

Reactions of Nucleophiles with Strained Cyclic Sulfonate Esters. Brønsted Relationships for Rate and Equilibrium Constants for Variation of Phenolate Anion Nucleophile and Leaving Group

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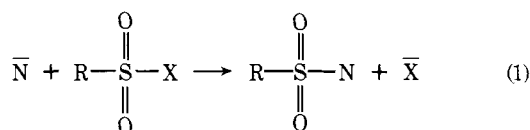
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Abstract: The reaction of phosphate dianion and phenolate anion has been measured with a series of substituted 2-hydroxyphenylmethanesulfonic acid sultones together with the equilibrium constants for the reaction with phenol. A similar series of reactions with substituted phenolate anions and 5-nitro-2-hydroxyphenylmethanesulfonic acid sultone was also measured for rate and equilibrium constants. The Brønsted β values for the rate constants compared with those for the equilibrium constants indicate considerable bond cleavage and bond formation at leaving and entering atoms in the transition state; moreover, the change in effective charge on the leaving sultone oxygen (-0.85) is almost exactly counterbalanced by the change in effective charge on the attacking phenolate oxygen ($+0.81$) consistent with a symmetrical transition state. The Brønsted selectivity of the equilibrium constants indicates that the oxygens of the sultone and of the product open-chain sulfonate adjacent to the aryl group bear effective charges of some $+0.7$ to $+0.8$ relative to unit negative charge on phenolate anion oxygen and zero charge on the oxygen of phenol; these results indicate that the sulfone group is considerably more electron withdrawing than hydrogen in this reaction.

Introduction

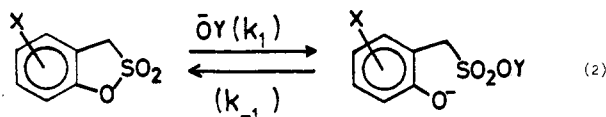
Substitution reactions of nucleophiles at a sulfonyl center (eq 1) by an addition-elimination process are of interest be-



cause the mechanism could be stepwise, with a pentacoordinate intermediate, or be concerted involving synchronous bond formation and cleavage. There has been considerable discussion centered on the distinction between these two mechanisms;¹ there seems to be a consensus that the concerted process predominates, at least in those sulfonyl group transfer processes which have been studied so far. The evidence for this is not clear cut, however, and involves heat capacity measurements^{1a} and nonlinear Hammett relationships.^{1b} Evidence involving "anti-Hammond" behavior as exhibited by Brønsted and Hammett parameters for a series of reactions of pyridines with benzenesulfonyl chlorides was shown by Rogne¹ⁱ to be consistent with the concerted mechanism.

A useful approach to elucidating the sulfonyl group transfer mechanism is the determination of Brønsted selectivity values for bond formation and bond cleavage for attacking nucleophile and departing group. The use of simple Brønsted β values only gives an approximate measure of the extent of bond cleavage or formation and a more meaningful parameter is that defined by Leffler,² namely, the ratio $\beta_1/\beta_{\text{eq}}$ where β_1 is the Brønsted β for the forward reaction and β_{eq} is that for the equilibrium. Only recently has this parameter or its analogue been used since β values for equilibria are in general difficult to obtain.

The reaction of nucleophiles with 2-hydroxyphenylmethanesulfonic acid sultones, first investigated in depth by Kaiser,^{1b,c} provides an excellent vehicle for investigating the electronic state of the sulfonyl group since an essentially symmetrical reaction (eq 2) may be studied with similar nu-



cleophiles (YO^- , phenolate anions) and leaving groups (with substituent X). This system has been shown^{3a} to prefer nucleophilic attack rather than an E-A mechanism^{3b} via a sulfene intermediate because of a unique form of stereoelectronic control already discussed by us.⁴ The system also has the advantage of being easily measured since the reactivity of the sultone²⁴ is high on account of ring strain;^{1b,c} the latter phenomenon also ensures that if a stepwise process with addition intermediate were involved there is no ambiguity as to the identity of the rate-controlling step.

We have demonstrated previously that we may measure the equilibrium constant and rate constants for reaction 2 for attack of phenolate anion on the 5-nitrosultone⁵ and this paper reports these measurements for a variety of Y and X parameters. Construction of Brønsted plots for k_1 and k_1/k_{-1} enables us to determine the position of the transition state relative to reactant and product states for exocyclic S-O bond formation and endocyclic S-O bond cleavage.

Experimental Section

Materials. Phenols (from B. D. H. Ltd.) were purified by recrystallization or by sublimation; 2-nitro-4-bromophenol was prepared from 4-bromophenol by nitration and had mp $88-90^\circ\text{C}$ (lit. $88-92^\circ\text{C}$).^{6a}

Sodium 3,5-dibromo-2-hydroxyphenylmethanesulfonate was prepared as follows: sodium 2-hydroxyphenylmethanesulfonate (3 g, 14.3 mmol) was dissolved in water (35 mL) and bromine 5 g, 31.4 mmol) added dropwise over a period of 30 min while stirring magnetically; the solution became yellow and slightly warm. The water was evaporated in vacuo and the salt dried by repeated evaporation with added ethanol. The solid was filtered, washed with ether, and dried (yield 4 g, 76% of theoretical). The salt (3 g, 8.38 mmol) was cyclized to the corresponding sultone by refluxing with phosphoryl chloride (17 mL, 180 mmol) for about 2 h. The excess acid chloride was removed in vacuo and the creamy residue transferred to approximately 40 mL of ice water with stirring. The mixture was stirred for 1 h, filtered, washed with a little ice-cold water, and dried in vacuo to yield 2.1 g of creamy white solid (79%) which was recrystallized from methanol after charcoal treatment.

The 3-nitro-5-bromo-2-hydroxyphenylmethanesulfonic acid sultone was prepared from the 5-bromo derivative via the method used for preparing the 5-nitrosultone (see Table I). Recrystallization of the product from ethanol gave pure material in 36% yield.

The 3,5-dinitrosultone was prepared from the 5-nitrosultone by the

Table I. Analytical and Physical Properties of Derivatives of 2-Hydroxyphenylmethanesulfonic Acid^a

Substrate	Mp, °C (lit.)	Found, %			Formula	Calcd, %		
		C	H	N		C	H	N
Sultone ^b								
3,5-Dinitro-	214-215	32.0	1.5	10.5	C ₇ H ₄ N ₂ O ₇ S	32.3	1.5	10.8
5-Bromo-3-nitro-	199-200	28.7	1.6	4.5	C ₇ H ₄ BrNO ₅ S	28.6	1.4	4.8
3,5-Dibromo-	112-113	25.4	1.4		C ₇ H ₄ Br ₂ O ₃ S	25.6	1.2	
5-Nitro-	148-150 (148.5-149.5) ^c							
5-Bromo-	147-148 (148-149) ^e							
5-Methoxy-	81-82 (81-81.5) ^e							
5-Methyl-	95-96 (96.1-96.5) ^e							
Unsubstituted	86-87 (86.1-87.1) ^d							
Phenyl Ester ^f								
3,5-Dinitro-	170-172	43.9	3.1	7.7	C ₁₃ H ₁₀ N ₂ O ₈ S	44.1	2.9	7.9
5-Bromo-3-nitro-	128-129	40.3	3.0	3.4	C ₁₃ H ₁₀ BrNO ₆ S	40.2	2.6	3.6
Substituted Phenyl 5-Nitro-2-hydroxyphenylmethanesulfonate								
4'-Methyl-	163-164	51.9	4.0	4.2	C ₁₄ H ₁₃ NO ₆ S	52.0	4.0	4.3
4'-Chloro-	168-169	45.8	3.4	4.2	C ₁₃ H ₁₀ ClNO ₆ S	45.4	2.9	4.1
3'-Chloro-	137-138	45.7	3.5	4.0	C ₁₃ H ₁₀ ClNO ₆ S	45.4	2.9	4.1

^a Analyses were by Mr. G. M. Powell of the microanalytical department of this laboratory using a Hewlett-Packard Model 185 CHN analyzer. Melting points were determined using a Kofler Thermospa hot stage instrument and are corrected. ^b All the sultones except the 5-nitro, 3,5-dibromo, 3,5-dinitro, and 5-bromo-3-nitro derivatives were purified by sublimation. ^c E. T. Kaiser, K.-W. Lo, K. Kudo, and W. Berg, *Bioorg. Chem.*, **1**, 32 (1971). ^d O. R. Zaborsky and E. T. Kaiser, *J. Am. Chem. Soc.*, **88**, 3084 (1966). ^e O. R. Zaborsky and E. T. Kaiser, *ibid.*, **92**, 860 (1970). ^f Phenyl substituted 2-hydroxyphenylmethanesulfonates.

method employed for the 5-nitrosultone. The material, in 50% yield, was purified by recrystallization from acetonitrile.

Other sultones were prepared according to literature methods (see Table I).

The preparation of phenyl esters was carried out by the following general procedure. The sultone (10 mmol) was dissolved in the smallest quantity of acetonitrile and then taken up to 5 mL with ethanol. The sodium salt of the phenol (10 mmol) was then added and the mixture swirled for about 15 min. The mixture was taken to acid pH with ethanolic HCl and then evaporated in vacuo. Trituration with water and ethanol gave a solid which was recrystallized from ethanol.

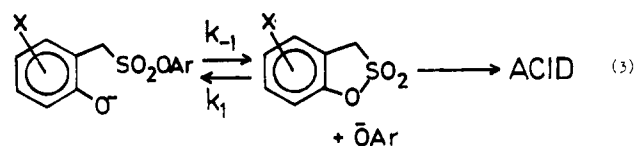
The substrates had infrared and NMR spectra consistent with their proposed structures and analytical and physical properties are given in Table I.

Other species such as buffers were either of analytical grade or were recrystallized or redistilled from bench grade materials. Acetonitrile was purified by the method of Lewis and Smyth^{6b} and water was doubly distilled from an all-glass apparatus.

Methods. The measurement of pH was carried out using a Pye-Dynacap instrument or a Radiometer pH meter PHM 62 calibrated with E. I. L. standard buffer powders to ± 0.01 pH units.

Reactions were followed spectrophotometrically in the thermostated cell compartments of Beckman DBG, Unicam SP800, or Unicam SP600 machines at suitable fixed wavelengths determined by repetitive scanning experiments using the SP800 instrument. A typical experiment involved adding an aliquot ($\sim 50 \mu\text{L}$) of a stock solution of sultone or ester dissolved in ethanol to 2.5 mL of a buffer-containing reagent such as phenolate or phosphate anions. The solution was added on the tip of a glass plunger which was used to mix the solution thoroughly by a pumping motion. Pseudo-first-order rate constants were generally determined from plots of $A_t - A_\infty$ vs. time on semilogarithmic graph paper ($A_t =$ absorption at time t). The pH of the buffer was measured before and after each experiment.

The values of k_{-1} were determined by four methods: (1) This involved the synthesis of the phenyl ester and the direct study of its hydrolysis. This method has been described before for the phenyl ester of the 5-nitro derivative where a sigmoidal pH dependence was observed for k_{-1} ;⁵ in the present experiments the kinetics were measured at different pHs to confirm that k_{-1} was pH independent; we worked in the region of the pH plateau where decomposition of the intermediate sultone (eq 3) never became rate limiting. (2) The second method involved the in situ synthesis of the phenyl ester followed by a study of its decomposition. This method was employed for only one compound, 4-methoxyphenyl-5-nitro-2-hydroxyphenylmethanesulfonate, which presented difficulties in its isolation as a crystalline product. (3) This method was used for unreactive phenolate anions with the



5-nitrosultone; these phenols had substituents with σ values in excess of 0.3. It was impossible to follow the reaction for 3-nitro- and 4-nitrophenol, however, because these phenols swamped the absorption in the visible region of the spectrum used to measure the 5-nitrosultone reaction. A buffer solution with the appropriate phenol (e.g., 4-ethoxycarbonylphenol) was prepared and the 5-nitrosultone stock solution added; in the case of the ethoxycarbonyl, cyano, acetyl, and formylphenols a two-phase reaction occurs (Figure 1) and this is analyzed by plotting $\log(A_t - A_\infty)$ vs. time. The equilibrium constant for the formation of the sultone (k_{-1}/k_1) is determined from the intercepts of the first and second linear phases at zero time (see Figure 1 for the meanings of the symbols). The rate constant for approach to equilibrium, determined from the first reaction phase (by plotting Δ_t vs. time on semilogarithmic graph paper), enables us to use the equilibrium constant to isolate k_{-1} and k_1 using eq 5. (4) The fourth approach involved measuring the rate constant for reaction of sultone with phenolate anion at varying concentrations of the latter; the intercept of the linear plot of the rate constant at zero phenolate concentration, when corrected for background hydrolysis of the sultone in the buffer, yields k_{-1} and the slope yields k_1 (see Figure 2). The rate law for the reaction, after background correction, is given by eq 5.

$$\frac{[\text{sultone}]}{[\text{phenyl ester}]} = \frac{\Delta_1 - \Delta_2}{\Delta_2} = \frac{k_{-1}}{k_1 [\text{phenolate}]} \quad (4)$$

$$k_{\text{obsd}} = k_1 [\text{phenolate}] + k_{-1} \quad (5)$$

The methods 3 and 4 do not apply to all the constituents of the set of reactions and only produce accurate data for k_{-1} when this and the apparent reverse rate constant ($k_1[\text{phenolate ion}]$) became commensurate.

Rate constants for reactions of other nucleophiles with the sultones were determined as described in the preceding publication⁵ and details of wavelength, concentration ranges, and pH ranges are given in the appropriate tables.

Equilibrium constants, where not determined directly from the experimental method (as in, for example, eq 4), were derived from the ratio of the forward to the reverse rate constants under the same conditions and are recorded in the tables.

Measurement of pK_a . Ionization constants of reagent phenols were measured by titration of the acid with standard alkali using Radi-

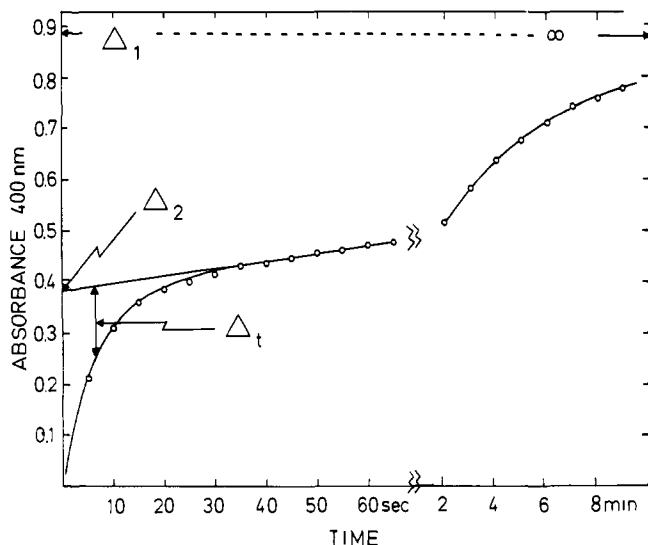


Figure 1. Reaction of 5-nitrosultone with 4-formylphenol buffer at 55.6 mM and pH 7.94. Fraction of base = 0.661. Conditions: 25 °C, ionic strength made up to 1 M with KCl; line is theoretical and the symbols refer to quantities used in calculating k_1 and k_{-1} .

Table II. Ionization Constants for Some Phenols^a

2-Hydroxy-phenylmethanesulfonic acid	pK_a^c	Phenol	pK_a
3,5-Dinitro-	2.4 ± 0.1^f	2,4-Dinitro-	4.11^b
5-Nitro-	6.0^5	4-Nitro-	7.14^b
5-Bromo-3-nitro-	5.7 ± 0.1^e	4-Bromo-2-nitro-	6.36^d
		2,4-Dibromo-	7.74^d

^a 25 °C. ^b Table III, footnote b. ^c 1 M ionic strength made up with KCl. ^d Ionic strength maintained at 0.002 M with KCl. ^e Measured spectrophotometrically at 430 nm. ^f Measured spectrophotometrically at 370 nm.

ometer equipment (REC 61 Servograph, REA Titratigraph, PHM 62 standard pH meter, TTT 60 titrator, and ABU 11 autoburet). The pK_a s of the phenyl sulfonates derived from reaction of phenolate and substituted sultones were determined spectrophotometrically; results are given in Table II.

Results

Reactions of phosphate dianion with substituted sultones obey good pseudo-first-order rate laws with rate constants proportional to phosphate dianion concentration. Since phosphate is transparent in the ultraviolet and visible spectrum we were able to measure the rate constants for all the sultones. Hydroxide attack on the sultones was obtained from intercepts at zero buffer concentration and the results are given with those for phosphate in Table III; where overlap occurs our results for phosphate term agree with those of Zaborsky and Kaiser.⁷ The data are plotted as Brønsted relationships in Figure 3.

Reaction of 5-nitrosultone with phenolate anions analyzed by methods 1, 2, and 3 gives results for k_1 and k_{-1} (Table IV) which fit single Brønsted and Hammett σ^- lines (Figures 4 and 5). There is no possibility of measuring even one component of the set by two different methods in order to obtain overlap: the equilibrium is not sufficiently favorable for us to synthesize sulfonate esters from sultone and phenols with substituents with Hammett σ values greater than 0.4. The position of the equilibrium also makes it impossible to measure k_{-1} for the phenols with substituents with Hammett σ values less than 0.4 by methods 3 or 4. The excellent fit to the linear free energy relationships, however, gives us confidence that the rate con-

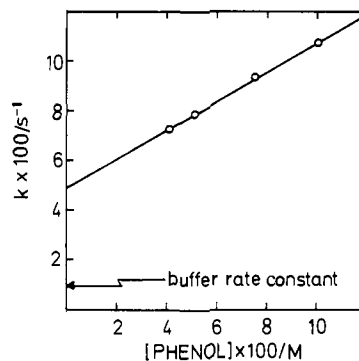


Figure 2. Plot of the rate constant vs. phenol concentration for reaction of phenolate anion with 5-bromosultone. Conditions: 25 °C, ionic strength made up to 1 M with KCl, fraction of base form of phenol = 0.344, pH 9.75, carbonate buffers at 0.095 M. Wavelength for kinetic study 320 nm; the experimental rate constant without phenol is indicated.

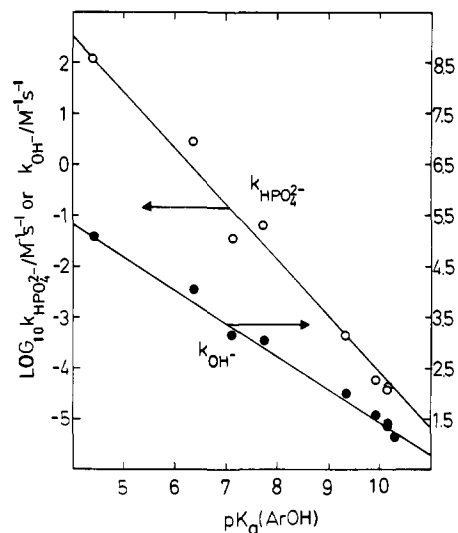


Figure 3. Brønsted plots for reaction of phosphate dianion (O) and hydroxide ion (●) with substituted sultones. Lines are theoretical from Table VI and data are from Table III.

stants from different methods refer to the same parameter. Figure 6 illustrates the fit of the phenolate anion data for k_1 to a broader comparison of the reactivity of RO^- groups toward the 5-nitrosultone.

Phenolate anion reacts with substituted sultones and the values of k_1 and k_{-1} (Table V) obey good Brønsted relationships (Figure 7), although the data are, of necessity, more sparse than those for the variation of the attacking phenolate ion. Method 1 was employed for the 5-nitrosultone, 5-bromo-3-nitrosultone, and the 3,5-dinitro derivative and method 4 for the 5-bromo- and 3,5-dibromosultones.

Table VI collects the equations governing the Brønsted relationships for the various reactions of nucleophiles with sultones.

The pK_a values obtained for the open-chain sulfonates are all lower than those for the corresponding phenols without the methanesulfonate group. Part of this reduction is probably due to the high ionic strength (1 M) used in the former cases compared with the small or zero ionic strength for the latter. The major part of the reduction is almost certainly due to the large inductive effect of the sulfone group acting through the methylene link.

The temperature dependence for the reaction of phenolate anion with the 5-nitrosultone was measured (taking into account the slight change in pK_a of phenol with temperature) and the pseudothermodynamic parameters ΔH^\ddagger and ΔS^\ddagger_{298} cal-

Table III. Reaction of Phosphate Dianion and Hydroxide Ion with Substituted 2-Hydroxyphenylmethanesulfonic Acid Sulfones^a

Substituent	pK _a ^{ArOH} ^b	λ, nm	k _{HPO₄²⁻, M⁻¹ s⁻¹ ^c}	k _{OH⁻} , M ⁻¹ s ⁻¹ ^c
3,5-Dinitro-	4.11	420	120 (4.9–5.87, 12) ^h	1.2 × 10 ⁵ (4.89–7.51, 20) ⁱ
5-Bromo-3-nitro-	6.36 ^d	440	2.9 (5.47–6.07, 14)	1.2 × 10 ⁴ (7.7–8.43, 19) ^j
5-Nitro-	7.14	400	3.7 × 10 ⁻² (6.34, 5)	1.4 × 10 ^{3f}
5-Bromo-	9.34	294	4.5 × 10 ⁻⁴ (6.34, 4)	95 (8–10, 5) ^g
Unsubstituted	9.95	282	5.8 × 10 ⁻⁵ (6.34, 7)	37 (8–10, 7) ^g
5-Methyl-	10.19	290	4.0 × 10 ⁻⁵ (6.34, 4)	24 (8–10, 5) ^g
5-Methoxy-	10.20	307	4.2 × 10 ⁻⁵ (6.34, 3)	21 (8–10, 6) ^g
3,5-Dibromo-	7.74 ^d	320	6.6 × 10 ⁻² (5.57–7.46, 13)	1.1 × 10 ³ (8.19–9.39, 16) ^l
5-Amino-	10.30			14 ^e

^a 25 °C, ionic strength maintained at 1 M with KCl. ^b pK_a of the phenol parent (that from the sulfone without the methanesulfonate group in the position ortho to the hydroxyl). Values except where stated are taken from J. Regenstein and W. P. Jencks, "Handbook of Biochemistry", 2nd ed, H. A. Sober, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1970. ^c Values in parentheses are, in order of citation, pH range and the total number of experimental points. ^d This work; ionic strength maintained at 0.002 M with KCl, 25 °C. ^e Value taken from Zaborsky and Kaiser.⁷ ^f Value from Deacon, Steltner, and Williams.^{4b} ^g Triethylamine buffer at 0.01 M concentration; comparison with the 5-nitrosulfone kinetics (see reference in footnote *f*) indicates that this buffer has negligible action compared with hydroxide ion at these pHs and no buffer corrections are therefore necessary. ^h Pyridine buffers; k_{H₂O} = 4.8 × 10⁻⁴ M⁻¹ s⁻¹. ⁱ 2,6-Lutidine and pyridine buffers; k_{pyr} = 0.18 M⁻¹ s⁻¹, pH 4.89–5.92, 16 points; k_{lut} = 0.26 M⁻¹ s⁻¹, pH 7.2–7.51, 8 points. ^j Tris buffer; k_{Tris} = 0.71 M⁻¹ s⁻¹, pH 7.77–8.43, 19 points. ^l Carbonate and Tris buffers; k_{carb²⁻} = 2.9 M⁻¹ s⁻¹, pH 8.84–9.39, 12 points; k_{Tris} = 7.2 × 10⁻² M⁻¹ s⁻¹, pH 8.19, 4 points.

Table IV. Forward and Reverse rate Constants and Equilibrium Constants for Reaction of Phenolate Anions with the 5-Nitrosulfone^{a,h}

Phenol	pK _a ^b	k ₁ , M ⁻¹ s ⁻¹ ^e	k ₋₁ , s ⁻¹ ^e	K, M ⁻¹
4-Methoxy-	10.20	390 (7.84, 5)	2.1 × 10 ⁻⁴ (7.6–8.2, 4) ^{h,i}	1.9 × 10 ⁶
4-Methyl-	10.19	160 (8.14, 5)	2.1 × 10 ⁻⁴ (7.6–8.2, 5) ^{h,j}	7.6 × 10 ⁵
Unsubstituted ^f	9.95	62	5.2 × 10 ⁻⁴	1.2 × 10 ⁵ ^d
3-Chloro-	9.02	25 (8.14, 5)	5.8 × 10 ⁻³ (7.6–8.2, 4) ^{h,j}	4.3 × 10 ³
4-Chloro-	9.38	48 (8.14, 6)	1.8 × 10 ⁻³ (7.6–8.2, 5) ^{h,j}	2.7 × 10 ⁴
3-Ethoxycarbonyl-	9.05 ^c	31 (8.00, 5)	6.5 × 10 ⁻³ ^{i,m}	4.8 × 10 ³
4-Ethoxycarbonyl-	8.50	6.5 (7.9, 5)	5.7 × 10 ⁻³ ^{i,m}	1.1 × 10 ³
4-Cyano-	7.95	3.8 (8.00, 5)	0.11 ^{i,m}	35
4-Acetyl-	8.05	4.0 (7.94, 5)	2.8 × 10 ⁻² ^{i,m}	140
4-Formyl-	7.66	1.4 (7.61–7.94, 5)	8.8 × 10 ⁻² ^{i,m}	16
2,2,2-Trifluoroethanol	12.43	6.6 × 10 ³ (7.84, 5)		

^a 25 °C, ionic strength maintained at 1 M with KCl. ^b See footnote *b* of Table III. ^c This work; 0.002 M ionic strength, 25 °C. ^d A small error is noted in a previous paper (Farrar and Williams)⁵ where *K* is quoted as 1.4 × 10⁵ M⁻¹. ^e There is a maximum of 10% error limit on these parameters. ^f Parameters for this reaction are from the reference in footnote *d*. ^h Figures in parentheses are pH and number of experimental points, respectively; buffer is *N*-ethylmorpholine at 0.04 M and the contribution to the decomposition of the 5-nitrosulfone by buffer is negligible. The hydroxide ion correction was estimated from data in Table III. ⁱ Experimental conditions as for the corresponding *k*₁ parameter. ^j Estimated via method 1. ^l Estimated via method 2. ^m Estimated via method 3.

Table V. Reaction of Phenolate Anion with Substituted 2-Hydroxyphenylmethanesulfonic Acid Sulfones^{a,o}

Sulfone	λ, nm ^h	pK _a ^{ArOH} ^b	k ₁ , M ⁻¹ s ⁻¹	k ₋₁ , s ⁻¹	K, M ⁻¹
5-Bromo-	320	9.34	1.9 (9.35–10.71, 19) ⁱ	3.5 × 10 ⁻² ⁱ	54
3,5-Dibromo-	320	7.74	60 (7.74–8.88, 21) ^j	1.0 × 10 ⁻² ^j	6.0 × 10 ³
3,5-Dinitro-	420 (275)	4.11	4.2 × 10 ⁴ (4.94–5.86, 12) ^l	2.0 × 10 ⁻⁶ ^c	2.1 × 10 ¹⁰
3-Nitro-5-bromo- ^g	440 (270, 290)	6.36	2.3 × 10 ³ (6.6–7.7, 14) ^m	3.2 × 10 ⁻⁴ (8.3–10.5, 11) ⁿ	7.2 × 10 ⁶
5-Nitro ^d		7.14	62 ^b	5.2 × 10 ⁻⁴ ^f	1.2 × 10 ⁵ ^f

^a 25 °C, ionic strength maintained at 1 M with KCl. ^b See footnote *b* of Table III. ^c Method 1. Rate constant for 25 °C calculated from the pseudothermodynamic parameters: Δ*H*[‡] = 23.3 ± 1 kcal/mol and Δ*S*₂₉₈[‡] = -6.5 ± 3 eu/mol derived from duplicate runs at 50.9, 56.0, 67.1, 72.6, and 81.1 °C with phosphate buffer (0.066 M, at 1 M ionic strength) at pH 6.03 (20 °C). A value for k_{OH⁻} from experiments at [KOH] = 0.1–1 M was determined to be 2.8 × 10⁻⁴ M⁻¹ s⁻¹ at 25 °C. ^d Pseudothermodynamic data for the parameters, Δ*H*^{‡(0)} (kcal/mol) and Δ*S*₂₉₈^{‡(0)} (eu/mol), respectively, follow: *k*₁, 11.1 ± 0.4, -13 ± 1.2; *k*₋₁, 19.7 ± 0.8, -7.2 ± 2.5; *K*(*k*₁/*k*₋₁), -8.6 ± 0.9, -5.8 ± 2.8. ^e Errors are noted in a previous publication (Farrar and Williams)⁵ but are not sufficient to alter our previous conclusions. ^f See Table IV. ^g A slight increase in rate constant at 1 M KOH over the values at lower pHs gives an approximate value of 2.7 × 10⁻⁴ M⁻¹ s⁻¹ for k_{OH⁻} for the alkaline hydrolysis of the phenyl ester. ^h Wavelength employed in the kinetic study for reaction of sulfone. Where method 1 is employed the wavelength for *k*₋₁ is given in parentheses. ⁱ Carbonate buffers; method 4. ^j Tris buffers; method 4. ^l Pyridine buffers. ^m Tris and phosphate buffers. ⁿ Carbonate and Tris buffers; method 1. ^o There is a maximum of 10% error in the kinetic parameters.

culated from eq 6 and 7. The parameters are recorded in Table V.

$$\Delta H^\ddagger = \Delta E_a - RT \quad (6)$$

$$k_{25} = \frac{kT}{h} e^{\Delta S_{25}^\ddagger/R} e^{-\Delta H^\ddagger/RT} \quad (7)$$

The decomposition of the phenyl ester of 2-hydroxy-3,5-dinitrophenylmethanesulfonic acid (*k*₋₁) was too slow to measure at 25 °C and the value of this was estimated from rate constants over a series of temperatures using eq 6 and 7; the pseudothermodynamic data for this reaction are collected in Table V.

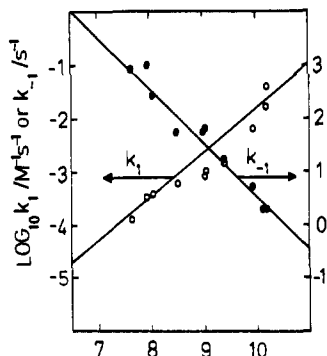


Figure 4. Brønsted plots for reaction of substituted phenolate anions with 5-nitrosultone: k_1 (○), k_{-1} (●). Lines are theoretical from Table VI and data are from Table IV.

Table VI. Brønsted Equations Governing the Parameters for the Reaction of Phenolate Anions, Hydroxide Ion, and Phosphate Dianion with the Sultones^e

Reaction	Equation ^{a,f}	
ArO ⁻ + 5-nitrosultone	$\text{Log } k_1 = 0.81 \pm 0.04 \text{ p}K_a^d - 5.96$	(0.978)
	$\text{Log } k_{-1} = -1.03 \pm 0.05 \text{ p}K_a^d + 6.91$	(0.978)
RO ⁻ + 5-nitrosultone	$\text{Log } k_1 = 0.87 \pm 0.02 \text{ p}K_a^b - 6.57$	(0.991)
C ₆ H ₅ O ⁻ + sultones	$\text{Log } k_1 = -0.85 \pm 0.1 \text{ p}K_a^c + 8.26$	(0.980)
	$\text{Log } k_{-1} = 0.84 \pm 0.1 \text{ p}K_a^c - 8.98$	(0.977)
Hydroxide ion + sultones	$\text{Log } k_{\text{OH}} = -0.64 \pm 0.02 \text{ p}K_a^c + 7.85$	(0.995)
	$\text{Log } k_{\text{HPO}_4^{2-}} = -1.10 \pm 0.04 \text{ p}K_a^c + 6.93$	(0.990)

^a Values in parentheses are the correlation coefficients. ^b The $\text{p}K_a$ refers to the ionization of the ROH species; see Figure 6 for details of the data source. ^c The $\text{p}K_a$ is that of the phenol corresponding to the sultone without the methanesulfonate group (see footnote ^b of Table V). ^d The $\text{p}K_a$ refers to the phenolate species. ^e Taken from data in Tables III–V and from Deacon, Steltner, and Williams.^{4b} ^f Errors are quoted in the equations as 90% confidence limits.

Discussion

Brønsted Selectivities for Equilibria in Acyl Group Transfer.

The equilibrium constants for formation of phenyl sulfonate from phenolate anion and substituted sultone increase with electron-withdrawing power of the substituents (Table V) and the selectivity toward the $\text{p}K_a$ of the phenol corresponding to the sultone is $\beta(k_1) - \beta(k_{-1}) = -1.69$ (see Table IV). The equilibrium constants for formation of substituted phenyl sulfonates from substituted phenolate anions and 5-nitrosultone decrease with increase in electron-withdrawing power of the substituent (Table IV) and the selectivity to the $\text{p}K_a$ of the substituted phenol is $\beta(k_1) - \beta(k_{-1}) = +1.84$ (see Table VI). This means that substituting a sulfonyl group (in sultone or open-chain form) for the proton of a phenol is favored by electron-donating substituents and the sulfonyl group (or sulfone) is more electron withdrawing than the proton.

The Brønsted selectivities may be interpreted as “effective” charges on individual atoms with respect to a defined charge or calibrating equilibrium;⁸ thus sultone or sulfonate ester have +0.69 and +0.84 unit of effective charge on the oxygen adjacent to the phenyl compared with a defined zero and –1 charge on the oxygen in phenol and phenolate anion, respectively.

For a constant acceptor atom one might compare electron-withdrawing powers of a series of acyl groups by the “effective” charge on this atom. We might have anticipated the relative electron-withdrawing power of the sulfone group from its σ_1

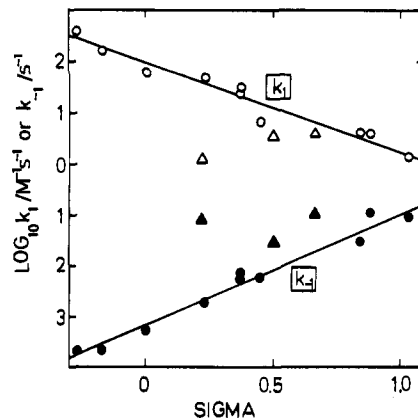


Figure 5. Hammett plots for reaction of substituted phenolate anions with 5-nitrosultone: k_1 (○), k_{-1} (●). Lines are theoretical; $\text{log } k_1 = -1.72 \sigma^- + 1.97$ ($r = 0.975$) and $\text{log } k_{-1} = 2.17 \sigma^- - 3.17$ ($r = 0.986$). σ and σ^- values are from G. B. Barlin and D. D. Perrin, *Q. Rev., Chem. Soc.*, **20**, 75 (1966); correlation coefficients using ordinary σ values are respectively 0.795 and 0.847. Triangles represent σ values for resonating substituents; data are from Table IV.

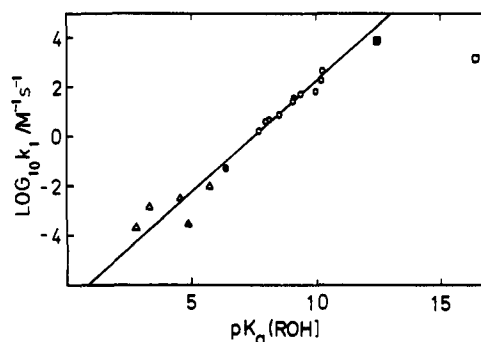


Figure 6. Brønsted plot for reaction of oxyanion nucleophiles with 5-nitrosultone. Line is theoretical from Table VI and data are from Table IV and from Deacon, Steltner, and Williams.^{4b} Phenolate anions (○), carboxylate anions (△), phosphate dianion (●), trimethylamine oxide (▲), hydroxide ion (□), and 2,2,2-trifluoroethoxide (■).

value, which is considerably more positive than that for hydrogen.⁹ Indeed, most acyl groups have positive σ_1 values and have been found to be more electron withdrawing than the proton in their equilibrium transfer reactions (Table VII). The σ_1 values alone do not allow a prediction to be made of the electron-withdrawing power of the acyl function as diagnosed by the effective charge on a common acceptor atom; for example, the sulfonyl and carbamoyl groups have significantly different σ_1 values (0.6 and 0.25, respectively)⁹ but very similar effective charges are observed on the adjacent oxygen acceptor atom (see Table VII). Moreover, the sequence $\sigma_1(\text{CO}_2^-) < \sigma_1(\text{H}) < \sigma_1(\text{COCH}_3) \sim \sigma_1(\text{CONH}_2)$ does not predict the observed sequence of effective charges (ϵ) on an oxygen acceptor atom: $\epsilon(\text{H}) < \epsilon(\text{CO}_2^-) < \epsilon(\text{COCH}_3) \sim \epsilon(\text{CONH}_2)$.

The low value of the effective charge on sulfur (see Table VII) in thiol esters was discussed by Hupe and Jencks¹⁰ and a possible explanation involves a balance of mesomeric and inductive effects. Unfortunately there are still too few data available at present to attempt to correlate the effective charge on a constant acceptor atom with a linear combination of σ_1 and σ_R . The CONH_2 and CONH^- groups induce effective charges on oxygen (+0.81 and +0.31) which are particularly easily rationalized because one would expect the electron-withdrawing power of the neutral acyl group to exceed that of the anionic one. However, the situation is not always as simple as this because the selectivity data indicate that the two phosphoryl groups $-\text{PO}_3^{2-}$ and $-\text{PO}(\text{OR})_2$ have similar elec-

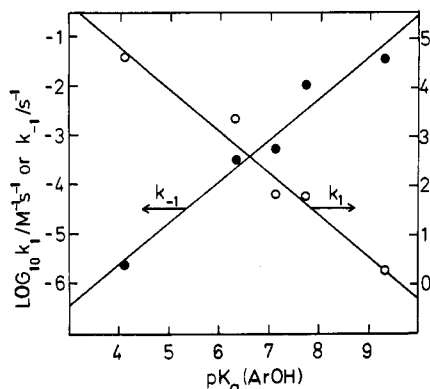


Figure 7. Brønsted plot for reaction of phenolate anion with substituted sultones: k_1 (O), k_{-1} (●); lines are theoretical from Table VI and the data are from Table V.

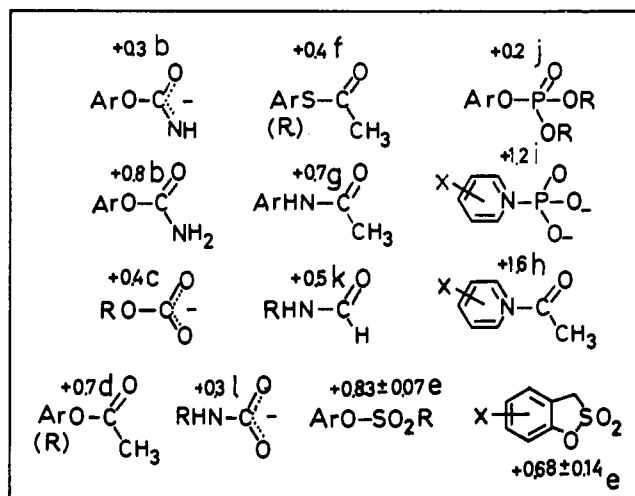
tron-withdrawing power; the atoms compared are different in the latter comparison (nitrogen and oxygen, respectively) but a change of atom from nitrogen to oxygen does not seem to change the effective charge for the acetyl group or the $-\text{CO}_2^-$ group (see Table VII).

At this stage it would not be worthwhile discussing the lower effective charge induced in the endocyclic sultone oxygen ($+0.69 \pm 0.14$) compared with that on the open-chain sulfonate oxygen ($+0.84 \pm 0.06$) except to note its existence. The value for the sulfonate oxygen is clearly the more accurate and it is possible that the difference is not significant because the 90% confidence limits allow overlap.

Thermodynamics of the Ring Opening of Sultones. The equilibrium constant for attack of phenolate anions on the 5-nitrosultone to form aryl sulfonates increases with electron-donating power of the substituent on the phenol and we may calculate from the Brønsted relationships (Table VI) that the equilibrium constant is approximately unity for 4-nitrophenolate. We choose the 4-nitrophenolate anion for comparison since it has, other things being equal, an equal propensity to depart as the sultone leaving oxygen. Since there will be considerable entropy decrease associated with the formation of the sulfonate this equilibrium constant indicates considerable enthalpy, presumably from release of ring strain, driving the reaction to the open-chain side. Production of sulfonate ester from phenolate anion and 5-nitrosultone has an entropy decrease of some 5.8 units/mol (Table V). This seems rather small in view of the fact that the reaction involves a fusion of two species and the consequent destruction of three degrees of translational and three of rotational freedom. The ionization of phenol and 4-nitrophenol is largely controlled by an entropy difference (some 10 units/mol); this has been ascribed¹¹ to the phenolate anion structuring the water solvent more than the 4-nitrophenolate because it is a stronger base. The different structuring power of the phenolate compared with 4-nitrophenolate could account for the low entropy loss on forming a sulfonate ester from a sultone. The enthalpy difference of 8.6 kcal/mol almost certainly comes mainly from the release of strain on opening the five-membered sultone ring. They may be compared with a heat of hydrolysis difference of 5–6 kcal/mol between ethylene sulfate and dimethyl sulfate.¹²

Variation of Attacking Phenolate Anion (YO^-). Table IV indicates that the rate constant for attack of substituted phenolate anion on the 5-nitrosultone is favored by electron-donating substituents and the β_{nuc} (or $\beta(k_1)$) for this is $+0.83$ (Table VI). The "raw" Brønsted β value, unless it is for a proton transfer, only gives a qualitative indication of effective charge on the attacking atom in the transition state of the rate-determining step. The effective charge on this oxygen is

Table VII. Effective Charges on Atoms Adjacent to Acyl Functions^a



^a The effective charges are relative to the defined charges on the appropriate species: $\text{Ar(R)S}^{-1.0}$, $\text{Ar(R)O}^{-1.0}$, $\text{XpyrH}^{+1.0}$, $\text{Ar(R)-NH}_2^{-1.0}$, Ar(R)NH_2^0 , Ar(R)OH^0 , Ar(R)SH^0 , and Xpyr^0 . The values are all rounded to the single place of decimals except those from this work. ^bH. Al-Rawi and A. Williams, *J. Am. Chem. Soc.*, 99, 2671 (1977). ^cC. K. Sauers, W. P. Jencks, and S. Groh, *ibid.*, 97, 5546 (1975). ^dJ. Gerstein and W. P. Jencks, *ibid.*, 86, 4655 (1964). ^eThis work; standard deviations are quoted. ^fFrom Hupe and Jencks.¹⁰ ^gW. P. Jencks, B. Schaffhausen, K. Tornheim, and H. White, *J. Am. Chem. Soc.*, 93, 3917 (1971). ^hA. R. Fersht and W. P. Jencks, *ibid.*, 92, 5442 (1970). ⁱS. J. Benkovic and E. J. Sampson, *ibid.*, 93, 4009 (1971). ^jDerived from data in S. A. Khan and A. J. Kirby, *J. Chem. Soc. B*, 1172 (1970). ^kA. R. Fersht and Y. Requena, *J. Am. Chem. Soc.*, 93, 3499 (1971). ^lThese figures are derived from the data for the equilibrium between primary amines, carbon dioxide, and the corresponding carbamate anion in water. The Brønsted relationship is somewhat scattered leading to uncertainty in the effective charge. Data are from the following sources: A. Jensen and R. Christensen, *Acta Chem. Scand.*, 9, 486 (1955); A. Jensen, R. Christensen, and C. Faurholt, *ibid.*, 6, 1086 (1952); A. Jensen, M. B. Jensen, and C. Faurholt, *ibid.*, 6, 1073 (1952); J. Olsen, K. Vejlbj, and C. Faurholt, *ibid.*, 6, 398 (1952); A. Jensen, M. B. Jensen, and C. Faurholt, *ibid.*, 8, 1129 (1954); M. B. Jensen, E. Jørgensen, and C. Faurholt, *ibid.*, 8, 1137 (1954); E. Jørgensen and C. Faurholt, *ibid.*, 8, 1141 (1954); M. B. Jensen, *ibid.*, 11, 499 (1957).

given by the equation

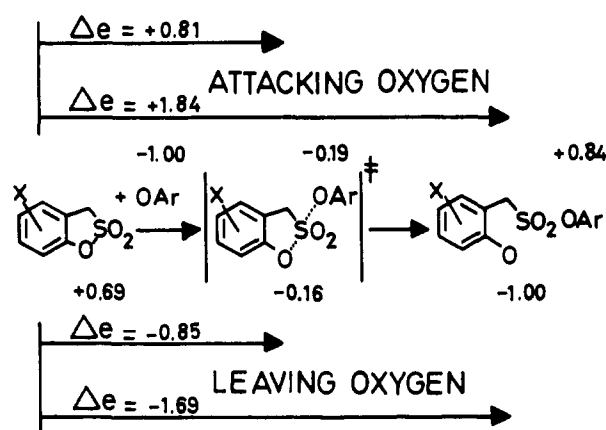
$$\epsilon_{\text{TS}} = \beta(k_1)/(\beta(k_1) - \beta(k_{-1}))|\epsilon_{\text{R}} - \epsilon_{\text{P}}| + \epsilon_{\text{R}} \quad (8)$$

where ϵ_{TS} , ϵ_{R} , and ϵ_{P} are the effective charges in the transition state, reactant, and product, respectively. The values ϵ_{P} and ϵ_{R} may be determined from a calibrating equilibrium involving proton transfer to the acceptor in question where the difference in effective charge on reactant and product atoms is defined as unity. In the present system the calibrating equilibrium is the ionization of phenols where we define the charge on the oxygen as -1 and zero in anion and neutral phenol, respectively. It follows that if the calibrating system is as above eq 8 reduces to $\epsilon_{\text{TS}} = \beta(k_1) + \epsilon_{\text{R}}$. This leads to a distribution of effective charges on the attacking oxygen of the phenolate in its reaction with sultone of -1.0 , -0.19 , and $+0.84$ in reactant, transition, and product states, respectively.

Variation of Leaving Group (X). Table V indicates that the rate constant for phenolate attack is favored by electron-withdrawing substituents (X) on the leaving group to the extent of a β_{lg} (or $\beta(k_1)$) = -0.85 (see Table VI). Treatment according to eq 8 gives rise to an effective charge of $+0.69$, -0.16 , and -1.0 on the leaving oxygen in reactant, transition, and product states, respectively. These values, with those for the attacking oxygen, are illustrated in Scheme I.

The change in effective charge on the leaving and attacking

Scheme I



oxygens is approximately half of the total change and indicates a balance of effective charge distribution during the sulfonyl group transfer and an essentially symmetrical transition state. If we can assume that there is a monotonic change in charge on the attacking and leaving atoms in proceeding from reactants to product then we can say that significant bond changes in attacking and leaving groups have occurred in the transition state and the extent of these is approximately half. Recent work has indicated that the Brønsted β and other selectivities may not be valid measures of relative bond order in the transition state.^{10,13} The effective charge is a perfectly valid quantity¹⁰ and is essentially a measure of the change in charge seen by substituents on an adjacent atom compared with a defined change in charge seen by the same substituents on the same atom in a calibrating equilibrium.

The Brønsted β for k_1 or k_{-1} for substituted sultones contains transmission terms for the effect of substituent through acyl group and through leaving atom. For this reason "raw" Brønsted β values are not valid measures of bond cleavage (or of change in charge) in this reaction; more complicated treatment than is possible here is necessary before we can use such data on their own. The effect of the two modes of transmission of charge is canceled when we divide $\beta(k_1)$ by $\beta(k_1/k_{-1})$ and here we are directly comparing the change going from reactant to transition state with the overall change from reactant to product as in the classical Leffler method. Thus, since we know the charge change on the oxygen in the ring going from reactant to product (or can define it), we then have a measure of the change on that oxygen going from reactant to transition state.

Hammett σ^- Dependencies. Attack of substituted phenolate anions on the 5-nitrosultone and the reverse reaction both exhibit Hammett σ^- dependencies (Figure 5); for this reaction there are three diagnostic substituents which undergo mesomerism with the anionic oxygen. The correlation coefficients for the regular σ relationship are significantly worse than those for the σ^- . It is significant that the reaction shows a σ^- dependence for forward and reverse directions: if full negative charge were destroyed in the attack of phenolates the reverse reaction should exhibit no change in charge on the oxygen which would then give rise to a σ relationship; this would, however, be difficult to observe as zero change in charge implies the reverse step has little bond fission to the transition state and therefore little selectivity to change in substituents. We believe that these results also mean that the transition state lies halfway along the reaction coordinate and we confirm this by the observation that the ρ values for the forward and reverse reactions are approximately of equal value (with, of course, opposite sign).

Variation of the leaving group with a constant attacking

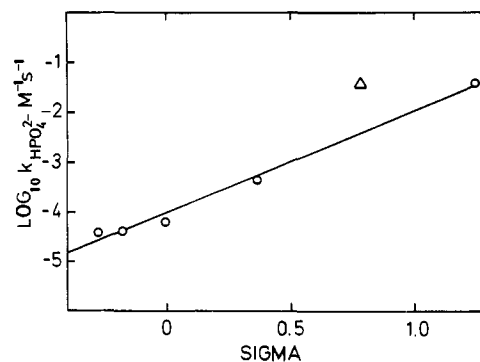


Figure 8. Hammett plot for the reaction of phosphate dianion with substituted sultones. The line is theoretical: $\log k_{\text{HPO}_4^{2-}} = 2.06\sigma^- - 4.00$ ($r = 0.992$); the correlation coefficient using ordinary σ value (see Figure 5) is 0.976; the triangle represents the σ value for the nitro substituent.

phenolate anion is difficult to study with a view to possible σ^- relationships because of synthesis problems in introducing substituents capable of mesomerizing with a para oxyanion and reactivity problems in reaction of the phenolate with sultones with nonmesomerizing substituents. We find a Hammett σ^- relationship for reaction of phosphate dianion with sultones where the reactivity problem is alleviated by use of high nucleophile concentrations. The Hammett σ^- relationships found by us for phosphate (Figure 8) and by Zaborsky and Kaiser⁷ for hydroxide ion indicate qualitatively that there is considerable change in charge on leaving oxygens consistent with a symmetrical transition state.

Stepwise Process. The increase in β_{1g} as the basicity of the oxyanion is reduced for attack on substituted sultones (Table VI) is in agreement with both a concerted and stepwise process which has a symmetrical transition state (Figure 9) and substantial bonding changes in attacking and leaving groups. The variation seems to be consistent with a naive application of the Hammond postulate. The "anti-Hammond" behavior discovered by Rogne¹¹ in the reaction of pyridines with arene-sulfonyl chlorides is more in line with a concerted mechanism since the transition state for this is unlikely to be symmetrical.

The large Brønsted values for leaving group departure and the Hammett σ^- relationships could result from an E1cB mechanism involving rate-limiting breakdown of the conjugate anion; this mechanism has been eliminated both experimentally³ and on theoretical grounds.⁴

A stepwise mechanism, with pentacoordinated sulfurane intermediates, could also explain the results if the breakdown of the intermediate were rate limiting and the transition state not symmetrical. This is unlikely if only one intermediate were involved (I) as expulsion of the OAr group (the reverse reaction) would not be preferred to the cleavage of the five-membered ring on two counts: (a) the aryl oxide nucleophiles studied here are of greater basicity than the aryl oxide constituting the departing anion in ring cleavage; (b) there is considerable strain energy in the ring activating it, compared with ordinary S-O bonds, to cleavage. There is also no evidence in the form of curvature in the Brønsted relationships for a change in rate-limiting step. This would not in any case be expected since the break should under normal circumstances occur at a $\text{p}K_a$ value less than approximately $\text{p}K_a = 6$, the $\text{p}K_a$ of the departing oxyanion in reaction of nucleophiles with 5-nitrosultone, because of the strain released in the forward step. There is no evidence of a breakdown to $\text{p}K_a = 2.8$ in reactions of RO^- nucleophiles with 5-nitrosultone (Figure 6).

The five ligands in an intermediate would be disposed at the five corners of a trigonal bipyramid, as, for example, in SF_4 or SOF_4 , and this introduces the complication of permutational

trigonal bipyramidal structure.^{16f} The stability of these species does not mean that the possible sulfurane intermediates in sulfonyl group transfer are likely to accumulate as the oxyanion provides driving force to expel a leaving group. In the case of ester group transfer where the ortho ester analogue of the intermediate is also a stable entity it is known that the tetrahedral intermediate (T^\ddagger) can have a half-life less than a vibration period.^{16k}

Speculations Concerning the Conservation of Effective Charge. It is interesting to speculate on the effective charge elsewhere in the molecule not directly accessible by experiment; in order to estimate this we must assume that the total effective charge in the system is conserved. This assumption may not be valid because the effective charges are not true charges as defined by electron densities. It is of course permissible to define a conservation law in which case the effective charges obtained by difference are those "seen" by the substituents as if they were on the calibrating atom. The meaning of such an effective charge, however, is obscure as it is not simple to relate it to the known behavior of the calibrating system; the difficulty lies in comparing the atom of the calibrating equilibrium with an atom or system of atoms residing in a different structure in relation to the substituents.

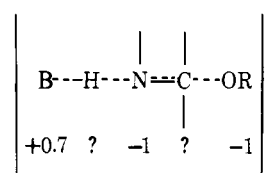
The first consideration in applying the conservation of effective charge is that the experimentally derived effective charges are calibrated against the same or analogous equilibria. There is no difficulty in the present case where all effective charges are against phenol ionization; in general the calibrating equilibria for sulfur, oxygen, or nitrogen are analogous as they involve the ionization of thiols, alcohols or phenols, and ammonium ions. The Taft and Hammett selectivity values for change in substituents are nearly identical for these equilibria; for example, the pK_a s for RCH_2OH and RCH_2SH ¹⁷ have ρ^* close to -1.4 and RNH_3^+ , $R_2NH_2^+$, R_3NH^+ , and RSH ^{17,18} have ρ^* -3.1 to -3.5 . Thiophenols and phenols have ρ^- values of -2.2 and -2.23 , respectively, for their pK_a s.¹⁹

If we assume that the effective charges in the transition state sum to -1 and the additional charge is located on the sulfone group then there is -0.69 , -0.65 , and -0.84 effective charge to dispose in reactant, transition state, and product. This implies that there is very little change in electronic structure of the sulfone group throughout the reaction consistent with a concerted pathway; it is not likely that the negative charge is disposed onto the aromatic ring via the CH_2SO_2 group because of the lack of linkage compared with the much easier passage to the oxygens.

The absence of a significant change in effective charge on the sulfone group as seen by the substituents is coupled with very large and compensating changes on attacking and leaving atoms. Where there is very little change in effective charge on attacking or leaving atoms the difference will naturally lead to negligible change seen by the substituents in the rest of the structure; since large bond changes presumably have not occurred this may not be construed as evidence for a concerted process. To our knowledge, only two cases have been reported, namely, attack of thiolate anion on a thiol ester and on an ester¹⁰ where only a small change ($+0.3$) of effective charge on the attacking thiolate is compensated by approximately the same (but negative) change on the leaving sulfur or oxygen; there is apparently no additional change to a more negative effective charge on the carbonyl oxygen and explanations for this have been proposed.²⁵

It is difficult at present to decide whether a conservation rule should be obeyed for effective charge and recent work is not enthusiastic over its validity.^{10,20} There seems to be no simple test of additivity as it is difficult to estimate effective charges for all atoms participating in the transition state. The most comprehensive examination so far has been on the base-catalyzed dehydration of carbinolamines where the effective charge

changes on attacking base and the nitrogen are $+0.7$ and -1 , respectively. Even in this system the value for the leaving oxygen cannot be estimated and a value (-1) derived from a



β_{1g} taken with the other effective charges indicates considerable imbalance. Even so the balance could be taken by the effective charge changes on the central carbon and the migrating hydrogen atoms.

Conclusions

This work demonstrates that the transition state for sulfonyl group transfer is symmetrically disposed between reactants and product. For a stepwise mechanism this means that the transition state of the rate-determining step is almost indistinguishable from the intermediate; decomposition of the intermediate to reactants or product is thus very likely to be extremely fast. It may be that in the present case the search for a distinction between concerted and stepwise paths is not appropriate because the lifetime of the intermediate is shorter than a vibration thus requiring a concerted mechanism.²¹ The latter condition might well hold; breakdown of a pentacoordinate phosphorus intermediate has been shown to be encounter limited²² and since P-O bonds are stronger than S-O bonds²³ it is likely that a sulfurane intermediate will be even more unstable. A distinction between concerted and stepwise mechanisms is possible if we may conserve effective charge; the absence of a significant change in effective charge on the sulfone through the reaction coordinate coupled with large changes on the attacking and leaving atoms is consistent with a concerted process. We shall have to await the results of further studies on conservation of effective charges before we can confidently use this evidence.

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- (25) It has been argued by a referee that a small change in charge could be consistent with a charge distribution arising from a fast averaging of permutational isomers in a stepwise pathway. If the rate-limiting step were the formation of the intermediate (as might be expected if the permutational isomerization were fast) then the effect "seen" would be that for the addition step and "averaging" would not be "seen". In any case the excess charge would reside on the sulfone oxygens and the sum of this (which would be "seen" as a difference) would always be unity no matter how the charge were disposed.

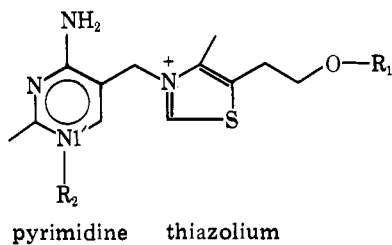
N^{1'}-Methylthiaminium Diiodide. Model Study on the Effect of a Coenzyme Bound Positive Charge on Reaction Mechanisms Requiring Thiamin Pyrophosphate

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Abstract: Thiamin (Ia), 4-aminopyrimidine (IIa), and 4-amino-5-methoxymethyl-2-methylpyrimidine (IIIa) were converted to the corresponding pyrimidinium methiodides Ib, IIb, and IIIb, respectively. The relative rates by Ib over Ia were found to be 2.5:1 for thiazolium ylide formation; ca. 3:1 for pyruvate decarboxylation (CO₂ loss), ca. 15:1 for acetoin formation from pyruvate, and about 4:1 for thiazolium ring opening. Thus Ib in all respects is a superior model catalyst to Ia. A plausible source of all the demonstrated rate enhancements is an electrostatic field effect of the positive charge in Ib destabilizing the positively charged ground states and/or stabilizing the carbanion and oxyanion-like transition states. The amine deprotonation p*K*_as of IIb and IIIb were determined to be near 12; hence the positive charge in Ib can be expected to convert the amino group into a weak acid. The possible relevance of these findings to thiamin pyrophosphate requiring enzymatic reactions is discussed.

The thiazolium ring of the coenzyme thiamin pyrophosphate (TPP) forms a covalent intermediate with the substrates of the enzymatic reactions requiring TPP.¹ A chemical role



R ₁	R ₂	Name
H		Thiamin (Ia)
H	CH ₃	<i>N</i> ^{1'} -Methylthiamin (Ib)
PO ₃ PO ₃ ³⁻		Thiamin pyrophosphate (TPP)

of the pyrimidine and dimethylenepyrophosphate portions of the coenzyme is still not clear, however. Nevertheless, both moieties have been substantiated to be essential for coenzyme activity. Via a number of elegant synthetic feats Schellenberger's group was able to demonstrate that while the amino group is not needed for the coenzyme to exhibit inhibitory properties, it is essential for catalysis.² The rest of the pyrim-

idine undoubtedly is important in the binding process. In model systems the thiazolium ring was found to form a weak molecular complex with tryptophan.³ More recently the pyrimidine moiety was also shown to interact with tryptophan according to fluorescence experiments.⁴ These results suggest potential binding mechanisms on the enzyme. Schellenberger and co-workers suggested that the amino group functions either as a proton acceptor (normal role for strongly basic amino groups) and/or in the transferral of acetaldehyde from coenzyme to solution.² The major difficulty with this proposal is that all related aminopurines, such as adenine,⁵ and amino pyrimidines, such as that in TPP⁶ and cytosine,⁵ possess very weakly basic and weakly nucleophilic amino groups. In fact, all these compounds beyond any doubt protonate and bind metal ions on the ring nitrogens preferentially rather than on the exocyclic amino group. Specifically, according to all x-ray crystallographic,⁷ nuclear magnetic resonance,⁸ and theoretical results⁹ *N*^{1'} is the site of proton binding in thiamin and TPP. It is also quite clear now that both soft, such as Ni(II), and hard, such as Mn(II), metal ions bind to the pyrimidine *N*^{1'} position in thiamin, albeit the Ni(II) binds stronger than the Mn(II)-¹⁰⁻¹³

Based on these facts, it occurred to us that the enzyme could activate the amino group catalytically, making it in fact a proton donor, as well as enhance the rates of several of the el-