 for the SO_3; carbon tetrachloride for the polymer, which is poorly soluble in SO_2) (393); (2) low dilutions (1 to 10%); (3) pure solvents; (4) low reaction temperature (−20 to 45°); (5) use of liquid SO_3 free of higher polymers; (6) efficient agitation; (7) concurrent feeding of reagents; (8) low molar excess of sulfonating agent; (9) use of a small reaction vessel; (10) use of vinyltoluene-containing polymers; and (11) rapid workup of the finished product. Liquid sulfur dioxide has proved especially useful as a reaction solvent for sulfonating polystyrene (394), and related materials such as styrene or vinyltoluene copolymers with acrylonitrile or maleic anhydride (44). Sulfur trioxide adducts, as with bis-(2-chloroethyl) ether (34, 171, 382), dioxane (35, 357, 418), thioxane (418), or acetone (74) also have been used. The first complex yields (394) a water-soluble sulfonate more easily than the second, but some cross-linking does occur, and stringent control is necessary.

Sulfonation of the copolymer is entirely heterogeneous. The problem in this case is not sulfone formation, but avoidance of straining and cracking of the polymer beads by too rapid reaction. Very little work has been reported on using SO_3 for this type of sulfonation. One patent (45) indicates some cracking of the copolymer beads using liquid SO_2 as solvent. A second patent describes treatment of a copolymer membrane using 1,2-dichloroethane as solvent (119). Similar membranes also have been sulfonated with benzoyl sulfate, made from SO_3 and benzoic acid (322).

$$C_6H_5COOH \xrightarrow{SO_3} C_6H_5COOSO_3H \xrightarrow{ArH} ArSO_3H + C_6H_5COOH$$

The benzoic acid is recovered and recycled.

3. Halogenated Benzenes and Alkylbenzenes

Chlorinated and brominated benzenes react immediately at room temperature with either liquid or vaporized SO_3, even though, as shown in Table XVII, halogenated benzenes sulfonate with more difficulty than the analogous unsubstituted hydrocarbons. Sulfur trioxide–dioxane conforms more closely to this statement, however, since it sulfonates benzene, but not chlorobenzene (449).

Monochloro-, iodo-, and -bromobenzenes are said to form only *para* sulfonates with SO_3 vapor (296),

although a small quantity of *ortho* sulfonate was reported from bromobenzene (344). Chlorobenzene has reacted with SO_3 in chloroform (130), but vaporized SO_3 without a solvent was used for 1,4-dichlorobenzene (308). Direct addition of liquid SO_3 to the undiluted organic compound over the range 25 to 105° was employed with chloro- (207), bromo-, 1-chloro-4-bromo-, 1,4-dibromo-, and 1,2,4-trichloro and tribromobenzenes (517). Sulfones usually are formed as by-products. The reaction of chlorobenzene with a mixture of SO_3 and $ClSO_3H$ to form the sulfonyl chloride is discussed subsequently under Halosulfonation. Hexachlorobenzene does not react with SO_3 even at 200° (17).

4-Iodotoluene, treated with SO_3 in chloroform, was sulfonated as expected *ortho* to the smaller methyl group (251). The position of the entering sulfonate was not established for 2-iodotoluene (316). Iodomesitylene, with SO_3 vapor, formed the sulfonate, together with mesitylenesulfonic acid and diiodomesitylene (500); diiodomesitylene gave these products and triiodomesitylene. 1,4-Diiodobenzene gave 10% sulfonic acid, together with some tri- and tetraiodobenzenes (94). Diiodothiophene undergoes similar disproportionation during sulfonation (474).

Benzotrichloride formed only *meta* sulfonate with SO_3 vapor (295); benzal chloride gave 10% *ortho*, 30% *meta* and 60% *para*. Benzotrifluoride was presumed to form *meta* sulfonate with SO_3 vapor at room temperature (558). 4-Methoxybenzotrifluoride, treated with SO_3 vapor at 0° and held at that temperature for 12 hours, was assumed to form the 3-sulfonic acid; during the long digestion period, the methyl group was largely removed, yielding the phenol (558). β-Bromoethylbenzene and 1-(β-bromoethyl)-2-chlorobenzene gave good yields of 4-sulfonate with SO_3 dissolved in methylene chloride (330), or with SO_3 vapor; a β-bromoethyltoluene was treated likewise. Some sulfone was formed from the first compound.

4. Amines and Anilides

(a) Ring Sulfonation.—1-Amino-2,4-dimethylbenzene is sulfonated in the 6 position by treatment with SO_3 vapor in tetrachloroethane, and refluxing at 145° (335). Benzanilide gives a poor yield of benzoylsulfanilic acid with SO_3 vapor without using a reaction solvent (164), showing that an amino-substituted ring reacts more easily than one with a carbonyl group.

Aniline is converted to the pyridine salt of sulfanilic acid by SO_3–pyridine at 170° (47). 4-Toluenesulfonanilide also is converted to the *para* sulfonate by the same reagent in 8 hours at 190° (42). Dimethylaniline likewise is sulfonated in the *para* position by SO_3–trimethyl- or triethylamines (11). In fact, SO_3–dimethylaniline is converted to this sulfonate simply upon warming to 60° (547). Similarly N-phenylpyrrolidine is converted to the *para* sulfonate in 25% yield by SO_3–pyridine at 112° in 10 hours, or in 61% yield with SO_3–dioxane in 1 hour at 80° (556).

The reaction of acetanilide with a mixture of SO_3 and $ClSO_3H$, to form the sulfonyl chloride, is discussed subsequently under Halosulfonation.

(b) Sulfamation.—Amines form sulfamates with SO_3 complexes at moderate temperature

$$RR'NH \xrightarrow{SO_3\cdot Amine} RR'NSO_3H\cdot Amine$$

(either or both R and R′ = H, aliphatic or aromatic)

The basic chemistry of the sulfamation reaction has been discussed and the various reagents compared (22). Sulfur trioxide–pyridine usually has been employed between room temperature and 100°, with excess pyridine as the reaction medium. Amines so reacting include aniline (92), methylaniline (287), 4-phenylaniline (92), 4-amino-4′-nitrodiphenylsulfone (43), 4,4′-bis-(4-aminobenzoylamino)-stilbene-2,2′-disulfonic acid and its methylamino analog—both disulfamated (3), 2-(4-aminophenyl)-6-methylbenzthiazole, and its methylamino analog (2). *para*-Phenylenediamines, N-monosubstituted with methyl, 4-tolyl, or 4-methoxyphenyl, were disulfamated similarly (293).

As shown in Table XVIII, sulfamate yields from nitroanilines increase with increasing alpha methylation of the complexing pyridine (440); since steric hindrance also increases correspondingly, this may be a factor.

TABLE XVIII
SULFAMATION OF NITROANILINES WITH SO_3–METHYLPYRIDINES

Compound sulfamated	Percentage yield of sulfamate			
	Pyridine	2-Methyl pyridine	4-Methyl pyridine	2,6-Dimethyl pyridine
2,4-Dinitroaniline	60–80	100	—	—
2,6-Dinitroaniline	0	21	—	26
4-Nitrodiphenylamine	6	70	3	83

This approach, using SO_3–2-methylpyridine, was extended to the disulfamation of 1,3-diamino-4,6-dinitrobenzene, and of 4,4′-diamino-3,3′-dinitrobiphenyl (441).

Sulfur trioxide–quinoline in excess quinoline sulfamates N-(4-aminophenyl)-acetoacetamide and 1-(3′-aminophenyl)-3-methyl-5-pyrazolone (258). Diphenylamine has been sulfamated with SO_3–dimethylaniline (287).

In a mixture of 2- and 4-ethylanilines, the 4-isomer sulfamates exclusively first for steric reasons, using SO_3–triethylamine in chloroform for 5 hours at room temperature (240); isomer separations can be so effected.

The amine complexes effect sulfamation in cold aqueous medium, since loss of the adduct by hydrolysis occurs more slowly. Aniline has been so treated with SO_3-pyridine (47). The trimethylamine complex has reacted in aqueous suspension with 2,5-diethoxyaniline (11).

Equimolar SO_3–dioxane converts aniline to 0° mainly

to the aniline salt of phenylsulfamic acid (253), a small quantity of sulfanilic acid also being formed as by-product. Thus, only half the aniline undergoes sulfamation. At room temperature, on the other hand, sulfamation of aromatic amines with excess SO_3–dioxane is quantitative in 5 minutes (484, 486), allowing use of this approach for analytical estimation of aniline, the three toluidines, a xylidine, 4-anisidine, benzidine, methylaniline and ethylaniline. Diphenylamine is sulfonated in the ring even with cooling. Nitroanilines and 2,4-dichloroaniline react only partially; sulfanilamide reacts on the amino but not on the sulfonamido group. N-Arylsulfamic acids are too unstable to isolate except as salts (253), therein differing from the N-alkyl analogs.

Sulfamation of aminophenols is discussed in a later section.

5. *Phenolic Compounds*

(a) Ring Sulfonation.—These compounds undergo ring sulfonation when treated with free SO_3, or with the SO_3 complexes at elevated temperature. Sulfation occurs with the SO_3 adducts at moderate temperature.

Phenol was monosulfonated with liquid SO_3 at 50°, disulfonated at 95°, and trisulfonated at 120° (137). 2-Cresol, guaiacol, 2-chlorophenol, 2,6-xylenol, and resorcinol likewise were monosulfonated above their melting points. Phenol has been disulfonated with SO_3 vapor (543), and monosulfonated in the 4-position by SO_3-pyridine at 170° (47). Equivalent SO_3 vapor selectively sulfonates the *meta* isomer in *meta-para*-cresol mixtures, allowing separation (151); the *meta* cresol is recovered by steam desulfonation. Thiophenol is oxidized by SO_3 (408)

$$2C_6H_5SH + SO_3 \rightarrow (C_6H_5S)_2 + SO_2 + H_2O$$

Salicylic acid reacts with liquid SO_3 in tetrachloroethylene suspension (207), and methyl salicylate with SO_3 vapor at 25 to 110° (241). Solid 3-hydroxy- (414) and 4-hydroxybenzoic (282) acids were treated with SO_3 vapor without a solvent, a rather cumbersome procedure. The same method was employed with 3-(4-hydroxyphenyl)-propionic (phloretic) acid (337).

At room temperature, SO_3–dioxane sulfonates anisole (449, 527a), but sulfates phenol (449); anisole also has been sulfonated with SO_3 vapor (111) as well as with SO_3–pyridine (477). The rate of reaction of 4-nitroanisole with SO_3 is reported in Table XVII. Diphenyl ether gives 93% of the 4-sulfonic acid with acetyl sulfate (442). Dodecyldiphenyl ether has been disulfonated by adding SO_3 dissolved in methylene chloride (436); this type of product is a commercial surfactant (147). Sulfur trioxide in chloroform monosulfonates diphenyl sulfide in 90% yield (128). Phenyl benzoate was mono- and trisulfonated in a heterogeneous reaction with SO_3 vapor (163); excess SO_3 also causes ester cleavage in this case.

(b) Sulfation.—The sulfation of phenols is always effected with SO_3 complexes at moderate temperatures—often below room temperature and never above 100°; at higher temperatures sulfonation occurs, as with phenol using SO_3–pyridine at 170° (47). Amine complexes have invariably been used, except for one reference to the sulfation of phenol with SO_3-dioxane (449). The reaction can be conducted either in anhydrous (Table XIX or in aqueous alkaline (Table XX) medium.

TABLE XIX
SULFATION OF PHENOLS IN ANHYDROUS MEDIUM WITH SO_3–AMINE ADDUCTS

Complexing amine	Phenol	Solvent	Temp., °C.	Reference
Pyridine	Phenol	None	50	47
Pyridine	Thiophenol	None	100	50
Pyridine	Phenol, thymol, eugenol	CS_2	45	520
Pyridine	2- and 4-nitrophenols	Benzene	80	102
Pyridine	Phenolphthalein	CCl_4	77	404
Pyridine	Phenol, cresols	Pyridine	0	175
Pyridine	4-Hydroxybenzoic acid	Pyridine	0	140
Pyridine	Dodecylphenol	Pyridine	25	383
Pyridine	Dibromosalicyl	Pyridine	45	291
Pyridine	Hydroquinone	Pyridine	65	95
Pyridine	*N*-Acetyl and *N*-lauroyl-*l*-tyrosines	Pyridine	100	380
Quinoline	Phenol	Quinoline	0	175
Dimethylaniline	Phenol, three cresols, eugenol, isoeugenol	CS_2	45–100	102
Dimethylaniline	Five xylenols	CS_2	45–100	123
Dimethylaniline	2-, 3-, and 4-aminophenols	CS_2	25	91
Dimethylaniline	Methyl salicylate	Dimethyl-aniline	25	360
Diethylaniline	Phenol	SO_2	−10 to 25	102

TABLE XX
SULFATION OF PHENOLS IN AQUEOUS MEDIUM WITH SO_3–AMINE ADDUCTS

Complexing amine	Phenol	Reference
Trimethylamine	Phenol	362
Trimethylamine	2-, 3-, and 4-cresols	362
Trimethylamine	2-, 3-, and 4-hydroxybenzoic acids	362
Trimethylamine	2- and 4-chlorophenols	362
Trimethylamine	2-, 3-, and 4-nitrophenols	362
Trimethylamine	2-Methyl-5-nitrophenols	361
Trimethylamine	Guaiacol	304
Triethylamine	2- and 4-phenylphenols	240
N-Ethylmorpholine	Phenol	304
N-Ethylmorpholine	Hydroquinone	406
Pyridine	Phenol	47

A study of the sulfation of phenol, the three cresols, the three nitrophenols, the three hydroxybenzoic acids, and 2- and 4-chlorophenols with SO_3–trimethylamine in aqueous sodium carbonate at 50 and 100° (362) showed yields to decrease as alkalinity, dilution or temperature increased. Yields varied from less than 1 to 84%. When sulfating under anhydrous conditions, the older technique involved adding $ClSO_3H$ to pyridine in chloroform, then adding the phenol in pyridine, and finally refluxing briefly; carbon disulfide or carbon tetrachloride were also used as solvents. A more satisfactory method (175) comprises dissolving the phenol in pyridine, cooling to 0°, adding the $ClSO_3H$, and at

once adding aqueous potassium hydroxide to form the potassium salt. This method is more rapid, and gives better yields of lighter-colored products. The same procedure can be employed with dimethylaniline, but pyridine works better with phenol, the cresols and polyalkylated phenols.

Ortho isomers sulfate with difficulty compared to the other two. With the cresols and chlorophenols, 40 to 70% yields of *ortho* sulfates can be obtained, however (362). With the nitrophenols, on the other hand, the maximum reported yield of *ortho* sulfate is 34% (362), compared to 94% for the *para* isomer (102). Salicylic acid gave less than 1% sulfate, while the other two isomers formed 43 to 69% (362). 4-Phenylphenol sulfates much faster than the 2-isomer—a difference which can be used for isomer separation (240). This difference in isomer reactivity may be explained by steric effects, or by the difference in the degree of dissociation of the phenolic hydrogen (11, 240). In the case of salicylic acid, interaction of the hydroxyl and carboxyl groups may be responsible (362), since methyl salicylate is sulfated in good yield with SO_3–dimethylaniline (360).

The sulfation of aminophenols is discussed in the next section.

6. *Aminophenols*

Although phenolic hydroxyl groups are sulfated, and aromatic amino groups are sulfamated, by the same reagents under the same general conditions, limited evidence (91, 93) indicates that either type of product can be obtained from the aminophenols without substantial contamination by the other. Available data, summarized in Table XXI, indicate that equivalent complexing base yields sulfate, excess base sulfamate. Aminonaphthols, discussed subsequently, behave similarly in some cases.

TABLE XXI
AMINOPHENOLS

Compound	Complexing base	Amount base used	Product	Reference
2-, 3-, and 4-aminophenols	Dimethylaniline	Equivalent	Sulfate	91
2-Aminophenol	Dimethylaniline	Excess	Sulfamate	91
2-, 3-, and 4-aminophenols	Pyridine	Excess	Sulfamate	91, 93
3-(4′-Aminobenzoylamino-)phenol	Pyridine	Excess	Sulfamate	259
2-Hydroxynaphthalene-3-carboxylic acid-4′-aminoanilide	None	SO_3 in tetrachloroethylene used	Sulfamate	259

7. *Mono- and Dicarboxylic Acids and Related Compounds*

Benzoic acid forms benzoyl sulfate with SO_3–dioxane at room temperature (449)

$$C_6H_5COOH \xrightarrow{SO_3} C_6H_5COOSO_3H$$

Molten benzoic acid is sulfonated conveniently on the ring by adding liquid (207) or vaporized (296) SO_3. Only the *meta* sulfonate is formed; sulfuric acid, on the other hand, forms other isomers (296, 376). Benzoyl sulfate is presumably the intermediate with SO_3 as with sulfuric acid (376), since the SO_3 does not boil out even though the reaction proceeds much above its boiling point (207).

Solid 4-toluic acid was treated with SO_3 vapor (180). A more convenient procedure is addition of liquid SO_3 to the molten toluic acids (207). 3,5-Dimethylbenzoic acid is converted to a mixture of the two possible isomers (381), both of which are abnormally oriented relative to the carboxyl group. Solid 4-*n*-propyl- and 4-isopropylbenzoic acids reacted with solid SO_3 (546).

Solid 3-chlorobenzoic acid is only partially sulfonated with SO_3 at room temperature (356). Complete reaction is realized by adding liquid SO_3 to the molten chlorobenzoic acids (207). Molten 4-bromobenzoic acid is sulfonated completely at 160° in one day (77).

3-Nitrobenzoic acid may decompose violently upon heating with liquid SO_3 (9).

Aromatic acid chlorides, upon heating with SO_3 for 3 hr at 110 to 160° form the sulfonyl chlorides of the acids

$$C_6H_5COCl \xrightarrow{SO_3} C_6H_4(1\text{-}COOH)(3\text{-}SO_2Cl)$$

This process has been applied to benzoyl, 2-toluyl, 4-chlorobenzoyl (324) and other (323) acid chlorides. Benzoyl chloride previously had (161) been thought to yield the carboxylic acid chloride of the sulfonic acid. A nitrobenzoyl chloride is reported (161) not to react.

Ethyl and amyl benzoates undergo ester cleavage before sulfonation occurs (164) with SO_3.

Benzonitrile reacts with SO_3 vapor (158)

$$2C_6H_5CN \xrightarrow{SO_3} C_6H_5C\overset{N}{=}\underset{O}{\overset{|}{C}}C_6H_5 \quad \underset{SO_2}{\overset{N}{=}}$$

4-Tolunitrile reacts similarly, as does also acetonitrile, which was discussed previously.

Benzamide is dehydrated by SO_3 to benzonitrile (162); apparently further reaction occurs, since hydrolysis of the reaction product gave a salt of sulfobenzoic acid. Melted with equivalent SO_3–pyridine at 150° for 2 minutes, benzamide gives an 80% yield of sulfamate (57). Benzenesulfonamide likewise forms 60% sulfamate at 200° in 5 minutes. Solid hippuric acid was partially converted to the sulfonate with SO_3 vapor (410).

Phthalic anhydride is 99% monosulfonated with SO_3 at 190–210° in 23 hours (526). With three equivalents of SO_3, the reaction is largely completed in 6 hours at 100° (189), and entirely complete after 10 more hours at 190°. This sulfonation also can be run in an auto-

clave (188), although such is not required, since the SO_3 apparently forms an adduct of some kind with the anhydride and therefore is retained in the reaction mixture as with benzoic acid. In the presence of mercuric sulfate, the 3,5-disulfonated anhydride is formed in 93% yield even in 8 hours (526). Isophthalic acid also is 98% monosulfonated by SO_3 at 205° (106, 242).

8. Sulfonic Acids

Benzenedisulfonic acid is commercially important for producing resorcinol. Although the monosulfonation of benzene proceeds with extreme ease, the introduction of the second sulfonic group requires drastic conditions, namely, heating several hours with excess SO_3 in the range 100 to 175° (8, 117, 296, 306, 455). Sulfur trioxide apparently gives only the *meta* disulfonate (296); sulfuric acid or oleum, on the other hand, forms *para* disulfonate to a degree depending upon reaction time and temperature.

If sulfuric acid is used for the monosulfonation of benzene and 65% oleum then is added to introduce the second group, as has been done commercially (196), much spent sulfuric acid is formed, yielding 6.5 tons equivalent gypsum by lime neutralization per ton of resorcinol produced. In contrast, a theoretically perfect process, using SO_3 for both steps, would require only 1.45 tons of reagent and would give no gypsum. This situation has naturally led to commercial interest in the stronger reagents, which, however, form more sulfone. The addition of sodium sulfate as a "sulfone inhibitor" has been suggested (455) for reducing it from 50% to the range from 4 to 14%. In another proposal (174), SO_3 is added to recycled disulfonic acid at 140°, with or without sodium sulfate sulfone inhibitor, followed by the introduction of benzene. In actual commercial practice, the first step has been effected with low strength oleum, and the second by adding SO_3 to the reaction mixture (221); this procedure represents a practical compromise between high formation of sulfone and production of a large quantity of spent acid. A major problem in working with benzene disulfonation has been analysis of the reaction products. Recent work (415) has shown that polarographic analysis may prove helpful. Optical methods also have been used (336).

Bromobenzenesulfonic acid is smoothly converted to the disulfonate in good yield by 10 hours of heating with SO_3 at 220° (328). Mesitylenedisulfonic acid gave a low yield of trisulfonate at 120° (25).

9. Nitro Compounds

Nitrobenzene reacts with SO_3 vapor at 140° (296). Substitution occurs only in the *meta* position; sulfuric acid, on the other hand, forms a small quantity of *para* isomer. Gradual addition of liquid SO_3 to nitrobenzene over the temperature range 100 to 150° is a practical sulfonation procedure; some sulfone is formed (9). Data for the rates of reaction of nitrobenzene, 4-nitrotoluene, and 4-nitroanisole with SO_3 are presented in Table XVII. The sulfonation of nitrobenzoic acid and nitrobenzoyl chloride is mentioned in the section on Carboxylic Acids. The reaction of nitrobenzene with a mixture of SO_3 and FSO_3H to form the sulfonyl fluoride is reviewed in the next section.

10. Halosulfonation Reactions

The conversion of aromatic compounds to sulfonyl chlorides can be effected by their addition to a mixture of SO_3 and $ClSO_3H$, the function of the former being to effect sulfonation, of the latter to convert the sulfonic acid to the sulfonyl chloride

$$RH \xrightarrow{SO_3} RSO_3H \xrightleftharpoons{ClSO_3H} RSO_2Cl + H_2SO_4$$

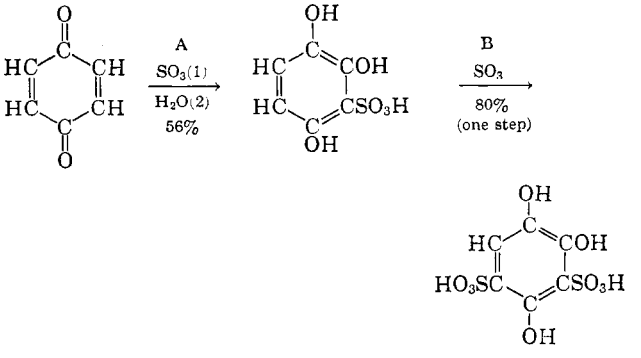
The sulfur trioxide is applied in quantity equivalent to the organic compound, while the chlorosulfonic acid is used in excess to drive the equilibrium as far to the right as possible. The reaction has been applied to benzene, chlorobenzene, 1,2,4-trichlorobenzene, and to acetanilide, and has been used to prepare the sulfonyl fluoride of nitrobenzene (8, 191, 207). It also has been applied to isophthalic acid (419). Sulfones are formed as by-products. The alternative approach, involving $ClSO_3H$ as the sole reagent, liberates equivalent HCl in the first step, and in the case of acetanilide yields a sulfonyl chloride of inferior stability.

The preparation of the sulfonyl chlorides of aromatic acids, by reaction of the acid chloride with SO_3, is discussed in a preceding section.

11. Miscellaneous Benzene Derivatives

Benzaldehyde (296) has been reported to yield only the *meta* sulfonate upon treatment with SO_3 vapor at 140°. Others, however, (9, 161) have found that the reaction gives mixtures containing only a small amount of the desired product, possibly because of the sensitivity of the aldehyde group to oxidation.

Benzoquinone (473) does not react with SO_3–pyridine, but it does react with SO_3–dioxane, depending upon the mole ratio used



In reaction A, the quinone reacts as a typical alkene

via a β-sultone or carbyl sulfate type intermediate, as discussed in a previous section. Reaction B is a typical phenol ring sulfonation. Toluquinone also undergoes a reaction similar to A, as does 1,4-naphthoquinone; *p*-xyloquinone, on the other hand, forms the mono- or disulfonated quinone, depending upon the proportions used; *m*-xyloquinone forms a monosulfonated quinone. These reactions parallel the behavior of mesityl oxide as shown in Table XV; there is a structural resemblance. Duroquinone, as expected, did not react, since it has no reactive hydrogen atoms.

B. NAPHTHALENE DERIVATIVES

1. Hydrocarbons

Although naphthalene sulfonation with sulfuric acid has been studied very extensively, little attention has been given to the use of SO_3. Side reactions, including sulfone formation and polysulfonation, are apparently extensive with SO_3 vapor (69, 150). With chloroform as solvent, an 88% yield of monosulfonate is obtained below 10° (130). Sulfur trioxide–dioxane (449) and SO_3–thioxane (340) sulfonate naphthalene at room temperature, and SO_3–pyridine at 170° forms mostly 1-sulfonate, with a little of the 2-isomer (47).

With more than one molar equivalent of SO_3, naphthalene yields different products depending upon conditions. With dimethyl or diethyl sulfates, or phosphorus oxychloride, as reaction solvents, 1.5 moles of SO_3 vapor at 25° gives the anhydride of 1-naphthalenesulfonic acid (299)

$$2C_{10}H_8 + 3SO_3 \rightarrow (C_{10}H_7SO_2)_2O + H_2SO_4$$

As noted earlier, benzenoid compounds also form anhydrides with excess SO_3, although adding dimethyl sulfate promotes their conversion to sulfones rather than to anhydrides. A 41% yield of 1,5-disulfonate results from the addition of two moles of SO_3 at 0 to 10° to naphthalene dissolved in chloroform (130). With three moles, the yield increases to 50%, which goes to 65% upon standing 24 hours. This shows that the disulfonate forms a stable adduct with the excess SO_3 and only slowly releases it for conversion of mono- to disulfonate (130). A 75% yield of very pure 1,5-disulfonate is claimed upon treating naphthalene dissolved in tetrachloroethylene with SO_3 at 20° (336).

1-Methylnaphthalene sulfonates quantitatively in the 4-position with SO_3–dioxane (226).

Dialkylated naphthalene sulfonates are commercial surface-active agents. Diamylnaphthalene has been sulfonated with SO_3 vapor at 60 to 109° (207); product performance is comparable to the sulfonate made with sulfuric acid. *tert*-Butylnaphthalenes have been sulfonated with SO_3 in liquid sulfur dioxide (349), as were also the C-16 to 20 long-chain alkylated naphthalene and tetralin (20). Dinonylnaphthalene reacted at −15° with 20 molar per cent excess SO_3 using a mixture of liquid sulfur dioxide and carbon tetrachloride as solvent (348).

Tetrahydronaphthalene (tetralin) is sulfonated in the 2-position with SO_3–dioxane (227), as is also 1,4-endoethylene-1,2,3,4-tetrahydronaphthalene (274). Decahydronaphthalene (decalin) is converted to an unidentified sulfonic acid in two hours by treatment with SO_3 vapor at 193° (121). Dehydrogenation undoubtedly occurs prior to sulfonation.

2. Naphthylamines

(a) Ring Sulfonation.—2-Naphthylamine is converted to the 1-sulfonate by treatment with SO_3 vapor in tetrachloroethane, then heating for 5 hours at 95° (499) or 2 hours at 145° (335). A 90% yield resulted.

(b) Sulfamation.—Sulfur trioxide–pyridine in excess pyridine sulfamates 1- and 2-naphthylamines (92), and disulfamates 1-amino-4-(phenylamino)-naphthalene (293). At 0°, 1-naphthylamine is sulfamated quantitatively with excess SO_3–dioxane in 5 minutes (486); slight ring sulfonation also occurs under similar conditions with 2-naphthylamine.

3. Naphthols

(a) Ring Sulfonation.—1-Naphthol gives a good yield of 2-sulfonic acid with SO_3–dioxane (226). 2-Naphthol is sulfonated in the 1-position with SO_3 vapor at 25° using tetrachloroethane solvent (498); with SO_3–dioxane it forms the 6-sulfonic acid (226).

(b) Sulfation.—The naphthols can be sulfated, similarly to the phenols, either in anhydrous or aqueous medium. 2-Naphthol reacted with SO_3–pyridine in carbon disulfide (520), and both naphthols have been sulfated at 100° for 4 to 8 hours with SO_3–dimethyl- or diethylanilines (102). 2-Nitro-1-naphthol reacted with SO_3–dimethylaniline in carbon disulfide (93), and 6-nitro-2-naphthol with SO_3–pyridine at 25° in excess pyridine (78). A study (175) has shown that the two naphthols preferably are sulfated with SO_3–dimethylaniline rather than with SO_3–pyridine; the reverse is true of phenol and the cresols. The preferred procedure involves cooling the naphthol, dissolved in dimethylaniline, to 0°, adding $ClSO_3H$, and then immediately converting to the potassium salt with aqueous KOH.

2-Naphthol is quantitatively sulfated by SO_3–trimethylamine in aqueous alkaline solution at room temperature (304). 1-Bromo-2-naphthol reacted similarly with SO_3-N-ethylmorpholine.

5-Benzamido- and 8-benzamido-1-naphthols have been sulfated with SO_3–triethylamine in both anhydrous and aqueous media (240). In the former case, using excess pyridine as solvent at room temperature for 24 hours, only the 5-isomer sulfated, since it is less sterically hindered. However, in aqueous medium only the 8-isomer reacted, since the 5-isomer is much less soluble and is therefore less available for reaction.

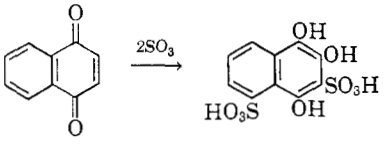
4. *Aminonaphthols*

2-Amino-7-naphthol and 5-amino-2-naphthol form the sulfamates with SO_3–quinoline in the presence of excess base (258), as does also 2-amino-6-naphthol hydrochloride with SO_3–pyridine using excess pyridine (91). The last compound gave the sulfate with SO_3–dimethylaniline in the absence of excess base using carbon disulfide as reaction medium (91). These reactions resemble those of the aminophenols, as discussed earlier. However, even with excess dimethylaniline, 2-amino-6-naphthol hydrochloride forms the sulfate (91), rather than the sulfamate as might be expected. 2-Amino-7-naphthol is reported to form the sulfamate with SO_3–quinoline even with a deficiency of base (259). 2-Amino-1-naphthol, as hydrochloride and as phthalamate, yields only sulfate, regardless of the reagent used and whether or not excess base is present (91).

5. *Miscellaneous Naphthalene Derivatives*

1-Nitronaphthalene, as indicated in Table XVII, reacts with dissolved SO_3 much faster than nitrobenzene, and at about the same rate as the halogenated benzenes (152). This is at least partially explained by the assumption that sulfonation occurs on the unnitrated ring.

1,4-Naphthoquinone reacts with SO_3–dioxane in the same manner as benzoquinone, as discussed earlier, except that the non-quinonoid ring also sulfonates (473)



1,2-Naphthoquinone, on the other hand, resembles the xyloquinones, since it forms a quinone disulfonate.

C. POLYCYCLIC COMPOUNDS

1. *Ring Sulfonations*

The sulfonation of polycyclic hydrocarbons with sulfuric acid gives mixtures of several mono- and disulfonates, a situation which is not greatly improved by varying conditions or even by accepting low total conversion to sulfonate (453). Considerably better results have been noted with SO_3 complexes. In the case of anthracene, the use of a mixture of sulfuric acid and acetyl sulfate greatly reduces disulfonation; the product comprises 20% disulfonate, 50% 1-monosulfonate and 30% 2-monosulfonate (41). Acetyl sulfate in the absence of sulfuric acid forms 50% each of the two monosulfonates. However, SO_3–pyridine yields only 1% of the 2-sulfonate at 165 to 175° (40, 41), the rest being the 1-isomer. In this case a paraffin hydrocarbon was employed as reaction solvent, and a 40% total conversion to sulfonate was obtained. At the same temperature, the use of nitrobenzene as solvent gave only 15–20% conversion, but the product was pure 1-sulfonate.

Phenanthrene behaves similarly. With concentrated sulfuric acid at 60°, it forms a mixture of four mono- and five disulfonic acids. In contrast, SO_3–dioxane gives 95% monosulfonation (433). Four sulfonate isomers were isolated with no significant change in yields over the range 0° (for 30 hours) to 60° (for 3 hours): 1- and 2-, 5 to 6% each; 3-, 25 to 32%; 9-, 24 to 30%. Indene also reacted with SO_3–dioxane, but the structures of the products were not determined (444).

Limited data suggest that fluorene reacts likewise. Although sulfuric acid gives a mixture, acetyl sulfate (532) forms the 2-sulfonate quantitatively, and SO_3 in chloroform yields 90% of the same sulfonate (129).

Sulfur trioxide–pyridine also can be used for the ring sulfonation of polycyclic compounds other than hydrocarbons. It has been suggested for sulfonating 3-hydroxypyrene and 3-hydroxychrysene in the presence of excess pyridine in 16 hours; the position of the sulfonate group was not established (278). It also reacts with 1-aminoanthraquinone, and with its chloro-, amino- and methoxy- derivatives, easily in the 2-position (222). With a solvent (such as nitrobenzene) the reaction requires 16 hours at 120°, but without a solvent it occurs at the surprisingly low temperature of 100°; the diamino compound reacts in only 2 hours without a solvent.

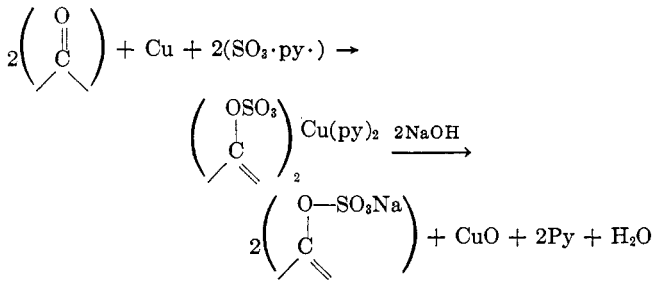
Anthraquinone, which sulfonates in a much more cleancut manner than anthracene because of the presence of the two carbonyl groups, gives favorable results with SO_3 vapor at 150–170° (412), forming the 2-sulfonic acid in 65% yield, with 10% quinone unreacted and 25% going to disulfonates. These results parallel those obtained with oleum, but no spent acid is formed with SO_3. At 130° no reaction occurs; at 200° oxidation is excessive.

Polycyclic mono- and diketones analogous to anthraquinone, but with larger fused-ring systems—namely, benzanthrone, benzonaphthone, dibenzpyrenequinone, isodibenzanthrone, and pyranthrone—are best sulfonated by making the SO_3 adducts at low temperature, and then warming them to 180° for 3 hours (315) to effect rearrangement to the sulfonic acid. Direct reaction with SO_3 at the higher temperature gives poor results. Anthraquinone forms a similar adduct (130), but conversion of it to the sulfonate has not been explored, since direct reaction at 170° proceeds satisfactorily, as stated above.

2. *Sulfation; Leuco Vat Dyes and Related Compounds*

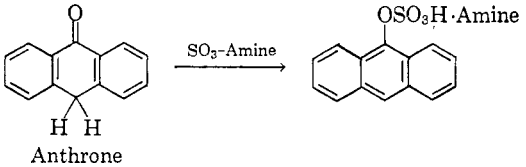
Sulfation of the leuco (or hydroxy) form of vat dyes, especially those derived from anthraquinone, has been used increasingly in industry since 1924 to achieve water solubility with consequent easy application to

textile fibers. Oxidation of the organic sodium sulfate in acid solution reconverts it on the fiber to the original insoluble keto form of the dye, thereby fixing it firmly. Combined reduction and sulfation of the dye is effected by heating with a metal (copper, iron or zinc) and SO_3–pyridine (or other amine complexes) by the reactions



This direct and widely applicable procedure is used to produce over 50 individual dyes (519). The general method involves adding $ClSO_3H$ to excess pyridine at 20° and then simultaneous addition of the dye and the metal with agitation in the range 40 and 80° over several hours. Aqueous sodium hydroxide is next added and the mixture steamed to recover pyridine; the yield of leuco sulfate is 80 to 90% (519). Pyridine has been the most commonly used base, but picolines are more suitable for certain dyes. Also, the metal and its degree of subdivision, as well as the temperature and time of heating, vary from case to case. A similar procedure, employing iron powder at 70° for 3 hours, was used in the laboratory for preparing the disulfates of anthraquinol, 6,12-dihydroxyanthracene, and 3,8-dihydroxy-1,2,6,7-dibenzypyrene (95). With 2-aminoanthraquinone and 2,6-diaminoanthraquinone, use of equivalent SO_3–pyridine at 40° yields the disulfate sulfamate (375).

9-Hydroxyanthracene (anthranol) derivatives (1- and 2-acetamino-, and 3-chloro-) are sulfated in 1 hour with SO_3–pyridine at 85° in excess pyridine (170); the same reagent was used with 10-acetoxyanthranol (169). Anthranol sulfates also are made under the same conditions from anthrone, 4-chloroanthrone and sodium-2-anthronesulfonate (170); 10-acetoxyanthrone reacted likewise in an anhydrous melt with SO_3–triethylamine for 3 minutes at 115° (406)



Anthrone

In the anhydrous vat dye reduction–sulfation process discussed above, SO_3–pyridine usually has given better results than complexes of cheaper bases (519). However, the discovery that the dyes could be reduced and sulfated in aqueous medium permitted use of the adducts from trimethyl- and triethylamines, and from N-ethylmorpholine (303, 305, 406). Reduction can be effected with sodium hydrosulfite, and sulfation can then be done at 30 to 50° in 1 to 4 hours, with pH control varying critically from one dye to another. When a free amino group is present, as in 2-aminoanthraquinone, the reduced compound is sulfamated as well as sulfated (303). Reduction and sulfation can be done simultaneously (236, 238). Aqueous sulfation at room temperature with SO_3–triethylamine also has been employed with 2-hydroxyanthraquinone (304), and with anthranol (406).

VI. Reaction with Heterocyclic Compounds

The sulfonation of O, N, and S five-membered heterocyclic rings has been studied extensively in the laboratory of the Soviet investigator A. P. Terent'ev. His standard technique involves heating the compound for several hours in the range 80 to 140°, usually at about 100°, with SO_3–pyridine in the presence of ethylene dichloride solvent.

A. Furan Derivatives

The sensitivity of many heterocycles to acid conditions makes the choice of a sulfonating agent difficult. Sulfuric acid, free SO_3, SO_3 in acetic anhydride, and SO_3–dioxane give only tar with furan, while sulfuric acid–pyridine and SO_3–trimethylamine do not react (480). Sulfur trioxide–pyridine performs satisfactorily, but not in the presence of excess pyridine; SO_3–picoline likewise gives good results.

Initial study of the sulfonation of furan using SO_3–pyridine at 100° for 8 to 10 hours with 1,2-dichloroethane solvent (478) showed that the yield of 2-monosulfonate could be increased from 30 to 90% by increasing the quantity of sulfonating agent. The same conditions gave 80% 3,5-disulfonate from 2-methylfuran, and the 3-monosulfonate from 2,5-dimethylfuran; 2-methylfuran formed the 5-monosulfonate in 1 month at room temperature (479). Subsequent repetition of this work by others (413) showed that the reaction products usually are mixtures—not single compounds as originally indicated—and that higher temperatures and proportions of sulfonating agent increase disulfonation. The results are summarized in Table XXII.

Table XXII
Furan Derivatives with SO_3–Pyridine

	Percentage yield (under conditions given)							
	8 hr. at 100° excess furan, no solvent		4 hr. at 35–65° excess SO_3–pyridine, solvent used		3 days at 25° excess SO_3–pyridine, solvent used		3 days at 25° equiv. SO_3–pyridine, solvent used	
	Mono	Di	Mono	Di	Mono	Di	Mono	Di
Furan	12–18	34–75	4	77–85	20–46	15–55	0–20	0–20
2-Methylfuran	0–20	50–58	48–56	30–33	36–44	36–42	28–64	0
2,5-Dimethylfuran	60–80	10–24	86–95	0	58–66	0	0–32	0

TABLE XXIII
THIOPHENE DERIVATIVES

Compound	Reagent[a]	Time, hr.	Temp., °C.	Product	Yield, %	Ref.
Thiophene	Free SO_3	1 month	25	2-Monosulfonate	50	475
Thiophene	B	10	25	2-Monosulfonate	86	475
Thiophene	B	10	100	2,4-Disulfonate	—	275, 475
Thiophene	C	—	—	2-Monosulfonate	75	476
2,5-Dimethylthiophene	C	—	—	3-Monosulfonate	95	476
2,5-Dimethylthiophene	B	—	—	3-Monosulfonate	94	476
2,5-Dimethylthiophene	A	—	130	3-Monosulfonate	75	476
2-Chlorothiophene	A	8	125	5-Monosulfonate	95	474
2-Bromothiophene	A	10	105	5-Monosulfonate	90	474
2-Iodothiophene	A	8	100	5-Monosulfonate	77	474
2-Iodothiophene	B	14	100–30	Thiophene, iodothiophene disulfonates	—	474

[a] A, SO_3–pyridine; B, $2SO_3$–pyridine; C, SO_3–dioxane; 1,2-dichloroethane solvent used for all runs except the first.

Benzofuran (coumarone) formed 100% 2-sulfonate in 10 hours at 100° (479), and 2-acetylfuran in 10 hours at 140° gave 83% of 5-sulfonate (481). Furan-2-carboxylic acid (pyromucic acid) decarboxylated during sulfation to form furan-2-sulfonic acid (479). Its acid chloride, on the other hand, gave the 5-sulfonic acid with pure SO_3 in methylene chloride solvent (212). Usually free SO_3 forms only tar with furan compounds, and it is noteworthy that in this case the reaction was conducted with a solvent below 0° to minimize decomposition.

B. THIOPHENE DERIVATIVES

Data on the sulfonation of these compounds are summarized in Table XXIII. They appear somewhat less acid sensitive than the furan analogs, since fair yields were noted in some cases even with free SO_3 and with SO_3–dioxane. 2-Iodothiophene gave some disproportionation to 2,5-diiodothiophene and thiophene in both runs, therein resembling *p*-diiodobenzene as discussed previously.

C. PYRROLE AND INDOLE DERIVATIVES

These compounds (see Tables XXIV and XXV) form relatively unstable sulfamates as primary products; these rearrange at higher temperatures or with a longer reaction time to the more stable sulfonates. As with the furans and the thiophenes, the 3-position is less reactive than the 2. The fact that 2-phenylindole gives a 95% yield of 3-sulfonate shows that the benzene ring in this position is comparatively unreactive.

D. PYRIDINE; ALKYL PYRIDINES

Ring sulfonation of pyridine yields the 3-sulfonate, which is of commercial interest as an intermediate for one method of producing nicotinic acid. A study employing oleum (320) showed that the free SO_3 in the oleum is the actual reagent; it gave 22 to 71% yields at 220 to 230° in 12 to 24 hours using mercury sulfate catalyst. The picolines reacted similarly, but yields were somewhat lower because of oxidative degradation at the methyl group. Heating SO_3–pyridine with mercury sulfate for 10 hours at 200° gave 46%, and for 29 hours at the same temperature 63% (183); 3-picoline in 12 hours at 200° formed 21% sulfonate. It was next found that 90 to 100% yields, based on pyridine, resulted at

TABLE XXIV
PYRROLE DERIVATIVES WITH SO_3–PYRIDINE

Compound	Time, hr.[a]	Temp., °C.	Product	Yield, %	Ref.
Pyrrole	10	100	2-Monosulfonate	90	491
1-Methylpyrrole	10	100	2-Monosulfonate	57	491
2-Methylpyrrole	10	100	5-Monosulfonate	54	491
2,4-Dimethylpyrrole	10	100	5-Monosulfonate	—	491
2,5-Dimethylpyrrole	5	100	3-Monosulfonate with	47	492
			3,4-Disulfonate	12	492
1,2,5-Trimethylpyrrole	5	100	3-Monosulfonate with	40	492
			3,4-Disulfonate	12	492
2,3,5-Trimethylpyrrole	5	100	4-Monosulfonate	25	492
1-Phenylpyrrole	8	100	2,4′-Disulfonate	25	491
1-(2-Tolyl)-pyrrole	8	100	2-Monosulfonate	45	491
1-Acetylpyrrole	11	100–10	2,4 and 2,5-Disulfonates	—	493
2-Acetylpyrrole	11	100–30	4-Monosulfonate with	—	493
			3,5-Disulfonate	—	493
2-Chloropyrrole	4	70	5-Monosulfonate (ether solvent)	40	495
2-Phenylazopyrrole	4	80	5-Monosulfonate (ether solvent)	50	495

[a] A large excess of reagent and 1,2-dichloroethane solvent used in all runs except as indicated.

TABLE XXV
INDOLE DERIVATIVES WITH SO_3–PYRIDINE

Compound	Time, hr.[a]	Temp., °C.	Product	Yield, %	Ref.
Indole	—	Cold	Sulfamate (water solvent)	—	471
Indole	—	80	Sulfamate (water solvent)	—	471
Indole	10	120	2-Sulfonate	90	471
2-Methylindole	10	120	No reaction	—	471
3-Methylindole	10	120	2-Sulfonate	55	471
2-Phenylindole	8	130	3-Sulfonate	95	496
1-Acetylindole	10	130	2-Sulfonate	50	496
3-Indoleacetic acid	10	110	2-Sulfonate	55	496
3-Indoleacetic acid	2.5	100	Sulfamate (pyridine solvent)	—	380
Acetyl-*d,l*-tryptophan	2.5	100	Sulfamate (pyridine solvent)	—	380
3-(Dimethylaminomethyl)-indole	8	130	A sulfonate	Trace	496
Carbazole	—	60	Sulfamate (pyridine solvent)	—	287
Carbazole	2	15	Sulfamate (SO_3-dimethylaniline used, chlorobenzene solvent)	—	90

[a] A large excess of reagent used for all reactions yielding sulfonates; 1,2-dichloroethane solvent used except as indicated.

225 to 230° in 5 to 6 hours in the presence of mercury sulfate provided 1.7 moles of SO_3 are used per mole of pyridine (416). It is noteworthy that this reaction can be conducted at atmospheric pressure much above the boiling point of SO_3 because of the formation of the complex $2SO_3$–pyridine.

2,6-Di-*tert*-butylpyridine behaves unusually because of strong steric shielding of the nitrogen atom, thereby preventing formation of the SO_3–pyridine complex. In marked contrast to pyridine itself, it sulfonates with SO_3 rapidly in the 3-position—that is, next to a *tert*-butyl group—even at −10° in liquid SO_2 (334, 367). It was at first thought that the sulfonate group in this compound was in the 4- rather than in the 3-position, since sulfonation in the carbocyclic series has not been noted in a position next to a group as sterically unfavorable as *tert*-butyl. This sulfonate is unusual, however, since it is water-insoluble and soluble in liquid SO_2, whereas the analogous dimethylpyridine-sulfonic acid behaves oppositely in both respects. 4-Chloro-2,6-di-*tert*-butylpyridine likewise sulfonates easily in the 3-position (367), as does 2-isopropyl-6-*tert*-butylpyridine (366a), but not 2,6-diisopropylpyridine.

E. MISCELLANEOUS HETEROCYCLIC COMPOUNDS

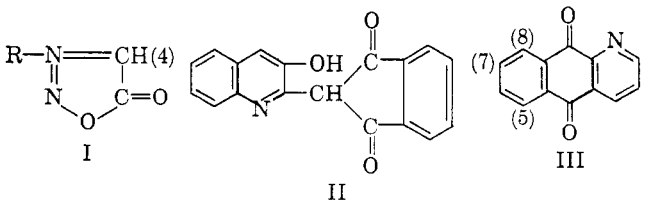
Acetyl-*l*-histidine hydrochloride undergoes ring sulfamation in 2.5 hours with SO_3–pyridine at 100° in excess pyridine (380).

3-Substituted sydnones (formula I below) are sulfonated easily in the 4-position with SO_3–dioxane at 40° (516); the substituents included phenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 3-chloro, and ethyl. The heterocyclic ring in this case sulfonates with great ease—even more easily than methoxyphenyl.

3-Hydroxyquinaphthalone (formula II below) forms an SO_3 adduct, which rearranges in very good yield to a sulfonic acid of unstated structure upon heating at 170° for 13 hours (288).

1-Azanthraquinone (formula III below) was sulfonated by four methods: 65% oleum with mercury catalyst at 95°; 65% oleum with mercury catalyst at 150°; 20% oleum at 145° and SO_3 at 170° (121). All four methods gave 5-, 7-, and 8-sulfonates, with the SO_3 procedure yielding nearly twice as much 7-isomer as any of the other three approaches. Evidently the benzenoid ring sulfonates more easily than the one containing nitrogen. Sulfur trioxide–pyridine did not react at all, which is as expected from the low reactivity of both the reagent and compound. Attempts to sulfonate 2,3-dimethyl-1-azanthraquinone in an analogous manner gave no identifiable product, as a result of excessive decomposition (122).

Dicyclopentadienyl iron can be mono- or disulfonated with acetyl sulfate in the range 25 to 46° depending on the amount of reagent used (544); the two sulfonic



groups are on different rings. The same reagent sulfonates cyclopentadienyl manganese tricarbonyl in excellent yield (112). Dicyclopentadienyl iron carboxylic acid, and its methyl ester, were monosulfonated on the ring without the carboxyl group with SO_3–dioxane at 0° (343).

2-Amino-5-nitro- derivatives of thiazole, pyrimidine and pyridine are sulfamated by SO_3-triethylamine in 30 minutes at 84° in 1,2-dichloroethane solvent (359).

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