Bond-Scission Processes in Sulfur Compounds.

VII.[1] Alkyl–Oxygen Scission in the Neutral and Alkaline Methanolysis of Methyl *p*-Nitrophenyl Sulfate

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Abstract: The kinetics of the alkaline and neutral methanolysis of methyl *p*-nitrophenyl sulfate have been measured by a spectrophotometric method over the range 25–45°. Activation parameters have been determined. Reaction in methanolic sodium methoxide yields only *p*-nitrophenyl sulfate (alkyl–oxygen scissin) *via* a second-order process. In initially neutral methanol two consecutive processes are observed: initial formation of *p*-nitrophenyl sulfate (alkyl–oxygen scission) and conversion of the latter to *p*-nitrophenol (sulfur–oxygen scission). The spectrophotometric method allowed measurement of the rate of formation of the intermediate and its rate of decomposition. No aryl–oxygen scission was detected.

Esters of sulfuric acid are of considerable biological importance[2–5] as well as of general utility in the organic laboratory as alkylating agents.[6] However, mechanistic studies of sulfate esters have in the past been limited to a few simple mono- and dialkyl or -aryl representatives and to some cyclic sulfates.[7–14] These studies have concentrated on establishing the mode of bond scission under different reaction conditions, especially towards basic and acidic reagents.

There has been no report up to date of an investigation of a mixed alkyl aryl sulfate. In this first study, methyl *p*-nitrophenyl sulfate was chosen for examination since this compound could reasonably be expected to undergo reaction by one or more of the various modes of bond cleavage: alkyl–oxygen, sulfur–oxygen, and aryl–oxygen scission. Our interest in this substrate was heightened by the possibility of an analogy with methyl *p*-nitrobenzenesulfonate, which has been found to modify the active site of α-chymotrypsin through specific methylation of the histidine-57 residue.[15] It has also been reported that methyl *p*-nitrobenzenesulfate alkylates specifically sulfhydryl groups in certain proteins and enzymes to yield the *S*-methyl derivatives.[16]

Methanolysis was chosen for our initial study because of anticipated unambiguity of product identification in scission by the different reaction modes. Results of the alkaline and neutral methanolysis are presented here. Some of the data have been reported in preliminary form.[17]

Experimental Section

Methyl *p*-nitrophenyl sulfate was prepared from *p*-nitrobenzenediazonium fluoroborate and dimethyl sulfate by the method of Whiting, *et al.*;[18] its characterization was described previously.[19] *p*-Nitrophenyl sulfate (Sigma Chemicals) was obtained as the potassium salt and found to be free of *p*-nitrophenol.[19] Sodium methoxide solutions were prepared by dissolving sodium metal in anhydrous methanol.

The kinetic measurements were performed in the majority of cases in a thermostated 20-mm cuvette situated in the cell compartment of a Unicam SP800 spectrophotometer, by repeated scanning over the uv spectral region. Temperatures were measured by means of a thermocouple. Runs were initiated by the addition of 0.05 ml of a stock solution of methyl *p*-nitrophenyl sulfate in ether to 4.95 ml of methanol, or sodium methoxide solution, to yield a substrate concentration of 5×10^{-5} *M* in 99% methanol 1% ether (v/v).

The reaction in initially neutral methanol was also run in a flask immersed in a thermostatted bath, with 5-ml aliquots removed periodically and quenched with base (0.05 ml of 5 *M* NaOH) for subsequent spectral examination.

Results

Alkaline Methanolysis. Reaction of methyl *p*-nitrophenyl sulfate (5×10^{-5} *M*) with methanolic sodium methoxide (1×10^{-3}–2×10^{-2} *M*) was characterized by a decrease in absorption due to substrate at 260 nm and a simultaneous growth in absorption at 283 nm characteristic of *p*-nitrophenyl sulfate, with a tight isosbestic point at 270 nm maintained throughout the course of reaction. The spectrum resulting on completion of the reaction corresponded quantitatively with that of *p*-nitrophenyl sulfate. Figure 1 shows the spectral changes obtained in a typical run.

Pseudo-first-order rate constants (k_{obsd}) were calculated from plots of log ($A_\infty^{283} - A_t^{283}$) *vs.* *t* or log ($A_t^{260} - A_\infty^{260}$) *vs.* *t*, which were linear for at least 80% reaction. The second-order rate constant was obtained as the slope of the line on plotting k_{obsd} *vs.*

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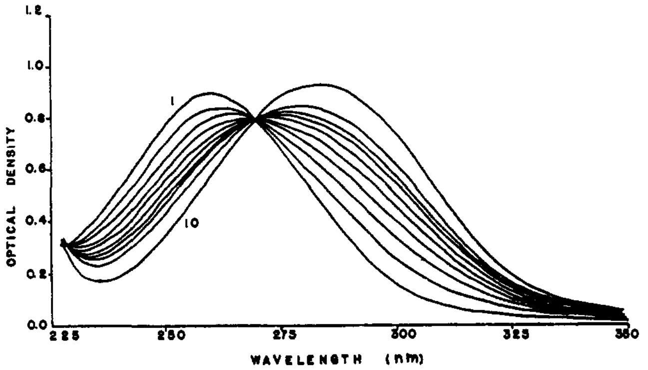

Figure 1. Spectral scans for the conversion of methyl *p*-nitrophenyl sulfate (5×10^{-5} *M*) to *p*-nitrophenyl sulfate by methanolic sodium methoxide (9.2×10^{-4} *M*) at 25°. Scan 1 taken after 1 min reaction, scan 10 after 100 min.

Table II. Kinetic Data for the Reactions of Methyl *p*-Nitrophenyl Sulfate in Methanol[a]

Temp, °C	10^3k_{obsd},[b] sec^{-1}	10^4k_{sol},[c] sec^{-1}	10^4k_{ArOH},[d] sec^{-1}	$(k_{obsd} - k_{sol})/$[CH$_3$ONa], M^{-1} sec^{-1}
25.0	4.05	5.56	1.25	0.507[e]
35.0	11.3	16.2	3.37	1.405
45.0	27.1	43.9	10.3	3.29

[a] As for Table I. [b] k_{obsd} is the pseudo-first-order rate constant as measured for the alkaline methanolysis using 6.90×10^{-3} *M* CH_3ONa–CH_3OH. [c] k_{sol} is the rate constant for the conversion of methyl *p*-nitrophenyl sulfate to *p*-nitrophenyl sulfate ion, as measured in the reaction in initially neutral methanol. [d] k_{ArOH} is the pseudo-first-order rate constant for the conversion of *p*-nitrophenyl sulfate ion to *p*-nitrophenol as measured in the reaction in initially neutral methanol. [e] The value 0.513 M^{-1} sec^{-1}, obtained from the plot of k_{obsd} *vs.* [CH$_3$ONa], was used to obtain the activation parameters given in Table III.

[CH$_3$ONa] and found to be 0.513 M^{-1} sec^{-1} at 25°. This line does not pass through the origin and the intercept is attributed to the neutral solvolysis reaction (k_{sol}).[20] The estimated specific rate of neutral solvolysis extrapolated from this plot is $5.1 \pm 0.5 \times 10^{-4}$ sec^{-1} (compared with a value of 5.56×10^{-4} sec^{-1} determined independently in the absence of methoxide ion; *vide infra*). A plot of log ($k_{obsd} - k_{sol}$) *vs.* log [CH$_3$ONa] is linear with a slope of 1.00, indicating that the alkaline methanolysis reaction is first order with respect to methoxide ion. The kinetic data obtained in this manner at 25° are recorded in Table I.

Table I. Kinetic Data for the Alkaline Methanolysis of Methyl *p*-Nitrophenyl Sulfate at 25°[a]

10^3[CH$_3$ONa], *M*	10^3k_{obsd}, sec^{-1}	$(k_{obsd} - k_{sol}{}^{b})/$[CH$_3$ONa], M^{-1} sec^{-1}
0.92	0.98	0.511
4.60	2.95	0.531
6.90	4.05	0.513
9.20	5.15	0.504
18.4	9.99	0.515

[a] All runs were performed with a substrate concentration of 5×10^{-5} *M*. The reaction medium contained 1.0% ether by volume. [b] The value of k_{sol} (5.1×10^{-4} sec^{-1}) is obtained from the intercept of the plot of k_{obsd} *vs.* [CH$_3$ONa].

Some limited rate data obtained at other temperatures are included in Table II.

Neutral Methanolysis. Evidence for a Consecutive Process. Under solvolytic conditions methyl *p*-nitrophenyl sulfate reacts with methanol to yield initially *p*-nitrophenyl sulfate, as indicated by a decrease in absorbance at 260 nm, an increase in absorbance in the 283-nm region, and an isosbestic at 270 nm; these spectral changes follow closely the observed changes in the alkaline methanolysis. However, the advent of a further reaction is indicated later in the run by a progressive shift in absorbance to longer wavelength during which time isosbestic behavior is absent. Toward the end of the reaction when the methyl *p*-nitrophenyl sulfate has largely disappeared, one observes the appearance of new isosbestic points at 243 and 295 nm, and the growth of an absorption maximum at 311 nm, characteristic of *p*-nitrophenol. The final spectrum corresponds quantitatively with that of *p*-nitrophenol in this reaction medium. These spectral changes are illustrated in Figure 2.

Although the reaction in initially neutral methanol has thus been observed to consist of two consecutive reaction steps of comparable rates, we have found that accurate values can readily be obtained for the rate constants for both steps of the reaction using standard log plots for the decrease in methyl *p*-nitrophenyl sulfate and for the increase in *p*-nitrophenol.

The rate constant for the first step of the reaction was initially obtained from a plot of log ($A_t - A_\infty$) *vs.* *t* at 260 nm (as in the alkaline methanolysis case), using only absorbance values for which isosbestic behavior at 270 nm was followed. The value of A_∞ at 260 nm was taken as the theoretical absorbance of the stoichiometric amount (5×10^{-5} *M*) of *p*-nitrophenyl sulfate at that wavelength as determined in the alkaline methanolysis reaction. The resultant plot yielded $k_{sol} = 5.11 \times 10^{-4}$ sec^{-1} over the initial straight portion but began to show curvature (to greater slope) at 0.8 half-life. It became apparent that a superior procedure was to plot the changes in absorbance at 243 nm or at 295 nm (the isosbestic points for the conversion of *p*-nitrophenyl sulfate to *p*-nitrophenol), since ($A_t{}^{243} - A_\infty{}^{243}$) and ($A_\infty{}^{295} - A_t{}^{295}$) are both proportional to the decrease in concentration of methyl *p*-nitrophenyl sulfate throughout the entire reaction. Both log plots were linear for 2.7 half-lives (85% reaction) and in agreement within ±1%, giving $k_{sol} = 5.56 \times 10^{-4}$ sec^{-1}. This value is considered to be more accurate than the "intercept" value obtained from the basic methanolysis study.

It should be noted that the consecutive reactions (eq 2–4), which are observed to occur in initially neutral methanol, result in an increase in the acidity of the unbuffered reaction medium. From the close agreement between the values for k_{sol} obtained in this and in the basic medium, we conclude that the conversion of methyl *p*-nitrophenyl sulfate to *p*-nitrophenyl sulfate (eq 2) is not acid catalyzed at the low acidities ([H$^+$] $< 10^{-4}$ *M*) incurred in the present study. A report on the extension of this study into more acidic media is forthcoming.

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(20) Throughout this paper the terms "neutral methanolysis" or "neutral solvolysis" are used to designate the uncatalyzed reaction of methyl *p*-nitrophenyl sulfate with methanol to give *p*-nitrophenyl sulfate and are not a description of the reaction conditions.

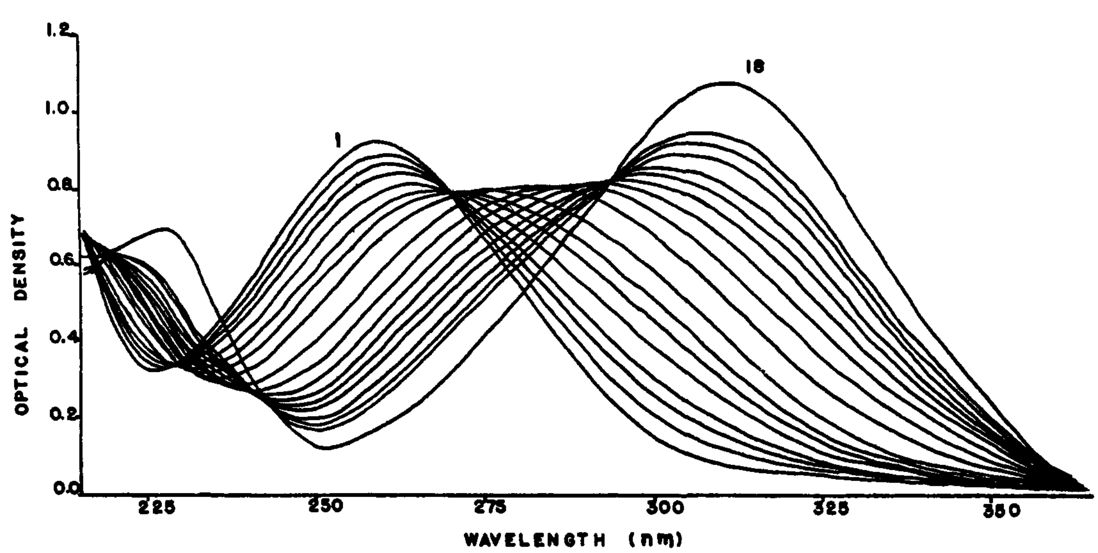


Figure 2. The reaction of methyl *p*-nitrophenyl sulfate (5×10^{-5} *M*) in initially neutral methanol at 25°, illustrating the two consecutive processes. Spectral scan no. 1 taken after 1 min reaction, scan no. 18 after 1400 min.

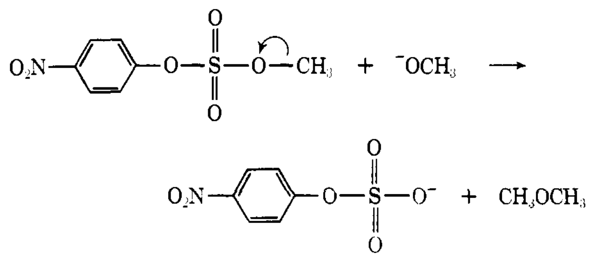
The rate constant for the second stage of the reaction (k_{ArOH}) was obtained from a plot of log ($A_\infty - A_t$) *vs.* t at 311 nm ($\lambda_{\max}$ for *p*-nitrophenol) using only spectral data obtained late in the reaction when isosbestic behavior was again observed. The plot was linear for 2.8 half-lives (covering the reaction interval 47 to 93% *p*-nitrophenol), giving $k_{\text{ArOH}} = 1.25 \times 10^{-4}$ sec^{-1} as the first-order rate constant.[21] This value is considered to contain no significant error due to remnants of the first stage of the reaction.[22]

Rate constants for the two processes at 35° were obtained similarly and are recorded in Table II. The increased reaction rate at 45° rendered the repeated scanning technique inconvenient during the early portion of the run, so that at that temperature the first stage of the reaction was followed at constant wavelength (260 nm). This is expected to increase somewhat the uncertainty in the derived rate constant (Table II), though the Arrhenius plot showed excellent linearity.

The rate of formation of *p*-nitrophenol in the methanolysis of methyl *p*-nitrophenyl sulfate could be followed in a different manner by quenching reaction aliquots in base and analyzing for *p*-nitrophenoxide ion at 390 nm. In these basic media *p*-nitrophenol was converted to *p*-nitrophenoxide ion and unreacted methyl *p*-nitrophenyl sulfate was transformed rapidly to *p*-nitrophenyl sulfate (in 0.05 *M* base, $t_{1/2} \simeq 25$ sec). Thus the spectral changes that one obtains have the appearance of *p*-nitrophenyl sulfate reacting to yield *p*-nitrophenoxide. After an initial induction period, the plot of log ($A_\infty - A_t$) at 390 nm *vs.* t is linear for 2.8 half-lives (covering the reaction interval 22 to 89% *p*-nitrophenoxide), yielding $k_{\text{ArOH}} = 1.29 \times 10^{-4}$ sec^{-1}, which is in satisfactory agreement with the value obtained by the direct method described above.

Discussion

It has been shown that methoxide ion reacts with methyl *p*-nitrophenyl sulfate solely by attack at the aliphatic carbon (alkyl–oxygen scission), with displacement of the *p*-nitrophenyl sulfate ion. Thus



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attack at the aromatic carbon, or at the sulfur atom, does not take place. Aryl–oxygen scission and sulfur–oxygen scission would yield *p*-nitroanisole and *p*-nitrophenoxide ion, respectively, which would have been readily identified spectrophotometrically had they been formed in the course of the reaction. The observed mode of scission is perhaps surprising in view of the fact that *p*-nitrophenoxide ion and the mesylate ion are both excellent leaving groups and that there are precedents for attack at such electrophilic centers in related systems. Sulfur–oxygen scission

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[21] The pseudo-first-order rate constant k_{ArOH} is the product of a second-order rate constant and the hydrogen ion concentration, the latter increasing throughout the reaction, from an initial value of zero, according to eq 2. The log plot was performed over a range of the reaction for which $[\text{H}^+] = (4.97 \pm 0.02) \times 10^{-5}$ *M*, on the assumption that the *p*-nitrophenyl sulfate (formed in eq 2) and the methyl hydrogen sulfate (formed on solvolysis of SO_3 in eq 4) will be completely dissociated. Thus the second-order rate constant for the second stage of the reaction is calculated to be 2.52 M^{-1} sec^{-1} at 25°.

[22] For a reaction system of two consecutive first-order reactions

$$\text{A} \xrightarrow{k_\text{A}} \text{B} \xrightarrow{k_\text{B}} \text{C}$$

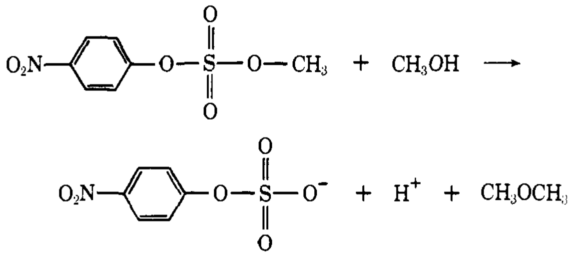
it is readily shown that

$$[\text{C}]_\infty - [\text{C}]_t = [\text{C}]_\infty \frac{k_\text{A}}{k_\text{A} - k_\text{B}} e^{-k_\text{B}t} \left[1 - \frac{k_\text{B}}{k_\text{A}} e^{(k_\text{B} - k_\text{A})t} \right]$$

and thus k_B may be obtained from a plot of log ($[\text{C}]_\infty - [\text{C}]_t$) *vs.* t provided that $1 \gg (k_\text{B}/k_\text{A})e^{(k_\text{B}-k_\text{A})t}$. This condition can apply late in the reaction only if $k_\text{A} > k_\text{B}$. Making the substitutions $k_\text{B}/k_\text{A} = \kappa$ and $t = n \cdot t_{1/2}^{\text{A}\rightarrow\text{B}}$ where $t_{1/2}^{\text{A}\rightarrow\text{B}} = \ln 2/k_\text{A}$, we obtain $(k_\text{B}/k_\text{A})e^{(k_\text{B}-k_\text{A})t} = \kappa \cdot 2^{(\kappa-1)n}$. For the run in question the log plot was begun at t = 8300 sec (*i.e.*, at $n = 6.7$ where $k_\text{A} = k_{\text{sol}} = 5.56 \times 10^{-4}$ sec^{-1}), and gave $k_\text{B} = k_{\text{ArOH}} = 1.25 \times 10^{-4}$ sec^{-1} (*i.e.*, $\kappa = 0.225$). For this combination of n and κ we obtain $\kappa \cdot 2^{(\kappa-1)n} = 0.006$. Thus the error in k_b, due to remnants of the first stage of the reaction, should be less than 1%.

occurs in part in the alkaline reaction of ethylene sulfate,[8] predominantly in cyclohexane-*cis*-1,2-diol sulfate,[7] and solely in catechol sulfate and diphenyl sulfate.[9] *p*-Nitrophenyl sulfate reacts with some nucleophiles in part by sulfur–oxygen scission and in part by aryl–oxygen scission.[13] Competition between sulfur–oxygen scission and aryl–oxygen scission is likewise balanced in the reactions of nucleophiles with *p*-nitrophenyl arenesulfonates.[23] Alkyl chlorosulfates[24] and fluorosulfates[1] also react by carbon–oxygen or sulfur–oxygen cleavage. Though in the present system steric hindrance will undoubtedly favor attack at the aliphatic carbon, it is probable that polarizability is also an important factor in determining the site of attack. Thus the electrophilic centers provided by sulfur and by aromatic carbon are expected to be more susceptible to attack by reagents with a higher polarizability than that of the methoxide ion. This point will be tested in future work.

The primary process in the reaction of methyl *p*-nitrophenyl sulfate in initially neutral methanol has been shown to be solvolytic displacement at the alkyl carbon, analogous to the methoxide ion reaction (eq 2).



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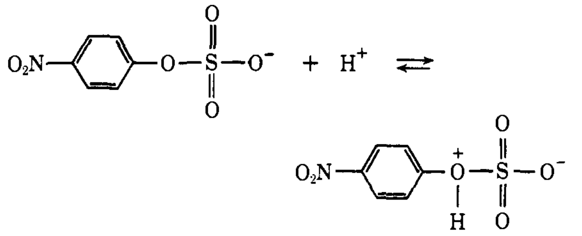
The secondary consecutive reaction, leading to *p*-nitrophenol, is most probably an acid-catalyzed process, *i.e.*, preequilibrium protonation of the phenolic oxygen followed by rate-determining elimination of SO_3 (eq 3 and 4). Previous studies have established the nature of the acid catalysis of *p*-nitrophenyl sulfate in aqueous media[12–14] and it is reasonable to assume that this mechanism will prevail in the methanolic medium of the present work.



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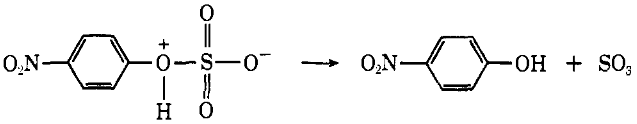

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Table III. Activation Parameters for the Alkaline and Neutral Methanolysis of Methyl *p*-Nitrophenyl Sulfate

Reaction	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$,[c] eu	$\Delta F^{\ddagger}$,[c] kcal/mol
Alkaline methanolysis[a]	16.9	−3.1	17.8
Neutral methanolysis[b]	18.9	−10.2	21.9

[a] Activation parameters derived from the second-order rate constant, $(k_{\text{obsd}} - k_{\text{sol}})/[\text{CH}_3\text{ONa}]$, as in Table II. [b] Activation parameters derived from the first-order rate constant, k_{sol}, as in Table II. [c] Calculated at 25°.

Activation parameters for the alkaline and neutral methanolysis of methyl *p*-nitrophenyl sulfate have been calculated from the rate measurements at three temperatures (Table II) and are listed in Table III. The $\Delta S^{\ddagger}$ value for the neutral methanolysis (−10.2 eu) may be compared with neutral aqueous solvolysis of dimethyl sulfate for which $\Delta S^{\ddagger} = -5.0$ eu.[11] The $\Delta H^{\ddagger}$ value in neutral methanolysis (18.9 kcal/mol) compares with $\Delta H^{\ddagger} = 21.1$ kcal/mol in aqueous solvolysis of dimethyl sulfate.[11] The similar activation parameters in the two cases suggest that methyl *p*-nitrophenyl sulfate and dimethyl sulfate undergo solvolysis by analogous mechanisms. The activation parameters in the alkaline methanolysis of methyl *p*-nitrophenyl sulfate are in accord with a normal bimolecular mechanism.

In conclusion, the neutral and alkaline methanolysis of methyl *p*-nitrophenyl sulfate proceeds solely by alkyl–oxygen scission and is closely analogous to the behavior of dimethyl sulfate in aqueous hydrolysis. The specificity of the reaction of methyl *p*-nitrophenyl sulfate is rather remarkable in view of the availability of the aryl carbon and the sulfur atom as alternative electrophilic centers. This specificity suggests that, like methyl *p*-nitrobenzenesulfonate,[15,16] methyl *p*-nitrophenyl sulfate could have utility in the alkylation of amino acids and proteins.

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