Sulfate Group Transfer between Nitrogen and Oxygen: Evidence Consistent with an Open "Exploded" Transition State

Andrew Hopkins, Richard A. Day, and Andrew Williams*

Contribution from the University Chemical Laboratories, Canterbury, England.
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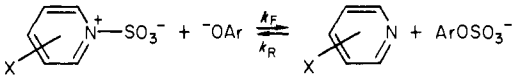
Abstract: Complete structure–reactivity studies are reported for both kinetics and equilibria in the transfer of the sulfate group ($-SO_3^-$) between pyridines (py) and phenols in aqueous solution at 25 °C. The equilibrium constant for the reaction is given



by the expression $\log K_{EQ} = (1.74 \pm 0.1)\, pK^{ArOH} - (1.24 \pm 0.02)\, pK^{Xpy} + 0.08$, which may be used to calculate equilibrium constants for the hydrolysis of aryl sulfates that are in excellent agreement with those estimated by Guthrie. The Leffler–Grunwald parameters ($\alpha = \beta_F/\beta_{EQ} = d \ln k_F/d \ln K_{EQ}$) for N–S fission (0.8 ± 0.05) and S–O formation (0.13 ± 0.002) are derived from structure variation in pyridine and phenol, respectively; we deduce from this that the controlling transition state has only weak N–S and O–S bonds and is symmetrical. Data drawn from the literature together with those from the present study are consistent with a concerted "in-line" sulfate group transfer. Significant amounts of isoquinoline do not retard the solvolysis of isoquinolinium-*N*-sulfonate in acetonitrile solutions (80%, v/v), consistent with the absence of free sulfur trioxide as an intermediate.

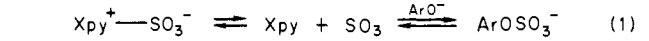
The transfer of the sulfate group ($-SO_3^-$) between donor and acceptor is an important chemical and biochemical process,[1,2] but there is little detailed study at present available with regard to the fundamental reaction and little information concerning equilibrium constants.

The main pathways available for the transfer of a sulfate group from donor to acceptor are dissociative, associative, and concerted displacements (Scheme I). A current problem related to eq 1 is whether the sulfur trioxide has a lifetime too short for it to diffuse into the bulk solution; the mechanism when this is so is called a preassociation stepwise process. Mechanisms 2 and 3 pose the problem of whether attack of the nucleophile is an "in-line" or "adjacent"[3] process. The strengths of the N–S and O–S bonds in the controlling transition state are also valuable pieces of evidence if eq 3 holds for a sulfate group transfer process. The evidence in the literature does not allow a clear cut distinction to be made between the overall paths analogous to eq 1–3 for sulfate group transfer. Benkovic and Benkovic[4a] show that transfer of sulfate from 4-nitrophenyl sulfate to amine nucleophiles requires the presence of the nucleophile in the controlling transition state. The low β_N[4] for amine attack and the large β_L for the hydrolysis of aryl sulfates[5] seem consistent with either a preassociation stepwise[6] or concerted mechanism. Trapping experiments point to considerable sulfur trioxide character in the transition state but do not entirely support a simple dissociative pathway for aryl sulfate hydrolysis.[6]

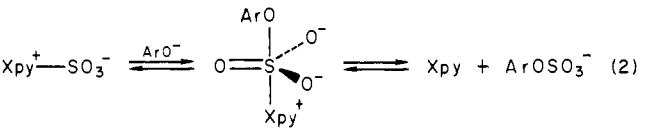
Structure–reactivity probes in sulfate group transfer reactions provide a powerful tool for investigating the electronic charge on the entering and leaving atoms in the transition state. Only β_N and β_L, respectively, are available for attack of nucleophiles on 4-nitrophenyl sulfate and the hydrolysis of aryl sulfates. Lack

Scheme I

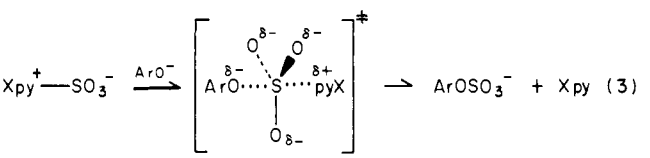
dissociative



associative

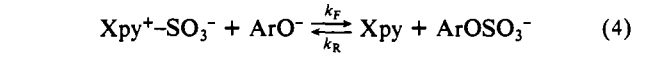


concerted displacement



of β_{EQ} values hinders the interpretation of the Brønsted parameters for rates; thus the low β_N could be allied with a low β_{EQ}, indicating essentially complete bond formation (between nitrogen and sulfur) from reactant to transition state.

We are fortunate to have discovered that the sulfation of phenols by substituted pyridinium-*N*-sulfonates (eq 4) may be followed



in both directions with little difficulty. We may therefore measure k_F, k_R, and K_{EQ} (k_F/k_R) as a function of leaving and entering groups. Consequent on the validity of the Leffler assumption[8] we shall be able, with the use of these data, to discuss the detailed electronic requirements of the transition state relative to reactant and product states. At the very least, we shall be able to determine the charge distribution in the transition state of the transfer reaction relative to the charge on phenolate oxygen and pyridinium nitrogen as standards.

Experimental Section

Materials. Pyridinium-*N*-sulfonates were prepared by two methods. The dry pyridine (0.43 mol) was mixed with chloroform (50 mL) and

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(3) We use the nomenclature "in-line" and "adjacent" as defined by Usher: Usher, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *62*, 661.
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(8) (a) Leffler, J. E. *Science (Washington, D.C.)* **1953**, *117*, 340. (b) Leffler, J. E.; Grunwald, E. "Rates and Equilibria of Organic Reactions"; Wiley: New York, 1963; p 157.

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Table I. Analytical Data for Pyridinium-*N*-sulfonates and Potassium Phenyl Sulfates[a]

pyridinium-*N*-sulfonate	found N/C	found S/%	formula	calcd N/C	calcd S/%
parent	0.229	19.8	$C_5H_5NSO_3$	0.230	20.1
3-methyl	0.190	18.6	$C_6H_7NSO_3$	0.190	18.5
4-methyl	0.188	18.3	$C_6H_7NSO_3$	0.190	18.5
3,4-dimethyl	0.166	16.9	$C_7H_9NSO_3$	0.166	17.1
3,5-dimethyl	0.165	17.4	$C_7H_9NSO_3$	0.166	17.1
isoquinoline	0.128	15.1	$C_9H_7NSO_3$	0.130	15.3

potassium phenyl sulfates	found/% C	H	N	S	formula	calcd/% C	H	N	S
parent	31.0	2.8		13.6	$C_6H_5KSO_4 \cdot H_2O$	31.3	3.0		13.9
3,4-dinitro	22.7	1.6	9.1	9.3	$C_6H_3KN_2SO_8 \cdot H_2O$	22.4	1.3	8.7	10.0
2,6-dinitro	22.7	1.4	8.8	10.2	$C_6H_3KN_2SO_8 \cdot H_2O$	22.4	1.3	8.7	10.0
2,3-dinitro	22.5	1.4	9.0	9.8	$C_6H_3KN_2SO_8 \cdot H_2O$	22.4	1.3	8.7	10.0
2,4-dinitro	22.7	1.2	9.2	10.0	$C_6H_3KN_2SO_8 \cdot H_2O$	22.4	1.3	8.7	10.0
4-chloro-2-nitro	23.8	1.5	4.5	10.7	$C_6H_3ClKNSO_6 \cdot H_2O$	23.2	1.3	4.5	10.5
2-chloro-4-nitro	23.6	1.3	4.8	10.0	$C_6H_3ClKNSO_6 \cdot H_2O$	23.2	1.3	4.5	10.5

[a] Microanalysis by A. J. Fassam using a Carlo Erba instrument; sulfur analysis was by oxidation of the compound followed by titration of the released sulfate with barium chloride.

cooled to 0 °C; chlorosulfonic acid (20 mL, 0.3 mol) was then added slowly, with the temperature maintained below 10 °C. After the addition was complete, the resultant crystals were quickly filtered, washed with cold chloroform to remove residual pyridinium hydrochloride, and dried in vacuo. This method[9] was only substantially successful for the parent pyridine, and a second method was used for the other members of the series:[10] The dry pyridine (0.06 mol) was mixed with dry 1,2-dichloroethane (50 mL) and cooled to 0 °C. Sulfur trioxide was distilled directly into the cooled mixture from 20% oleum in a dry, air-tight, glass apparatus. Addition was ceased well before an equivalent amount of sulfur trioxide had been absorbed (measured by weighing the apparatus). The cold mixture was filtered, and the crystals were washed with cold 1,2-dichloroethane and dried in vacuo.

Owing to the avidity of water for pyridinium-*N*-sulfonates, literature melting points are completely unreliable. Elemental analysis is difficult because the materials are very hygroscopic and special apparatus would be needed for accurate work. Values of the N/C ratio are given in Table I which compare well with the theoretical as these will not be affected by a weight change. Sulfur analysis gave tolerably good results in our hands (Table I).

Potassium phenyl sulfates were prepared by the method of Burkhardt[11] using the modification of Fendler and Fendler[5] for the more reactive compounds. Chlorosulfonic acid (2.33 mL, 35 mmol) was slowly added with stirring to a mixture of *N,N*-dimethylaniline (11.73 mL, 125 mmol) in carbon disulfide (12.5 mL) at −5 to −10 °C. After addition was complete the mixture was warmed to 35 °C and the required phenol added at once; the mixture was stirred for 1 h, cooled, and poured into stirred aqueous KOH (4 M, 50 mL) kept at 0 °C. The precipitate was filtered, washed with cold ethanol, and dried in vacuo. Recrystallization resulted in hydrolysis, but the washed, dried original products gave good analyses (Table I) allowing for one water of crystallization.

The structures of the pyridinium-*N*-sulfonates and potassium phenyl sulfates were consistent with their infrared (Perkin-Elmer 237) and NMR (Jeol 100 MHz) spectra (we are grateful to Dr. D. O. Smith, who kindly ran the NMR spectra).

Components for buffers were purchased as analytical grade where possible and in other cases redistilled or recrystallized from bench grade material. Amines were usually recrystallized as their hydrochloride salts and phenols sublimed or recrystallized from petroleum ether (bp 60–80 °C). Pyridines were redistilled onto KOH pellets immediately prior to use. Acetonitrile was purified by the method of Lewis and Smyth,[12] and water used throughout the experiments was doubly distilled from glass. Deuterium oxide was obtained from Prochem at a 99.7% enrichment.

Methods. The spectrophotometric method for following reactions involved adding 20 to 50 μL of a solution of the substrate in acetonitrile (pyridinium-*N*-sulfonates) or water (potassium phenyl sulfates) to 2.5 mL of buffer in a silica cell in the thermostatted cell compartment of a Pye-Unicam SP 800 instrument. The stock was added on the tip of a glass rod, and two or three vertical strokes in the cell initiated the reaction and allowed an accurate zero time to be recorded. The progress of the reaction was followed by repetitive scanning of the spectrum (using an SP 825 program controller) in order to determine an optimum wavelength for measuring the rate constants. In the case of the aryl sulfates the absorbance change was largely that of the phenol product. Kinetics were measured at 25 or 50 °C ± 0.1 °C as required, and the pH was measured before and after the reaction on a Radiometer PHM 62 instrument calibrated to ±0.02 pH unit with E.I.L. standard buffers. Reactions were normally followed over 7 half-lives and pseudo-first-order rate constants estimated from plots of $A_t - A_\infty$ vs. time using semilogarithmic (two cycle) graph paper. In the case of very slow reactions the absorbances at infinite time were obtained by complete hydrolysis under strong conditions followed by reconstitution of the buffer to the required pH, and rate measurements were carried out until more than a half-life had been completed.

Reaction rates for pyridinium-*N*-sulfonates with phenol could not be measured spectrophotometrically because the absorbances of the phenol and pyridines coincided. A method based on HPLC assay of product phenyl sulfate was employed. Equation 5 illustrates the competition of

$$\mathrm{Xpy^+{-}SO_3^-} \xrightarrow{[\mathrm{PhO^-}]k_{\mathrm{PhO^-}}} \mathrm{Xpy + PhOSO_3^-}$$
$$\xrightarrow{k_w} \mathrm{Xpy + SO_4^{2-}} \qquad (5)$$

phenolate ion and water for a pyridinium-*N*-sulfonate to give phenyl sulfate and sulfate dianion. Phenyl sulfate does not hydrolyze to sulfate under the conditions of the experiment (pH 9 to 10), so that assay of the product phenyl sulfate and a knowledge of the original pyridinium-*N*-sulfonate concentration will lead to $k_{\mathrm{PhO^-}}$ as in eq 6. Since k_w is known

$$k_{\mathrm{PhO^-}} = [\mathrm{PhOSO_3^-}]_\infty k_w / [\mathrm{PhO^-}]([\mathrm{py^+{-}SO_3^-}]_0 - [\mathrm{PhOSO_3^-}]_\infty) \quad (6)$$

$k_{\mathrm{PhO^-}}$ may be determined. In a typical experiment phenol (5 mL, 0.2 M pH 9.65) was placed in a screw-topped test tube and kept at 25 °C. Pyridinium-*N*-sulfonate (~25 mg) was added with shaking to dissolve it as rapidly as possible and the solution was kept until the reaction was complete (using a time calculated from the known k_w for the sulfonate). The solution was acidified to pH 2 to 3, extracted with chloroform (5 mL) to remove most of the phenol, and subjected to HPLC analysis on a reversed phase column (Lichrosorb RP8 10 μm, 25 cm × 4.5 mm), kindly packed for us by J. A. Holland of Shell Research Ltd., Sittingbourne. The HPLC apparatus was a Pye-Unicam instrument comprised of an LC-XPD pump, LC-UV detector, LC-XP Dialamix, and PM-8251 single pen recorder. The eluent was a 35% methanol/aqueous solution containing as the aqueous component *tert*-butylammonium phosphate (TBAP); the aqueous solution was prepared by diluting 130 mL of TBAP (from BDH Ltd.) to 2 L with water and adjusted to pH 7.00 with phosphoric acid. The aqueous stock was diluted 1 in 10, filtered through a Millipore ultra filter, and used directly. The chromatogram was calibrated with standard solutions of potassium phenyl sulfate, and the column conditions for the assay were 22 °C, flow rate 2 mL/min, and pressure 88 bar.

Identity of products is available from the HPLC work on phenyl sulfate formation as well as from the final spectra in the kinetics. Identity of the sulfate dianion product and kinetics of the pyridinium-*N*-sulfonate may be determined with a sulfate ion selective electrode. The electrode

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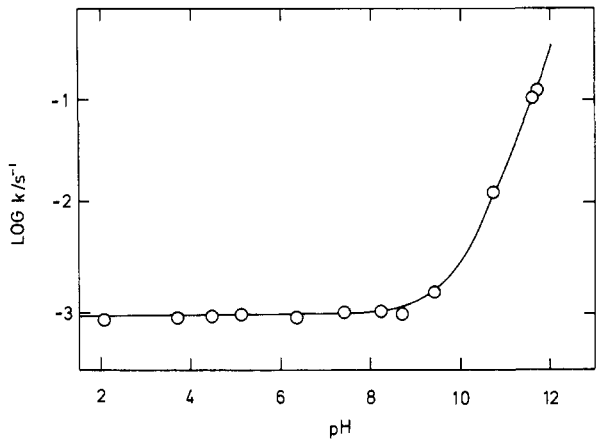


Figure 1. Dependence on pH of the hydrolysis of pyridinium-*N*-sulfonate (points extrapolated to zero buffer concentration, 25 °C, 1 M ionic strength). Line is theoretical from data in Table III.

was constructed essentially by the method of Takaishrili[13c] and comprised an outer casing of glass containing a standard silver electrode dipped in electrolyte (0.02 M KCl, 0.2 M Na_2SO_4) with a semipermeable PVC membrane covering the orifice which dips into the assay solution. The membrane was prepared by mixing analytical grade barium sulfate (1.2 g) with powdered PVC (0.8 g) and di-*n*-butyl phthalate (0.24 g) in a mortar with a few drops of cyclohexanone. The mixture was formed into a 4-cm-diameter petri dish, allowed to swell (24 h) and then dried at 70 °C for 72 h. A disk of the material (1 cm diameter and 1 to 2 mm thick) was cemented to the end of the sleeve of the electrode and activated by storage in Na_2SO_4 solution (0.1 M) for 48 h. The response to sulfate ion was Nernstian over the required range (10^{-4}–10^{-1} M) when sulfate was used with a calomel reference cell at pH 8.1.

Kinetics were measured by observing the change in emf with time at 25 °C after initiation of the reaction by adding pyridinium-*N*-sulfonate to buffer (tris(hydroxymethyl)aminomethane 0.1 M, 0.5 FB (fraction of free base), pH 8.1, 5 mL). The mV readings were converted to sulfate ion concentrations by using a calibration curve, and the pseudo-first-order rate constant was measured in the normal way; phenolate buffers were found to poison the electrode. Brønsted correlations of the various kinetic parameters were carried out with a Texas Instruments TI-51III calculator.

Results

Product Analysis. Repetitive scanning of the UV–vis spectrum during reactions of pyridinium-*N*-sulfonates and aryl sulfates gave spectra with tight isosbestic points consistent with simple 1:1 stoichiometries. Final spectra coincided with those of pyridines or phenols expected as products—the latter excluding any possibility of aromatic nucleophilic attack in the aryl sulfates. Sulfate analysis via the sulfate selective electrode indicated complete liberation of the sulfur as sulfate ion for the reaction of pyridinium-*N*-sulfonate in aqueous buffer at pH 8.1. Chromatographic analysis of the product of reaction of phenolate ion with substituted pyridinium-*N*-sulfonates indicated phenyl sulfate. The fate of the sulfur in reactions of pyridinium-*N*-sulfonates with amine buffers is most likely aminosulfonates, as the former reagents are well known sulfonating agents for amines; strongly basic tertiary amines give persistent ammoniosulfonates.[13b] The low deuterium oxide solvent isotope effect on the reaction of 4-picoline with 2,4-dinitrophenyl sulfate and on the reaction of pyridinium-*N*-sulfonate with acetate ion indicates a nucleophilic reaction rather than general base catalysis. The hindered amines give low rate constants compared with unhindered analogues, confirming that a nucleophilic reaction rather than general base catalyzed hydrolysis is occurring.

Kinetics. Reactions obeyed good pseudo-first-order kinetics over at least 80% of the progress; for slow reactions initial rates were proportional to the initial substrate concentration. Decomposition of pyridinium-*N*-sulfonate was carried out by using a sulfate selective electrode as well as spectrophotometrically. The observed rate constants (Tris buffer at 0.1 M, FB = 0.5, pH 8.1, 25 °C) from both methods, 8.3×10^{-4} s^{-1} (ion selective) and 9.5×10^{-4} s^{-1} (spectrophotometric), agree within the experimental limits. The errors in the ion selective electrode method made spectrophotometry the method of choice for kinetic studies.

(13) (a) Takaishrili, O. G.; Motsonelidye, E. P.; Karachentseva, Y. M.; Davitaya, P. I. *Zh. Anal. Khim.* **1975**, *30*, 1629. (b) Kubas, G. J.; Larsen, A. C.; Ryan, R. R. *J. Org. Chem.* **1979**, *44*, 3867. (c) Rys, P. *Angew. Chem.* **1977**, *16*, 807. (d) We are indebted to Professor J. P. Guthrie for this suggestion.

Table II. Reaction of Nucleophiles with Pyridinium-*N*-sulfonate[a]

nucleophile	pK^{NuH}	$k_F/(M^{-1}\ s^{-1})$
Primary Amines		
Tris	8.10	1.44×10^{-2}
ethyl glycinate	7.84	0.629
glycine	9.59	1.00
ethanolamine	9.49	0.794
n-propylamine	10.52	1.32
methyl β-alaninate	9.24	0.562
aminoacetonitrile	5.57	0.123
diaminoethane (monobasic)	7.57	0.355
diaminoethane (dibasic)	10.25	1.76
semicarbazide	3.65	1.69×10^{-2}
aniline	4.54	2.4×10^{-2}
hydrazine	8.57	2.5
Tertiary Amines		
triethanolamine (TEA)	7.77	1.12×10^{-2}
N-ethylmorpholine	7.70	1.23×10^{-2}
N,*N*-diethanolamine	9.95	0.085
triethylamine	10.65	0.123
trimethylamine	9.76	38.9
1,4-diazabicyclo[2.2.2]octane (dabco) (monobasic)	3.87	1.36
Dabco (dibasic)	9.00	15.1
N-methylpiperidine	10.21	0.501
Oxygen Nucleophiles		
acetate	4.64	1.17×10^{-3} (1.25×10^{-3})[b]
phosphate (dibasic)	6.40	1.25×10^{-3}
carbonate (dibasic)	10.32	6.31×10^{-3}
cacodylate	6.14	1.23×10^{-2}
water	−1.70	0.951×10^{-3}[c]
hydroxide ion	16.5[21]	0.195

[a] Ionic strength maintained at 1 M with KCl, 25 °C, kinetic wavelength 268 nm. [b] Value for deuterium oxide solvent. [c] Water concentration taken as 55.5 M.

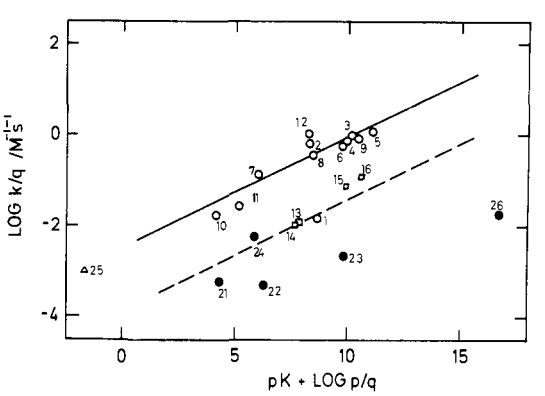


Figure 2. Brønsted type dependence of the reaction of nucleophiles with pyridinium-*N*-sulfonate (1 M ionic strength, 25 °C). Data are from Table II; the numbering scheme refers to Table II and the open circles refer to primary amines, closed circles to oxy anions and open squares to tertiary amines. The solid regression line (for primary amines) is from parameters in Table VII and the dashed line is for values for phenolate ion attack calculated from eq 8 at 0.1 M ionic strength.

Reactions of Substituted Pyridinium-*N*-sulfonates with Nucleophiles. Decomposition of substituted pyridinium-*N*-sulfonates in buffers obeys a rate law (eq 7) where k_w is a water and k_{OH}

$$k_{obsd} = k_w + k_N[N] + k_{OH}[OH^-] \quad (7)$$

is an hydroxide term. A plot of k_{obsd} vs. pH at buffer concentrations where buffer effects are negligable is illustrated in Figure 1 for pyridinium-*N*-sulfonate. Increasing buffer concentrations

Table III. Reaction of Nucleophiles with Substituted Pyridinium-*N*-sulfonates (k_F)[a]

pyridine	pK^{Xpy}	k_{Phe}[b,c,d,g]	k_{Tris}[b,h]	k_{TEA}[b,h]	k_{OH}[b,g]	$k_{H_2O} \times 10^5/s^{-1}$
parent	5.17	3.83	14.5	11.1	19.5[f]	95.0
3-methyl	5.68	1.11	5.66	4.88	8.21	11.3
4-methyl	6.02	0.65	2.65	2.13	3.33	2.65
3,5-dimethyl	6.13	0.40	2.39	2.29	2.34	2.40
3,4-dimethyl	6.52	0.176	0.725	0.694	1.12	1.28
isoquinoline[c]	5.42	2.44[e]	8.89		12.5	38.0

[a] Ionic strength kept at 1 M with KCl except where stated, 25 °C, kinetics followed at 268 nm (except for isoquinoline at 319 nm). [b] Units M^{-1} s^{-1}. [c] Ionic strength 0.1 M. [d] Measured by product analysis of the reaction of the pyridinium-*N*-sulfonate in phenol buffer with the water rate constant as the standard reference. [e] Direct spectrophotometric measurement. [f] Ryss and Kotlyar (*Kinet. Katal.* 1970, *11*, 244) found 1.37×10^{-3} s^{-1} at an indeterminate ionic strength. [g] $\times 10^2$. [h] $\times 10^3$.

Table IV. Reaction of Substituted Phenolate Ions with Isoquinolinium-*N*-sulfonate[a]

phenol buffer	p*K*	$k_F \times 10^2/(M^{-1}\ s^{-1})$
parent	9.95	2.44
3.5-dimethyl	10.19	2.85
2,5-dimethyl	10.41	3.30
2,4-dimethyl	10.60	3.46
3-chloro	9.02	1.50
2,3-dimethyl	10.54	3.45
4-chloro	9.38	1.86
2,6-dimethyl	10.63	3.46
3-methyl	10.05	2.62

[a] Ionic strength = 0.1 M, 25 °C, kinetics measured at 319 nm.

at a given pH causes a linear increase in rate constant, and a plot of the slope $\Delta k_{obsd}/\Delta$[total buffer] against FB is linear with zero intercept at FB = 0 for Tris for the decomposition of pyridinium- and isoquinolinium-*N*-sulfonates. Phenolate ion was found to be the reactive species for the reaction of isoquinolinium-*N*-sulfonate in phenol buffers. The values of k_N for other buffer species (eq 7) are recorded in Table II, and the Brønsted type correlation between log k_N and pK^{NH} is illustrated in Figure 2.

Values of k_N for Tris, water, triethanolamine (TEA), and phenolate ion for a series of substituted pyridinium-*N*-sulfonates are given in Table III. Rate constants for all except the phenolate buffers were obtained by the usual kinetic approach. Phenolate terms were obtained by the product analysis method, relying on the accurate knowledge of k_w as a standard to obtain k_{PhO^-}. Analysis using a range of phenolate buffer and pyridinium-*N*-sulfonate concentrations gave consistent results assuming eq 7 holds; a further confirmation that the results are bona fide is that the values obey an excellent Brønsted type relationship, including the point for isoquinolinium-*N*-sulfonate which was determined by the kinetic method directly. The rate constants for the reaction of substituted phenolate ions with isoquinolinium-*N*-sulfonate are recorded in Table IV. The effect of ionic strength on reactions of pyridinium-*N*-sulfonates with nucleophiles is negligible.

Reactions of Substituted Pyridines with Aryl Sulfates. The decomposition of aryl sulfates in substituted pyridine buffers was followed spectrophotometrically and obeyed good pseudo-first-order kinetics. The rate law is second order in the pyridine base and substrate, and the data are collected in Tables V and VI.

Brønsted Type Correlations. The correlations of the rate constants with the p*K* of the attacking nucleophile or of the leaving group are excellent, and the parameters are recorded in Table VII. The parameters k_R and k_F for eq 4, the reaction of phenolate ions with pyridinium-*N*-sulfonates, can each be correlated by a two-parameter equation, and the least-squares fit to the data is given by eq 8 and 9; the equilibrium constant is correlated by eq 10.

$$\log k_F = (0.23 \pm 0.01)\ pK^{ArOH} - (0.99 \pm 0.04)\ pK^{Xpy} + 1.45 \quad (8)$$

$$\log k_R = (0.25 \pm 0.02)\ pK^{Xpy} - (1.51 \pm 0.11)\ pK^{ArOH} + 1.37 \quad (9)$$

$$\log K_{EQ} = \log (k_F/k_R) = (1.74 \pm 0.1)\ pK^{ArOH} - (1.24 \pm 0.02)\ pK^{Xpy} + 0.08 \quad (10)$$

Table V. Reaction of 4-Picoline with Aryl Sulfates[a]

phenyl sulfate	λ/nm[c]	$k_R \times 10^5/(M^{-1}\ s^{-1})$	pK^{ArOH}
2,6-dinitro	400	178	3.71
2,4-nitro	400	59.2 (60.0)[b]	4.11
3,4-dinitro	400	0.666	5.41
2,3-dinitro	420	0.873	4.97
4-chloro-2-nitro	420	0.0137	6.45
2-chloro-4-nitro	406	0.206	5.48

[a] Ionic strength = 0.1 M, 25 °C. [b] D_2O. [c] Wavelength for kinetics.

Table VI. Reaction of Substituted Pyridine Nucleophiles with 2,4-Dinitrophenyl[a] and 3,4-Dinitrophenyl[b] Sulfates

pyridine	pK^{Xpy}	$k_R \times 10^4/(M^{-1}\ s^{-1})$ 2,4-DNP	3,4-DNP
parent	5.17	3.67	0.446
3,5-dimethyl	6.13	7.31	0.782
3,4-dimethyl	6.52	8.48	0.882
3-methyl	5.68	5.07	0.567
4-methyl	6.02	5.92	0.741

[a] 25 °C, ionic strength maintained at 0.1 M with KCl. [b] 50 °C, ionic strength at 0.1 M. [c] Kinetics measured at 400 nm. [d] These values where comparable agree with those reported by Fendler[4b] for 39 °C; we note a minor error in the magnitude of $k_{2(hydr)}$ in Table II of the latter paper.

Table VII. Summary of Brønsted Type Equations for Sulfate Group Transfer[a,b]

reaction	correlation[e]
$ISQ^+\text{-}SO_3^-$ + ArO^-	$\log k_F = 0.23 \pm 0.01\ pK^{ArOH} - 3.89 \pm 0.07$ (0.997)
$ArOSO_3^-$ + 4-picoline	$\log k_R = -1.51 \pm 0.11\ pK^{ArOH} + 2.64 \pm 0.57$ (0.990)
Xpy + 2,4-$DNPOSO_3^-$	$\log k_R = 0.25 \pm 0.02\ pK^{Xpy}$[c] $- 4.79 \pm 0.12$ (0.944)[d]
$Xpy^+\text{-}SO_3^-$ + PhO^-	$\log k_F = -0.99 \pm 0.04\ pK^{Xpy} + 3.63 \pm 0.25$ (0.990)
$Py^+\text{-}SO_3^-$ + amines[f]	$\log k_F/q = 0.19 \pm 0.03\ (pK^{amine} + \log p/q) - 2.02 \pm 0.2$ (0.951)
$Xpy^+\text{-}SO_3^-$ + Tris	$\log k_F = -0.85 \pm 0.05\ pK^{Xpy} + 2.55 \pm 0.32$ (0.998)
$Xpy^+\text{-}SO_3^-$ + TEA	$\log k_F = -0.81 \pm 0.08\ pK^{Xpy} + 2.63 \pm 0.48$ (0.998)
$Xpy^+\text{-}SO_3^-$ + OH^-	$\log k_F = -0.95 \pm 0.04\ pK^{Xpy} + 4.23 \pm 0.24$ (0.995)
$Xpy^+\text{-}SO_3^-$ + water	$\log k_F = -1.43 \pm 0.21\ pK^{Xpy} + 4.29 \pm 1.21$ (0.957)

[a] Except where stated ionic strength is maintained at 0.1 M with KCl and temperature at 25 °C. [b] ISQ = isoquinoline, $Xpy^+\text{-}SO_3^-$ = substituted pyridinium-*N*-sulfonate, 2,4-$DNPOSO_3^-$ = 2,4-dinitrophenyl sulfate. [c] Reaction of pyridines with 3,4-dinitrophenyl sulfate at 50 °C had $\log k_R = 0.25 \pm 0.02\ pK^{Xpy} - 5.65 \pm 0.07$ (0.996). [d] The slope of this line is close to that observed by Fendler at 39 °C (0.22).[4b] [e] Value in parentheses is the correlation coefficient. [f] Other nucleophiles from Table II are not included in the correlation; the correlation is for primary unhindered amines.

Table VIII. Solvolysis of Isoquinolinium-*N*-sulfonate in 80% Acetonitrile/Water (v/v) in the Presence of Increasing Concentrations of Isoquinoline[a,d]

[isoquinoline]/M	$k_{obsd} \times 10^3/s^{-1}$ [c]	$k_{calcd} \times 10^3/s^{-1}$ [b]
	pH 8.00	
0	9.9	9.9
0.34	10.2	<8.9
0.51	9.96	<8.5
0.68	9.9	<8.1
1.02	9.96	<7.5
	pH 9.27	
0	10.0	<10.0
1.02	10.0	<7.6

[a] 25 °C, 0.05 M ionic strength, Tris buffer at pH 0.01 M. [b] Calculated from eq 12; k_0 is the rate constant at zero added isoquinoline, and the value quoted is an upper limit. [c] Kinetics measured at 350 nm; results of several runs; errors less than $\pm 0.5 \times 10^{-3}$ s^{-1}. [d] The varying volumes of isoquinoline were compensated by dioxane which was shown to have no effect on the rate constant for hydrolysis of the sulfonate up to 12% (v/v).

Mass Action Experiment. Isoquinolinium-*N*-sulfonate decomposition was measured in the presence of isoquinoline at concentrations up to 1 M. The kinetics are readily measured with high precision because the absorption change for the substrate is at a wavelength outside the major absorption of the isoquinoline. In order to obtain relatively large isoquinoline concentrations we had to employ a solution with high acetonitrile content; this also had the advantage of reducing the water concentration. We estimated the relative reactivity of water and isoquinoline toward sulfur trioxide (k_w/k_{isq}; see eq 12) by measuring the sulfate and isoquinolinium-*N*-sulfonate formed when sulfur trioxide (generated by warming oleum in a stream of nitrogen) was passed through a solution (at −15 °C, with an ethylene glycol/solid CO_2 mixture) which had a composition of acetonitrile/water/isoquinoline = 15.3/4.44/1.0 M. The isoquinolinium-*N*-sulfonate was assayed by observing the change in absorbance at 350 nm ($\Delta E_{350nm} = 490$) at pH 8.02. Sulfate analysis of the completely hydrolyzed product (we are indebted to A. J. Fassam for carrying out the barium sulfate titrations) gave the inorganic sulfate produced in the reaction by difference from the isoquinolinium-*N*-sulfonate. The ratio of the water to isoquinoline rate constants is derived from eq 11. The value k_w/k_{isq} has considerable error as the assay for

$$k_w/k_{isq} = ([\text{total inorganic sulfate}] - [isq^+\text{–}SO_3^-])/[isq^+\text{–}SO_3^-] \quad (11)$$

the isoquinolinium-*N*-sulfonate cannot be made instantaneously. There is also the possibility that the ratio will depend on temperature, and the value obtained (average of two results, 0.71) is most likely an *upper* limit (see Discussion).

The decomposition of isoquinolinium-*N*-sulfonate shows *no variation* in rate constant in concentrations of isoquinoline up to 1 M when a solvent composition identical with that from the partitioning experiments with sulfur trioxide is used. The values of the rate constants are larger than in water alone, and the decrease expected from the ratio k_w/k_{isq} in the acetonitrile/water solution (calculated from eq 12) is well outside the expected error

$$k_{calcd} = k_0[H_2O]k_w/(k_{isq}[ISQ] + [H_2O]k_w) \quad (12)$$

in the measurements (see Table VIII). The varying amounts of isoquinoline were compensated by adding sufficient dioxane to keep the total additive volume constant.

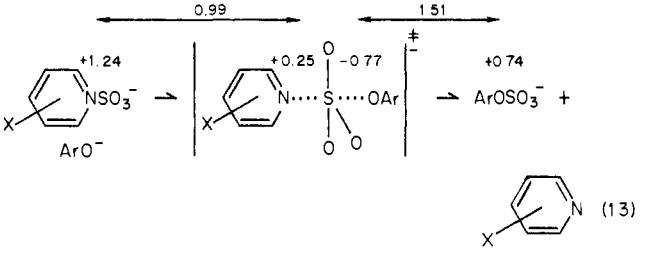
The possibility that the zero change in rate constant is due to a cancellation of effects was checked by using different additives in place of the isoquinoline. *tert*-Butyl alcohol up to 1.27 M (12%) gave no change in rate constant outside the experimental error ($9.96–9.84 \times 10^{-3}$ s^{-1} at pH 8.00); acetone and ethyl acetate gave small decreases ($9.96–9.36 \times 10^{-3}$ s^{-1} and $9.90–8.78 \times 10^{-3}$ s^{-1}, respectively, at pH 8.00). Addition of 2,6-lutidine, 2,4,6-collidine, and pyridine at concentrations up to 1 M (12% v/v) gave very large rate increases in the rate constant as expected from the incursion of the bimolecular reaction transferring sulfate to the new pyridine acceptor.

The mass-law results depend on a knowledge of the ratio k_w/k_{isq}, which has been obtained by adding sulfur trioxide to an 80% acetonitrile solution containing water and isoquinoline. The drawback of this type of measurement is that the selectivity may well be disguised by the mixing[13c] and by the microscopic composition of the surface in contact with the gaseous sulfur trioxide/nitrogen mixture.[13d] The value obtained for k_w/k_{isq} is undoubtedly an upper limit. It is not conceivable that solute water could react with sulfur trioxide faster than solute isoquinoline under competition conditions where mixing is not important. The calculated values of rate constant in Table VIII are *upper* limits based on k_w/k_{isq} being an upper limit. A further difficulty may be that microscopic aggregation of some sort might reduce the effective concentration of isoquinoline leading to spuriously low rate retardations. We feel that this effect is not very important as the major component of the system is acetonitrile in which isoquinoline is completely miscible. Aggregation effects are known for pyridines in water where the pyridines tend to form nonpolar domains, but acetonitrile is a much less structured solvent than water (it owes its high dielectric constant to the large nitrile dipole moment) and there is no evidence for aggregation there. We find also that the solvent composition employed here is well away from turbidity points that occur at low acetonitrile concentrations. Tests using sensitive light scattering equipment (Aminco-Bowman spectrofluorimeter fitted with a ratio photometer) reveal no gross aggregation; the excitation wavelength was 450 nm, and 90° scattering was measured at the same wavelength. Very little 90° scattering was observed; that observed was of the same order of magnitude as that for pure regular liquids.

Discussion

Transition-State Structure for Transfer from Pyridine to Phenolate Ion. The Brønsted data from this work for the effect of variation of leaving group and nucleophile on rates and equilibria indicate an essentially symmetrical transition state with relatively little charge change on the entering nucleophile.

Since we know the β values for all the parameters for breaking and forming bonds, we can delineate the effective charges and the Leffler α values for the complete system (eq 13); the value



of α for N–S *fission* is −0.99/−1.24 = 0.8 and for O–S *formation* is 0.23/1.74 = 0.13. The transition state thus has little change in effective charge[14] on the nucleophile and a large change in the departing leaving group relative to the reactant state. The data are consistent with weak bonding in the transition state between sulfur and entering and departing atoms and with a symmetrical transition state. This is consistent with either a concerted displacement mechanism ($S_N2(S)$) with an "open" transition state[6] or a preassociation stepwise process. There is little conceptual difference between a concerted mechanism with an open transition state and one where sulfur trioxide is solvated by incoming and outgoing groups. The present analysis yields more information than one where only β_L or β_N values are available and for which the standard equilibrium is an ionization rather than the reaction in question. Nevertheless we should point out that the standard equilibrium refers to the solvated reactants and products so that the structure of the transition state deduced from the structure–

(14) Deacon, T.; Farrar, C. R.; Sikkel, B. J.; Williams, A. *J. Am. Chem. Soc.* **1978**, *100*, 2525.

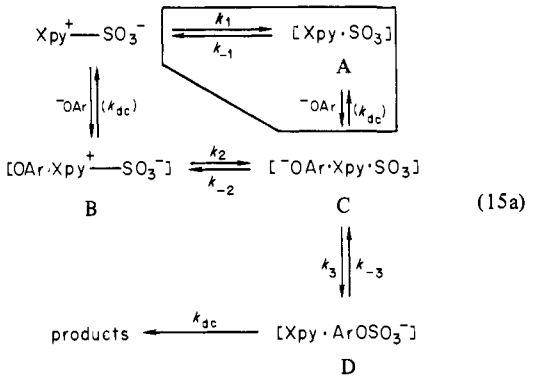
reactivity approach will reflect this; the structures in eq 13 should strictly include solvation and should not be simple bonding diagrams. Designation of effective charges on atoms is perfectly valid if the figures are taken for the atoms in the solvated state.

Recent work from this laboratory[15] shows that while zwitterionic *N*-arylsulfamates react in a bimolecular mechanism with carboxylate ion (eq 14) *no* intramolecular nucleophilic reaction occurs

$$ArNH_2^+SO_3^- + RCO_2^- \xrightarrow{-ArNH_2} RCO{-}O{-}SO_3^- \xrightarrow{water} \text{product} \quad (14)$$

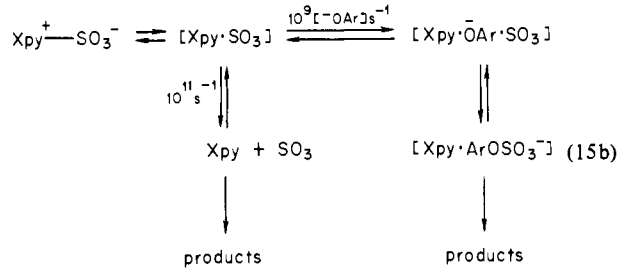
with the hydrolysis of *N*-(2-carboxyphenyl)sulfamic acid. Model building using Dreiding and CPK space-filling models indicates that the "in-line"[3] concerted transfer of the sulfate group is impossible in the intramolecular case. This is evidence that the unconstrained intermolecular mechanism is an "in-line" process. We should add that a somewhat complicated argument using apicophilicity rules developed for phosphorus[16] can be used to exclude the "adjacent" path for a stepwise displacement in the intramolecular case, but this requires the formation of a full S–O bond in the transition state, and the present data are not in accord with this.

The preassociation mechanism where an intermediate such as SO_3 in the encounter complex C has a lifetime shorter than that of the diffusion process may be applied to the present case (eq 15a); the preassociation pathway through B, C, and D is taken



(15a)

when the complex C reverts to B faster than ^-OAr diffuses away to give A. The pathway to products through complex A in the enclosure of eq 15a may be drawn out as a separate scheme (eq 15b) and may be excluded because diffusion of ^-OAr into A



(15b)

competes with the diffusion out of the complex A by SO_3. The latter is at a rate constant of approximately 10^{11} s^{-1} whereas the former is at approximately $10^9 \times [^-OAr]$ s^{-1}. Since the phenolate ion concentration never exceeds about 0.1 M in the present experiments, the mechanism predicts that scarcely any reaction flux should lead to aryl sulfate product and as this product is formed A cannot contribute significantly to the reaction.

The Brønsted type data are consistent with weak bonds between sulfur and the entering and leaving groups in the transition state for the sulfate group transfer reaction. The present work distinguishes between stepwise and concerted mechanisms (eq 2 and 3) if the apical bond of the intermediate of eq 2 can be taken to be a single bond analogous to that in the tetracoordinated sulfur species. No such distinction would be possible, however, if the intermediate in eq 2 had extraordinarily weak apical bonds and was close in structure to the transition state for the rate-limiting step. There is precedent for such weakly bonded apical atoms; Martin and his co-workers[17] indicated that the lengths of the apical S–O bonds in a bicyclic analogue of the pentacoordinate intermediate were much longer than those of the equatorial, indicating a bond order of 0.74. We must await further developments in either structural studies of pentacoordinated sulfur species or in detailed mechanistic studies for the solution of this fine distinction between closely similar mechanisms.

Unsaturated Intermediates. The observation of second-order kinetics for the transfer of sulfate from pyridinium-*N*-sulfonate to phenols and other nucleophiles excludes the dissociative mechanism with free sulfur trioxide as an intermediate (eq 1). The mass action experiment which demonstrates no effect of added isoquinoline on the hydrolysis of isoquinolinium-*N*-sulfonate (Table VIII) provides evidence against sulfur trioxide or its complex with an organic Lewis base as an intermediate in solvents with considerable organic content (eq 16).

$$^+isq{-}SO_3^- \rightleftarrows isq + SO_3 \xrightarrow{water} \text{product} \quad (16)$$

Figure 2 indicates that the water reaction analyzed for a bimolecular mechanism for the attack on pyridinium-*N*-sulfonate has a rate constant close to that expected from the Brønsted type correlation for other uncharged nucleophiles; this is consistent with water participating in a mechanism similar to that for the other nucleophile acceptors. It seems to us very unlikely that a nucleophile essentially much weaker than amines or oxy anions will cause a change in pathway from a mechanism with some nucleophile–sulfur bonding in the transition state to one with *less* bonding as required by the dissociative mechanism (eq 1).

The trapping experiments of Benkovic and Benkovic[7] where methanol competes with water on an approximately equal footing for sulfur trioxide and salicyl sulfate (neutral hydrolysis) are consistent with the conclusion, reinforced by this work, that the controlling transition state in sulfate group transfer has preponderant sulfur trioxide character.

Electropositivity of the Sulfate Group (SO_3^-). Brønsted β_{EQ} values against pyridine and phenol ionization indicate +1.24 and +0.74 effective charge[14] on nitrogen and oxygen, respectively, in pyridinium-*N*-sulfonate and aryl sulfate anion. The positive effective charge is consistent with a sulfonate group more electropositive than hydrogen despite its carrying negative charge and is similar to the charge induced by the phosphonate dianion (Table IX). The sulfonate anion is as effective as the sulfonyl group in inducing positive charge on oxygen, consistent with the sulfone group insulating the ether atom effectively from the substituents. This effect is probably due to the ether oxygen interacting with the highly electropositive sulfur atom at short range more effectively than with the oxy anion at longer range and has been noted previously by Bell.[18] This phenomenon may be taken as evidence that substituent effects from the pyridine and aryl groups on the N–S and O–S bonds are mutually exclusive. A carbonyl group might be expected not to be as good as the sulfone as an insulator, and this is reflected in an increase in positive effective charge on an ether oxygen of **1** in Table IX compared with **4** as the carbamate anion is protonated. The hydrogen carbonate ion (**7**) has a more negative effective charge than the acetate (**10**).

Thermodynamics of Sulfate Group Transfer. So far as we are aware the only values of equilibrium constants for hydrolysis of sulfate esters are those for adenosine phosphosulfate (APS)[19] and for alkyl and aryl sulfates estimated theoretically by Guthrie.[20] Guthrie obtained equilibrium constants (Table X) from ther-

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(16) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70.
(17) Perozzi, E. F.; Martin, J. C.; Paul, I. C. *J. Am. Chem. Soc.* **1974**, *96*, 6735.
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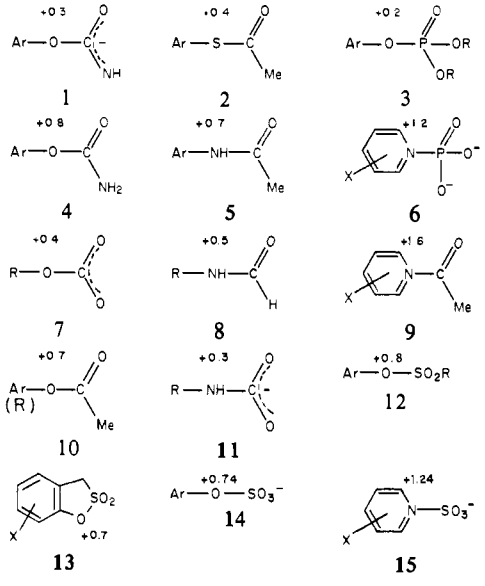
(19) (a) Robbins, P. W.; Lipmann, F. *J. Biol. Chem.* **1957**, *229*, 837. (b) Gregory, J. D.; Lipmann, F. *Ibid.* **1957**, *229*, 1081.
(20) Jencks, W. P.; Cordes, S.; Carriuolo, J. *J. Biol. Chem.* **1960**, *235*, 3608.

Table IX. Effective Charges Induced by Various Acyl Functions[a]



[a] Details for species 1 to 13 are taken from ref 14 and 14 and 15 from this work.

Table X. Comparison of Equilibrium Constants for Hydrolysis of Sulfate Esters with Literature Values[20]

ester	log $K_G°$ [a]	pK^{ROSO_3H} [b]	pK^{ROH}	log $K_A°$ [a]
2,4-dinitrophenyl	13.86	−5.66	4.1	14.38
4-nitrophenyl	11.30	−4.86	7.1	11.36
phenyl	8.92	−3.88	9.98	8.24
methyl	4.19	−3.54	15.54	3.79

[a] $K_G°$ and $K_A°$ are the values from Guthrie's work[1] and the present, respectively, for the equilibrium $[ROH][H_2SO_4]/[ROSO_3H]$ using the equation $\log K_A° = pK^{ROH} - pK^{ROSO_3H} - pK_W + pK^{H_2SO_4}$ [b] $- 1.74\ pK^{ROH} + 28.71$. [b] From ref 1.

mochemical data using the assumption that the equilibrium constant for an esterification involving sulfuric acid (eq 17) equals

$$H^+ + H_2O + ROSO_3^- \rightleftharpoons ROH + H_2SO_4 \quad (17)$$

the known value for the analogous reaction involving a sulfonic acid. These equilibrium constants may be estimated from our data if we assume that eq 10 holds for all oxyanions including hydroxide (throughout this work we follow the convention that water activity is unity); transfer of sulfate to a common pyridine acceptor from hydrogen sulfate or $ROSO_3^-$ ions leads to the equilibrium constant (eq 18 and 19) if the pK of water is taken

$$ROSO_3^- + HO^- \rightleftharpoons RO^- + HOSO_3^- \quad (18)$$

$$\log K_{EQ} = -1.74\ pK^{ROH} + 28.71 \quad (19)$$

as 16.5.[21] The equilibrium constants for eq 17 derived from eq 19 and the appropriate ionization constants (Table X) are in very good agreement with Guthrie's results, giving us confidence in the validity of the data from both laboratories. That the value for methanol is in good agreement supports the assumption that the free energy relationship (eq 19) applies to oxyanions in general.

The equilibrium constant for the hydrolysis of APS (eq 20) may

$$APS^{2-} \rightleftharpoons AMP^{2-} + SO_4^{2-} \quad (20)$$

$$APS^{2-} + P_2O_7^{4-} \rightleftharpoons ATP^{4-} + SO_4^{2-} \quad (21)$$

$$ATP^{4-} \rightleftharpoons AMP^{2-} + P_2O_7^{4-} \quad (22)$$

be obtained from that for transfer of the adenosyl group from sulfate to pyrophosphate (eq 21)[19] and for degradation of ATP to AMP (eq 22).[20] The data for the latter equilibrium are in doubt;[20] taking the value generally believed to be correct,[20] we estimate the equilibrium constant for eq 20 at pH 8, 25 °C, as 1.95×10^{14} M in good agreement with the value calculated (5.49×10^{13} M) by using eq 19 and appropriate ionization constants.

Efficiency of the Sulfate Group Transfer in Synthetic Reactions. Equation 10 predicts that transfer from pyridine to phenol is favored by weakly acidic phenols and weakly basic pyridines. The effect of pH in a synthetic system must be considered because the ROH groups only react in their ionic form. At a pH below that of the pK of the hydroxyl group but above the pK of pyridine the equilibrium constant is given by eq 23.

$$ROH + Xpy^+\text{–}SO_3^- \rightleftharpoons RO\text{–}SO_3^- + Xpy + H^+$$

$$K = K_{EQ}K_a^{ROH}/[H^+] \quad (23)$$

If water is an acceptor the product involves sulfate dianion above pH 2, and the equilibrium constant for alcohols at pH's below the pK of the hydroxyl group is given by eq 24. Synthesis of the

$$ROSO_3^- \rightleftharpoons ROH + H^+ + SO_4^{2-}$$

$$\log K = -0.74\ pK^{ROH} + 16.7 + pH \quad (24)$$

alkyl sulfate for alcohols with pK > 19.88 becomes possible at pH values below 2; this synthesis is clearly of hypothetical importance as there are no regular alcohols with such high pK values. It is known that alcohols (such as methanol) form their sulfates in concentrated sulfuric acid, and we can calculate that $[MeOSO_3H]/[MeOH][H_2SO_4] = 2.3 \times 10^{-3}\ M^{-1}$ using appropriate ionization constants and eq 19. The apparent unfavorable equilibrium constant could easily yield synthesis because the water activity will be considerably reduced in concentrated sulfuric acid solutions and there is a small driving force from the mass action effect of the concentrated sulfuric acid at approximately 5 M.

It is possible to compare acetyl phosphate and sulfate as acetylating agents from the above linear free energy relationships even though these reactions proceed by *acetyl* group transfer. Acetyl phosphate acetylates ethanol with a pH-independent equilibrium constant (log K = 3.80) from pH 7 to 12 (eq 25),

$$CH_3CO\text{–}OPO_3^{2-} + EtOH \rightleftharpoons CH_3CO\text{–}OEt + HPO_4^{2-} \quad (25)$$

derived from the equilibrium constant for hydrolysis of acetyl phosphate[22] and that for ethyl acetate.[23] The acetyl sulfate equilibrium constant (eq 26, log K = 8.18 + pH) is pH dependent

$$CH_3CO\text{–}OSO_3^- + EtOH \rightleftharpoons CH_3CO\text{–}OEt + H^+ + SO_4^{2-} \quad (26)$$

from 2 to 14 and may be obtained from the equilibrium constant for ethyl acetate hydrolysis, the pK of acetic acid, the ionic product of water, and the equilibrium constant for the hydrolysis of acetyl sulfate calculated from eq 10. Acetyl sulfate is thus a much more powerful acetylating agent than acetyl phosphate, and the involvement of a proton in the product (eq 26) increases this efficiency at high pH's. We may estimate the equilibrium constant for acetyl transfer from sulfate when the reaction is analogous to that of the phosphate (eq 25) (K = $([CH_3COOEt][HSO_4^-])/([EtOH][CH_3COOSO_3^{2-}]) = 10^{10.17}$); this value is very much larger than that for the phosphate. Figure 3 shows that the equilibrium constants for hydrolysis of acetyl derivatives are correlated quite well with the pK of the leaving hydroxyl function. Thus the acetyl sulfate is a good acetylating agent because the pK of the HSO_4^- is about ten units less than that of HPO_4^{2-}. The good correlation of Figure 3 provides further evidence that our equilibrium results are consistent with the literature and gives us further confidence in the validity of our results.

We may calculate the effectiveness of sulfamic acids as sulfating agents for alcohols[24] (eq 27) assuming these reagents have similar

$$NH_3^+\text{–}SO_3^- + ROH \rightleftharpoons NH_4^+ + ROSO_3^-$$

$$(\log K = 1.74\ pK^{ROH} - 1.24\ pK^{NH_4^+} + 0.06) \quad (27)$$

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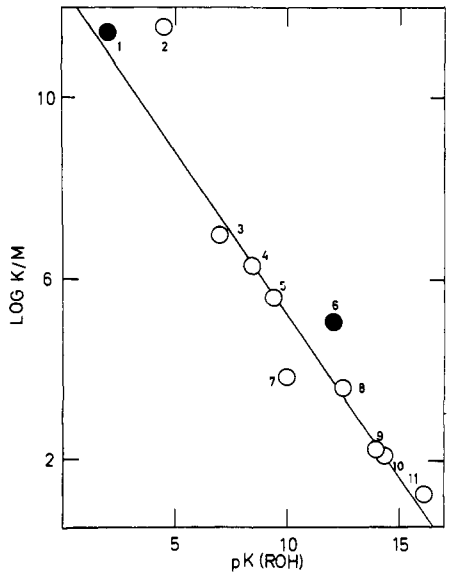


Figure 3. Brønsted type dependence of the equilibrium constant for acetate hydrolysis ([MeCOOH][HOR]/[MeCOOR]) on the pK of the hydroxyl function (HOR). Data are as follows: (1) $AcOSO_3^-$ (estimated from this work); (2) Ac_2O (Jencks, W. P.; Barley, E.; Barnett, R.; Gilchrist, M. *J. Am. Chem. Soc.* **1966**, *88*, 4464); (3) 4-nitrophenyl acetate;[22] (4) 3-nitrophenyl acetate;[22] (5) 4-chlorophenyl acetate;[22] (6) $AcOPO_3^{2-}$;[22] (7) phenyl acetate;[22] (8) trifluoroethyl acetate;[23] (9) choline acetate;[23] (10) chloroethyl acetate;[23] (11) ethyl acetate.[23] The ionic species from (1) and (6) are $HOSO^-_3$ and $HOPO^{2-}_3$, respectively; the other points involve neutral reactants and products. The equation of the least-squares line is log K = −0.78 pK (ROH) + 13.2 (r = 0.964).

reactivity to pyridinium-*N*-sulfonates. Since sulfamic acid has a pK of approximately unity,[25] the equilibrium will become progressively less favorable as the pH increases (eq 28) between the

$$([ROSO_3^-][NH_4^+])/([NH_2SO_3^-][ROH]) = KK_a^{ROH}/K_a^{NH_4^+}K_a^{NH_3^+SO_3^-}[H^+] = 10^{10.34-pH} \quad (28)$$

pH's corresponding to the pK's of ammonia and sulfamic acid.

Nucleofugality. Recently Stirling[26] has introduced the term nucleofugality as the propensity of a leaving group to depart from a system. The "ranking" of a nucleofuge depends, among other things, on bond-forming processes in the reacting molecule used as a standard. Although bond-forming processes will always occur, we have shown that the transfer of the sulfate group involves relatively little bond formation with sulfur and the entering nucleophile. The ranking of the rate constants for the departure of the leaving groups should therefore be relatively free of effects due to the substrate. Figure 4 illustrates the hydrolysis of sulfonates as a function of the leaving group pK. Two clear leaving group types are apparent: the aryloxy anion and the tertiary amine. The tertiary amine is more reactive by about 3 orders of magnitude for a given pK than the aryloxy group, in accord with previous results[27] for the decomposition of tetrahedral intermediates in carbonyl forming eliminations. A further point is that the triethylamine leaving group is better than predicted by its pK, and we suggest some sort of steric acceleration effect as an explanation of this.

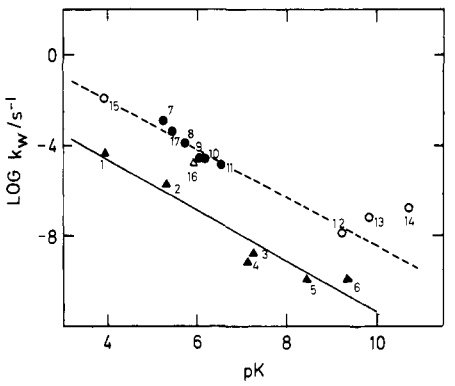
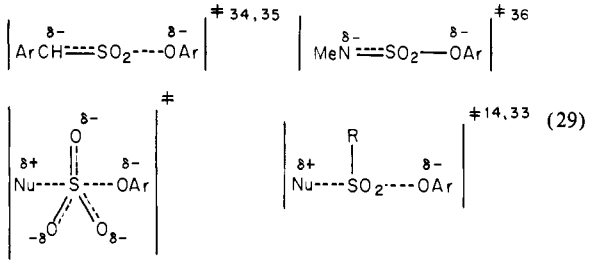


Figure 4. Transfer of the sulfate group from a donor to water. Data are from various sources and at different temperatures and ionic strengths. (▲) Substituted phenyl sulfates at 25 °C:[4a,5,28] (1) 2,4-dinitrophenyl; (2) 2,5-dinitrophenyl; (3) 2-nitrophenyl; (4) 4-nitrophenyl; (5) 3-nitrophenyl; (6) 4-carboxyphenyl. (●) Pyridines (this work) at 25 °C: (7) parent; (8) 3-picoline; (9) 4-picoline; (10) 3,5-lutidine; (11) 3,4-lutidine. (○) Substituted sulfamates (25 °C): (12) $NH_3^+SO_3^-$;[29] (13) $Me_3N^+SO_3^-$;[30] (14) $Et_3N^+SO_3^-$;[30] (15) 1-naphthyl sulfamate;[15,31] (16) $PhOPO_2^-OSO_3^-$;[32] (17) isoquinoline.

A Family of Sulfone Group (X–SO_2–) Transfer Mechanisms. There is now convincing evidence that the sulfonyl group (R–SO_2–) is transferred by a concerted displacement mechanism[14,33] unless it possesses a labile proton on an atom α to the sulfone.[34,35] The controlling transition states for sulfyl group transfer to a nucleophile are illustrated in eq 29. The aminosulfonates[36] and



(29)

arylmethanesulfonates[34] have a sufficiently basic anion to expel the aryloxy anion without assistance from the entering nucleophile, and the mechanism involves the formation of a discrete intermediate. The sulfonate anion is only weakly basic (pK < 0), and the nucleophile is involved in the bonding to effect expulsion of the leaving group. Sulfonyl group transfer where there is no electron-donating atom in the substrate will require considerable participation by the nucleophile to expel the aryloxy anion; this leads to a stronger Nu–S bond and less advanced S–O bond fission in the transition state compared with the sulfate group transfer mechanism, as is observed.[34b]

Cross-Correlation Effects. Since we have utilized essentially four linear free energy correlations of the type log $k = \beta$ pK + C, it is impossible to define any cross-correlation terms of the type first discussed by Miller[37] involving $pK^{ArOH}pK^{Xpy}$. It is unlikely that these are important because we are able to use the two-parameter eq 8–10 to calculate data accurately over a large change in pK. Values of β for nucleophiles other than phenolate or pyridines are quite similar (Table XII) except that for attack on pyridinium-*N*-sulfonates. No evidence of curvature is found in the Brønsted correlations, and the attack of pyridines on 2,4-dinitrophenyl and 3,4-dinitrophenylsulfates have similar β_N values (Table VI). We are encouraged in our belief that there are no cross-correlation terms, contrary to those found by Gorenstein[38]

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and Kirby[39] for phosphate ($-P(O)(OR)_2$) transfer, by the weak bonding between entering and leaving groups and the sulfur in the controlling transition state.

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Registry No. 14·K (Ar = Ph), 1733-88-6; **14**·K (Ar = 3,4-$(NO_2)_2C_6H_3$), 86260-33-5; **14**·K (Ar = 2,6-$(NO_2)_2C_6H_3$), 86260-34-6; **14**·K (Ar = 2,3-$(NO_2)_2C_6H_3$), 86260-35-7; **14**·K (Ar = 2,4-$(NO_2)_2C_6H_3$), 72119-41-6; **14**·K (Ar = 4-Cl, 2-$NO_2C_6H_3$), 86260-36-8; **14**·K (Ar = 2-Cl, 4-$NO_2C_6H_3$), 86260-37-9; **15** (X = H), 42824-16-8; **15** (X = 3-Me), 55546-46-8; **15** (X = 4-Me), 86260-30-2; **15** (X = 3,4-$(Me)_2$), 86260-31-3; **15** (X = 3,5-$(Me)_2$), 86260-32-4; TEA, 102-71-6; DABCO, 280-57-9; isoquinolium-*N*-sulfate, 53854-50-5; phenoxide, 3229-70-7; 3,5-dimethylphenoxide, 67303-73-5; 2,5-dimethylphenoxide, 64502-87-0; 2,4-dimethylphenoxide, 86260-38-0; 3-chlorophenoxide, 18938-14-2; 2,3-dimethylphenoxide, 86260-39-1; 4-chlorophenoxide, 24573-38-4; 2,6-dimethylphenoxide, 25117-01-5; 3-methylphenoxide, 20227-79-6; ethyl glycinate, 459-73-4; glycine, 56-40-6; ethanolamine, 141-43-5; *n*-propylamine, 107-10-8; methyl β-alaninate, 4138-35-6; aminoacetonitrile, 540-61-4; diaminoethane, 107-15-3; semicarbazide, 57-56-7; aniline, 62-53-3; hydrazine, 302-01-2; *N*-ethylmorpholine, 100-74-3; *N*,*N*-diethanolamine, 111-42-2; triethylamine, 121-44-8; trimethylamine, 75-50-3; *N*-methylpiperidine, 626-67-5; acetate anion, 71-50-1; phosphate dianion, 14066-19-4; carbonate dianion, 3812-32-6; cacodylate, 15132-04-4; water, 7732-18-5; hydroxide ion, 14280-30-9.

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Phase Separation and Reactivity Changes of Phenyl Ester Substrate and Imidazole Catalyst in the Dialkylammonium Bilayer Membrane

Toyoki Kunitake,* Hirotaka Ihara, and Yoshio Okahata

Contribution No. 666 from the Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka 812, Japan. *Received October 4, 1982. Revised Manuscript Received May 17, 1983*

Abstract: A phenyl ester substrate and an imidazole catalyst that possess the azobenzene chromophore and are capable of bilayer formation were synthesized. Distribution of these amphiphiles in the dialkylammonium bilayer matrix was examined by using blue shifts due to cluster formation of the azobenzene chromophore. Formation of the substrate cluster was promoted by increased concentrations in the matrix and by the liquid crystal-to-crystal phase transition of the matrix. Formation of the catalyst cluster was promoted, in addition to these factors, by neutralization of the anionic histidine head group due to the change of the medium pH or due to complexation with Cu^{2+} ion. The rate of alkaline hydrolysis of the clustered substrate was smaller than that of the isolated (monomeric) substrate: $^1/_{19}$ at 10 °C, pH 11.8. The Arrhenius plots show inflection regions near the phase transition of the matrix due to changing monomer–cluster ratios. The activation energy of the hydrolysis of *p*-nitrophenyl *N*-carbobenzoxy-L-phenylalaninate was 27 kcal/mol in the partially rigid bilayer matrix but decreased to 14 kcal/mol in the fluid matrix. This change was attributed to the formation of the catalyst cluster in the rigid matrix. The present study provides the first example of the reaction control by phase separation.

The physiological function of the biomembrane is closely related to the mode of distribution and the corresponding activity change of membrane enzymes.[1-6] In spite of the overriding physiological importance of the regulation of activity of these enzymes, its molecular understanding is lagging because of the inherent difficulty arising from the complexity of the system. Thus, the molecular mechanism of regulation may be tested more readily by using simplified, synthetic systems.

Our aim in the present series of investigation is to establish the relation between the mode of distribution (phase separation in particular) of reacting species (catalyst, substrate, etc.) and their reactivities in the synthetic bilayer matrix. The relationship, if established, would provide useful information for understanding the mode of action of membrane enzymes and for designing synthetic catalysts with regulatory functions.

Recently, it was shown in these laboratories that phase separation of single-chain ammonium amphiphiles with the azobenzene moiety can be detected spectroscopically.[7] When a sonicated aqueous mixture (molar ratio, 1:10) of azobenzene amphiphile **1** and dialkylammonium amphiphile **5** (n = 18) was maintained at 50 °C, λ_{max} of the azobenzene chromophore appeared at 355 nm, indicating the presence of monomeric azobenzene species. The monomer peak disappeared upon cooling, and a new peak due to the azobenzene cluster appeared at 316 nm. The spectral change was reversible. This finding provides a new, facile technique for detection of phase separation in the synthetic membrane system, and a variety of novel functions are conceivable on the basis of this technique. For instance, phase separation of probe molecules in the bilayer matrix can be regulated by the interaction of the surface receptor (neutral and protonated ethylenediamine moiety) and added ions, and this system can be applied quite generally to detection of chemical singnals.[8]

We applied this technique to examine phase separation and the resulting reactivity changes of a phenyl ester substrate and a imidazole catalyst in the dialkylammonium bilayer matrix. Amphiphile **2** was selected as membrane-forming substrate because

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