[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE]

A Kinetic Study of Alkylation by Ethyl Arylsulfonates

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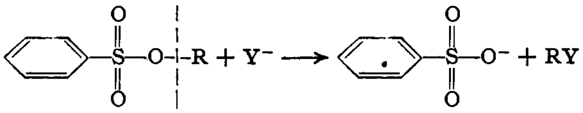
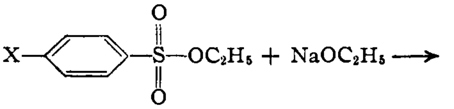
Alkyl esters of aromatic sulfonic acids function as strong alkylating agents[1] toward various types of organic compounds, this reaction occurring by alkyl-oxygen fission[2] according to the general scheme



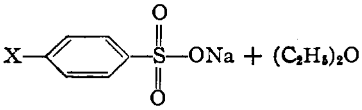
where R = alkyl group; Y^- = a nucleophilic reagent, *e. g.*, EtO^-, PhO^-, RS^-, I^-, etc.

Although various types of substituted benzenesulfonates are known and might conceivably be used, the vast majority of experimental alkylations have been carried out with the alkyl *p*-toluenesulfonates. Whereas the effect of nuclear substituents on the reactions of alkyl benzoates has been investigated extensively,[3] no such study has been made of the effect of nuclear substituents on the reactivity of alkyl esters of arylsulfonates. To do so seemed of considerable theoretical as well as potentially practical interest.[4] Such studies as have been made deal primarily with the hydrolysis of these compounds. It has been noted that with increasing nuclear halogen substitution, the ester is more readily saponified by alcohol.[5,6] The rate of the solvolytic reaction of ethyl toluenesulfonate and the rates of displacement of toluenesulfonate ion by chloride, bromide, iodide and hydroxyl ions has been studied kinetically.[7] Demeny's study[8] of the effect of a substituent in the aromatic nucleus upon the rate at which an alkyl sulfonate *hydrolyzes* demonstrated that a nitro group has a powerful accelerating influence while a *para* methyl reduces the reaction rate.

In this paper we present the results of a study of the influence of the *para* substituent on the reactivity of ethyl benzenesulfonate with sodium ethoxide in absolute ethanol solution.



where X = CH_3O, CH_3, H, Br and NO_2



The progress of this irreversible reaction was followed by titration of the unreacted sodium ethoxide at suitable time intervals with 0.05 *N* hydrochloric acid. Apparently the strong nucleophilic character of the ethoxide ion causes this reaction to take place readily at moderate temperature without observable side-effects. All of the rate constants reported in this study are based on an approximately equal initial concentration (0.05 molar) of each of the reactants. By trial, it was found that 35° was a suitable temperature at which to measure the relative reaction rates over a major part of the reaction. The measurements were repeated at a 10° interval to permit an approximate calculation of the energies of activation. The particular group of substituents selected represents a wide range of electronic character, varying from the electron-repulsion of the methoxy group to the electron attraction of the nitrogroup, as exhibited in the benzene series.

p-Methoxybenzenesulfonyl chloride was prepared in 66% yield by the direct chlorosulfonation of anisole. High yields of the ethyl esters were obtained by reacting the corresponding sulfonyl chloride with an equimolar quantity of sodium ethoxide in alcohol or alcohol-ether solution under mild conditions.

Experimental

Aryl Sulfonyl Chlorides.—*p*-Toluenesulfonyl chloride, benzenesulfonyl chloride, *p*-bromobenzenesulfonyl chloride and *p*-nitrobenzenesulfonyl chloride were purchased from the Eastman Kodak Company.

***p*-Methoxybenzenesulfonyl Chloride.**—The literature on the preparation of this compound was very incomplete and in one case quite erroneous. This substance apparently was first synthesized by Moody[9] by sulfonation of anisole followed by treating the salt with phosphorus pentachloride. Although Huntress and Carten[10] prepared a small quantity of the compound by the action of chlorosulfonic acid on anisole, they did not isolate it, but immediately converted it into the sulfonamide in 53% yield. Gebauer-Fülnegg and Meissner[11] in a study of the action of chlorosulfonic acid on anisole made the statement, "An anisole monosulfonyl chloride could not be prepared in spite of extensive variations in reaction conditions."

Anisole (40 g., 0.37 mole) was dissolved in 150 ml. of chloroform and the solution cooled in an ice-salt-bath to −8°. Chlorosulfonic acid (86.2 g., 2 equiv., 0.74 mole) was added dropwise, as rapidly as possible while maintaining the internal temperature at 0°. Addition time was twenty minutes. The ice-bath was removed and the temperature allowed to approach room temperature during thirty minutes with continuous stirring. The solution

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(1) (a) For a review of this field see Connor's chapter in Gilman, "Organic Chemistry," 2nd ed., Vol. I, John Wiley and Sons, New York, N. Y., 1943, p. 895; (b) Suter, "Organic Chemistry of Sulfur," John Wiley and Sons, New York, N. Y., 1944, pp. 514-539.

(2) Ferns and Lapworth, *J. Chem. Soc.*, **101**, 273 (1912).

(3) (a) Watson, "Modern Theories of Organic Chemistry," 2nd ed., Oxford University Press, 1942; (b) Hammett and Pfluger, THIS JOURNAL, **55**, 4079 (1933).

(4) Suter, ref. 1b, p. 527, mentions the desirability of a comparative study of these esters.

(5) Kastle and Murrill, *Am. Chem. J.*, **17**, 290 (1895).

(6) Boyle, *J. Chem. Soc.*, **97**, 211 (1910).

(7) McCleary and Hammett, THIS JOURNAL, **63**, 2254 (1941).

(8) Demeny, *Rec. trav. chim.*, **50**, 60 (1931).

(9) Moody, *Ber.*, **26**, ref. 606 (1893).

(10) Huntress and Carten, THIS JOURNAL, **62**, 603 (1940).

(11) Gebauer-Fülnegg and Meissner, *Monatsh.*, **50**, 55 (1928)

was poured onto chopped ice and the mixture transferred to a separatory funnel with an additional 200 ml. of chloroform. The chloroform extract was washed with three small portions of ice-water, dried with anhydrous sodium sulfate, filtered and redried with Drierite. On evaporating the chloroform solution under reduced pressure there remained a pale yellow liquid which crystallized on cooling and scratching. Yield was 54.7 g. (72%) of crude sulfonyl chloride. The product may be purified by recrystallization from boiling hexane (10 volumes) to give colorless crystals, m. p., 40–42° in 52% yield.

It was found that purification may be accomplished more efficiently by vacuum distillation. *p*-Methoxybenzenesulfonyl chloride boiled at 103–105° at 0.25 mm. (bath temp., 120–135°) to give a colorless distillate in 66% yield. The product had a m. p. of 41–42°, which is in agreement with values recorded in the literature.[12]

Anal.[13] Calcd. for $C_7H_7ClO_3S$: Cl, 17.16; S, 15.52. Found: Cl, 16.89; S, 15.38.

Ethyl Arylsulfonates—General Procedure.—The sulfonyl chloride (0.1 mole) was dissolved in 100 ml. of absolute ethanol in a 250-ml. three-necked flask fitted with a mercury-sealed stirrer, reflux condenser, dropping funnel and thermometer. In those cases where the sulfonyl chloride is not very soluble in ethanol (*e. g.*, *p*-nitro- and *p*-bromobenzenesulfonyl chloride) 75 ml. of ether was used. The flask was surrounded by a cold water-bath to maintain an internal temperature of 20°. A solution of 0.1 mole of sodium ethoxide in 100 ml. of ethanol (prepared by dissolving sodium in ethanol and standardizing the solution against standard hydrochloric acid) was added dropwise with continuous stirring. The reaction time varied somewhat with the reactivity of the sulfonyl chloride but was generally run until a test portion (10 drops) was no longer alkaline to phenolphthalein. The *p*-methoxy compound required forty-five minutes whereas the *p*-nitro was run for 145 minutes.

The suspension was poured into 300 to 500 cc. of water (sufficient to dissolve the precipitated sodium chloride) and the mixture thoroughly extracted with 200 ml. of chloroform. (Where ether was used as a solvent, the reaction mixture was first evaporated at reduced pressure to remove all of the ether.) The aqueous layer was extracted with two additional portions (100 ml.) of chloroform and the combined extract washed successively with 50 ml. of water, 150 ml. of saturated sodium bicarbonate and two 60-ml. portions of water.

The chloroform solution was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness at reduced pressure. With the exception of the *p*-nitro ester, the crude esters thus obtained were all purified by fractional vacuum distillation, the intermediate constant-boiling fraction being retained for kinetic study.

Ethyl *p*-Nitrobenzenesulfonate.—The crude, pale-yellow ester obtained in 81% yield (m. p., 91–91.5°) was recrystallized from absolute ether to give practically colorless crystals; m. p. 92–92.5°, in 70% yield. Demeny[8] reported m. p. as 92°.

Anal. Calcd. for $C_8H_9NO_5S$: N, 6.06; S, 13.87. Found: N, 6.01; S, 13.88.

Ethyl *p*-Methoxybenzenesulfonate.—The pure ester was obtained as a colorless liquid in 83% yield after fractional vacuum distillation, b. p., 137–139° at 0.3 mm. (bath temp., 164–169°), n^{20}D 1.5230.

Anal. Calcd. for $C_9H_{12}O_4S$: C, 49.98; H, 5.60; S, 14.83. Found: C, 49.84; H, 5.53; S, 14.88.

This compound was recently reported by Carr and Brown[12b] who prepared it in a different manner.

Ethyl *p*-Bromobenzenesulfonate.—The pure ester (obtained in 74% yield) distilled at 111–113° at 0.15 mm. (bath temp., 132–135°), f. p., 39.0–39.1°. Krafft and Roos[14] reported the m. p. as 39.5°.

Ethyl *p*-Toluenesulfonate.—The pure ester distilled at 108–109° at 0.35 mm.; bath temp., 121–123°. The freezing point was 32.2° which is in agreement with the value reported by McCleary and Hammett,[7] m. p., 32.2–32.3°.

Ethyl Benzenesulfonate.—Although this ester can be prepared by the general procedure given above, it was prepared by the pyridine method[15] which is useful for esters which cannot be made from the sodium alkoxide. Benzenesulfonyl chloride (Eastman Kodak Co. 32, 36 g., 0.2 mole) was dissolved in 100 ml. of dry pyridine and the solution cooled to −8°. Absolute ethanol (11.7 ml., 0.2 mole) was now added from a pipet and the temperature kept between −8 and −5°. Crystallization of pyridine hydrochloride commenced after several minutes and the mixture was kept at −5° for a total of twenty-two minutes. Sulfuric acid (250 ml. of 5 *N*, pre-cooled to 3°) was now added rapidly, with cooling, thereby liberating a colorless oil which settled to the bottom of the flask. The oil was extracted with chloroform and this solution was treated in the described manner. The pure ester (obtained in 75% yield) distilled at 96–98° at 0.3 mm. (bath temp., 109–113°), n^{20}D 1.5092.

Kinetic Technique.—The apparatus consisted essentially of a thermostatically controlled (±0.04°) water-bath fitted with clamps to hold a series (usually 7) of stoppered test-tubes and several 100-ml. volumetric flasks. Since it was not deemed desirable to mix a standardized solution of the ethyl arylsulfonate in ethanol with a standard solution of sodium ethoxide in ethanol (both solutions equilibrated to constant temperature) because of possible ester alcoholysis prior to mixing, a weighed amount of the ester (0.005 mole) in a small, thin glass vial (11 × 40 mm.) was added directly to an ethanol solution of sodium ethoxide already equilibrated to temperature. This was done in the following manner. The reaction vessel was a 100-ml. volumetric flask calibrated to correct for the thermal expansion of ethanol at the specific reaction temperature plus the volume-displacement of the glass vial. A solution of sodium ethoxide in ethanol, as close to 0.1 molar as expedient, was prepared in a 100-ml. volumetric flask and standardized against 0.05 *N* hydrochloric acid. A 50-ml. aliquot (0.005 mole) was then added to the calibrated flask and sufficient ethanol added to bring the volume to a point such that the addition of the ester-containing vial (after temperature equilibration) would bring the final volume close to the calibration mark. The final volume adjustment was thus made immediately after the addition of ester. The flask containing the ethoxide solution (representing about 99+% of the mass) could thus be accurately adjusted to the reaction temperature and the vial containing the ester only approximately adjusted in a separate tube. In all cases except the *p*-nitro, dissolution of the liquid ester was sufficiently rapid so that zero time was essentially that of the moment of mixing. The solid nitro-ester, which has the lowest alcohol solubility, was finely powdered; zero time being taken as of one-half time of solution. Owing to the graphic method of determining the rate, this factor had no bearing on the determination of the value of *k*.

As soon as the ester was completely dissolved, the homogeneous solution was aliquoted in seven, 10-ml. portions to the equilibrated, stoppered test-tubes. This was necessitated by the low alcohol-solubility and consequent crystallization of the sodium salts of the arylsulfonic acids. The pipet used in making these transfers was also calibrated for the thermal expansion of ethanol. At suitable time intervals, an aliquot-containing tube was removed from the water-bath and plunged into a Dry Ice–acetone mixture to stop the reaction. The cold mixture was then carefully diluted with 100 ml. of carbon dioxide-free water and titrated with 0.05 *N* hydrochloric acid using phenolphthalein as the indicator. Each run thus gave seven points with which to plot a graph.

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(12) (a) Fichter and Tamm, *Ber.*, **43**, 3036 (1910); m. p. 42–43°; (b) Carr and Brown, THIS JOURNAL, **69**, 1170 (1947), m. p., 41.0°.

(13) The microanalyses were performed by G. L. Stragand of the University of Pittsburgh.

(14) Krafft and Roos, *Ber.*, **25**, 2257 (1892).

(15) Patterson and Frew, *J. Chem. Soc.*, **89**, 332 (1906); Tipson, *J. Org. Chem.*, **9**, 235 (1944).

Rate Calculations.—Since we were dealing with a nucleophilic displacement we postulated second-order kinetics and determined the rate constant, k, from the simplified equation for second-order reactions in which initial concentrations of reactants are equal; $k_2 = x/ta(a - x)$, where a = initial concentration of sodium ethoxide in moles/liter and x = moles per liter which have reacted in time t. The reported values of k (expressed in min.$^{-1}$ moles^{-1} liter) were determined graphically by plotting the function $x/(a - x)$ against t which resulted in a straight line with a slope equal to ak. This value was checked by plotting $1/(a - x)$ against t, the slope of the resulting line being directly equal to k. The excellent straight line relationship which we observed in every case, the graphs having been plotted over a major part of the course of each reaction, substantiated our assumption of second-order kinetics.

In Table I, we present a typical experimental record for the determination of the value of k in a specific reaction. The figures of column 5 and the inverse of the figures in column 3 were plotted against t to give a value of $k_2 = 0.235$. By using the equation[16] $k(t_2 - t_1)a = [x_2/(a - x_2) - x_1/(a - x_1)]$ or $\Delta(x/a - x)$ (column 6), the interval values of k_2 (column 7) may be obtained.

TABLE I

REACTION OF ETHYL BENZENESULFONATE WITH SODIUM ETHOXIDE AT 45°

Concn. of ester = 0.0489 molar
Concn. of ethoxide = 0.0504 molar

Time, min.	Acid titer*	$a - x$ m./l.	x m./l.	$x/(a - x)$	$\Delta[x/(a - x)]$	k_2
0	9.78	0.0489				
20	8.05	.0402	0.0086	0.215	0.215	0.220
40	6.74	.0337	.0152	.451	.236	.241
60	5.90	.0295	.0194	.658	.207	.211
90	4.85	.0242	.0246	1.017	.359	.245
120	4.17	.0208	.0280	1.345	.328	.224
150	3.59	.0179	.0309	1.724	.379	.258
180	3.17	.0158	.0330	2.085	.361	.246

* = ml. of 0.05 N hydrochloric acid used in titration of aliquot.

Since the rate constant for each ester was determined at two temperatures only, the energy of activation, E, was evaluated from the integrated expression[17]

$$E = \frac{2.303RT_2T_1}{(T_2 - T_1)} \log \frac{k_2}{k_1}$$

Results and Discussion

The rate constants, obtained at two temperatures, for the reaction of *para*-substituted ethyl benzenesulfonates with sodium ethoxide in ethanol solution are given in Table II. The substituents are listed in ascending order of ester reactivity which is also the order of relative electron-recession from the seat of the reaction, *i. e.*, the alkyl–oxygen bond in the ester.

TABLE II

Substituent X	Rate constant t, °C.	k_2	Relative reactivity at 35°	Energy of activation cal.	log PZ
p-CH_3O	35	0.0321	0.42	21,670	12.12
	45	.0977			
p-CH_3	35	.0484	.63	20,820	11.69
	45	.141			
p-H	35	.0769	1.00	21,750	12.56
	45	.235			
p-Br	35	.172	2.24	22,240	13.25
	45	.539			
p-NO_2	35	.901	11.8	24,040	15.25
	25	.241			

A comparison of the relative reactivity of these esters at 35° indicates a twenty-eight fold variation in the relative velocity constants, indicating the desirability of investigating the alkylating efficacy of arylsulfonic esters other than those of p-toluenesulfonic acid.

Due largely to the work of Hammett,[18] linear relationships have been found to apply between

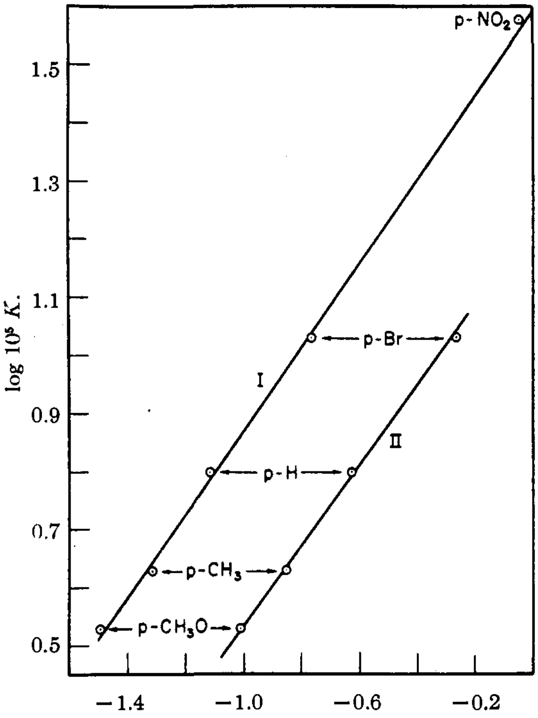

Fig. 1.—Relationship of log 10^5 K and log k, where K = dissociation constant of substituted benzoic acid; k = rate constant for reaction of substituted ethyl benzenesulfonate with sodium ethoxide in ethanol at (I) 35° and at (II) 45°.

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[16] Rice, "The Mechanism of Homogeneous Organic Reactions," Chemical Catalog Co., New York, N. Y., 1928, p. 24.

[17] Moelwyn-Hughes, "Kinetics of Reactions in Solution," Oxford University Press, Oxford, 1933, p. 30.

[18] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 184.

the rate and the equilibrium constants of practically all side chain reactions of benzene derivatives substituted in the *meta* or *para* positions. In accordance with this relationship we have plotted in Fig. 1, as ordinates the logarithms of the dissociation constants of several substituted benzoic acids[19] and as abscissas the logarithms of the rate constants (Table II, column 3) for the reaction of similarly substituted ethyl benzenesulfonates with ethoxide ion. In view of the satisfactory linear relationship resulting, the present example can be added to the list of reactions tabulated by Hammett.

Since in the Arrhenius equation, $k = PZe^{-E/RT}$, the collision frequency Z varies but little from one reaction to another, it is apparent that the influence of a polar substituent on the velocity constant may be due to an effect on the energy of activation, E, or on the probability factor P, or both. For most reactions of nuclear substituted benzene derivatives it is commonly observed that the influence of substituents is almost entirely upon changes in E.[20] In several instances, however, it has been observed that substituents cause appreciable changes in the PZ term of the equation, *e. g.*, the acid hydrolysis of ethyl benzoates,[21] the alcoholysis of benzyl chlorides,[22] and the hydrolysis of arylsulfuric acids.[23] In the present investigation, since E has been estimated from values of k obtained at only two reaction temperatures, it probably is not to be considered accurate to more than ±1000 calories. From the results given in Table II it may be seen that although there is a slight trend to E, the individual values are grouped about the average of 22,100 calories almost within limits of the estimated experimental error.

Following Branch and Nixon,[22] the logarithm of the probability factors in the Arrhenius equation have been calculated from the relationship $\log PZ = \log k_{35} + E/2.3RT$ and are included in Table II. The values of log PZ listed are in the general region of those usually associated with reactions between ions and neutral molecules and belong to the class characterized by Moelwyn-Hughes as "normal" reactions. In view of the near-constancy of E, and the definite trend to the values of log PZ, it would appear that we have here an additional example of a case in which the effect of polar substituents is mainly on the PZ term of the Arrhenius equation. It may be noted from Table II that although the effect of a *para*-methoxy substituent on the velocity constant is in accord with its electron-repulsive character, its effect on E and log PZ is anomalous.

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Summary

Details have been worked out for the synthesis of *p*-methoxybenzenesulfonyl chloride by direct chlorosulfonation of anisole. The preparation and purification of five substituted ethyl benzenesulfonates are described.

The effect of a nuclear substituent on the alkylating efficacy of alkyl benzenesulfonates has been investigated by a study of the relative reaction rates of these esters with sodium ethoxide in ethanol. This reaction followed second-order kinetics.

The value of the rate-constants increased in the order $p\text{-CH}_3\text{O} < p\text{-CH}_3 < p\text{-H} < p\text{-Br} < p\text{-NO}_2$, which is in agreement with the electronic influence exhibited by these groups on the dissociation constants of substituted benzoic acids. Good quantitative accord was also observed with Hammett's relationship for the effect of structure on reactivity.

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[19] Dippy, *Chem. Rev.*, **25**, 151 (1939).

[20] (a) Watson, ref. 3a, p. 78; (b) Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 207.

[21] Timm and Hinshelwood, *J. Chem. Soc.*, 862 (1938).

[22] Branch and Nixon, THIS JOURNAL, **58**, 2499 (1936).

[23] Burkhardt, Horrex and Jenkins, *J. Chem. Soc.*, 1649 (1936).