**Isolation of L-671,239.** Cell extracts were diluted with water to lower the methanol concentration to 50%, and the labeled product was adsorbed onto a column of SP-207 resin (Mitsubishi) previously equilibrated with 50% methanol. The resin was washed with 3 bed volumes of 65% methanol before the L-671,329 was eluted with 100% methanol. The resulting material was adsorbed to a column of HP-20 resin (Mitsubishi) and eluted in a similar fashion. As a final purification step, preparative-scale HPLC was performed with a Dupont Zorbax C18 column (21.2 mm × 25 cm) eluted isocratically at 37 °C with acetonitrile/water (48:52) at a flow rate of 15 mL/min. Under these conditions, the retention time of L-671,329 was approximately 12 min. Analytical HPLC on a Beckman Ultrasphere C18 column (4.6 mm × 25 cm) was used to monitor the purification. The column was operated isocratically at 37 °C with acetonitrile/water (50:50) at a flow rate of 0.75 mL/min. The column effluent was monitored at 210 nm, and L-671,329 had a retention of 11.2 min. Fractions with >98% purity (by peak integration) were combined, and yields from feeding experiments performed on a 1-L scale ranged from 10 to 20 mg.

**Spectroscopy.** $^{13}C$ NMR spectra were acquired in $CD_3OD$ at 100 MHz with use of Waltz 16-proton decoupling on a Varian XL-400 instrument at ambient temperature. Chemical shifts are given in parts per million referenced to $CD_3OD$ at 49.0 ppm as internal standard. Spectra of labeled and natural abundance L-671,329 were recorded with identical operating parameters. Conclusions regarding positions enriched with $^{13}C$ were based upon the assignments published previously,[2] although some of the myristate methylene carbons needed to be reassigned (see Table I).

**Acknowledgment.** We thank our colleagues R. Schwartz and D. Sesin for useful suggestions regarding purification procedures and C. Caldwell, P. Durette, M. Hammond, and E. Inamine for stimulating discussions regarding this research.

**Registry No.** L-671,329, 120692-19-5; L-Tyr, 60-18-4; L-Pro, 147-85-3; L-Leu, 61-90-5.

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(31) The experiments with $^{14}C$ precursors were performed in the same way except that the radionuclides were added as a single dose to a final concentration of 0.5 $\mu$Ci/10 mL, and the incubations were allowed to proceed for only 6 h, which was sufficient time for the uptake of >90% of the precursor by the cells. The presence of radiolabeled L-671,329 in methanol extracts was demonstrated by TLC on silica gel 60 F (Merck) with a mobile phase of 1-butanol/acetic acid/5% ammonium hydroxide (12:3:1.5 by volume) followed by radioautography with X-Omat AR film (Kodak).

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# Metal Ion Catalysis in Nucleophilic Displacement Reactions at Carbon, Phosphorus, and Sulfur Centers.[1] 4. Mechanism of the Reaction of Aryl Benzenesulfonates with Alkali-Metal Ethoxides: Catalysis and Inhibition by Alkali-Metal Ions

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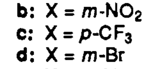
*Contribution from the Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6.* *Received June 28, 1990*

**Abstract:** The rates of the nucleophilic displacement reactions of aryl benzenesulfonates (**1a–f**) with alkali-metal ethoxides (LiOEt, KOEt, and KOEt in the presence of complexing agents) in anhydrous ethanol at 25 °C have been studied by spectrophotometric techniques. For all esters studied, the order of reactivity is LiOEt < $EtO^-$ < KOEt. Metal ion catalysis ($K^+$) and inhibition ($Li^+$) are proposed to occur via reactive alkali-metal ethoxide ion pairs. Second-order rate constants for free ethoxide and metal–ethoxide ion pairs are calculated. Hammett treatment of leaving-group effects results in correlation of rate data with $\sigma^0$ substituent constants and large $\rho$ values of 3.0 (KOEt), 3.1 (LiOEt), and 3.4 ($EtO^-$). A rate-determining transition state having well-advanced EtO–S bond formation but little S–OAr bond breakage is proposed. The similarity of the $\rho$ values for KOEt, LiOEt, and $EtO^-$ implies that alkali-metal ions do not significantly alter the extent of S–OAr bond breakage in the transition state. However, metal ions do stabilize the transition state to differing degrees. Equilibrium constants for association of $K^+$ and $Li^+$ with the transition state are calculated, and it is concluded from the relative magnitudes of these values ($Li^+$ < $K^+$) that solvated metal ions interact with the transition state, rather than bare metal ions. Hammett plots of the free energy of association of metal ions with the transition state indicate that leaving-group substituent effects on metal ion binding in the transition state are small ($\rho = -0.39$ ($K^+$) and $-0.23$ ($Li^+$)) and lead to the conclusion that more electron-rich transition states bind metal ions more strongly.

## Introduction

We have undertaken systematic studies of the mechanism of the nucleophilic substitution reactions of carbon-, phosphorus-, and sulfur-based esters, including the effects of alkali-metal ions on these reactions. Previous reports have outlined the observation of alkali metal ion catalysis in the reactions of alkali-metal ethoxides and phenoxides with *p*-nitrophenyl diphenylphosphinate (**2**),[1c,d,f] as well as alkali metal ion catalysis and inhibition in the reactions of alkali-metal ethoxides with *p*-nitrophenyl benzenesulfonate (**1a**).[1e–g] The present study deals with the mechanism of the nucleophilic displacement reactions of alkali-metal ethoxides (KOEt, LiOEt, and $EtO^-$) with aryl benzenesulfonates (**1a–1f**)



**1a:** X = *p*-$NO_2$
**b:** X = *m*-$NO_2$
**c:** X = *p*-$CF_3$
**d:** X = *m*-Br
**e:** X = *p*-Cl
**f:** X = H

**2**

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(1) This paper is an extension of our series on Bond Scission in Sulfur Compounds. Previous papers in this series are the following: (a) Buncel, E.; Wilson, H.; Chuaqui, C. *J. Am. Chem. Soc.* **1982**, *104*, 4896. (b) Buncel, E.; Chuaqui, C.; Wilson, H. *J. Org. Chem.* **1980**, *45*, 2825. (c) Buncel, E.; Dunn, E. J.; Bannard, R. A. B.; Purdon, J. G. *J. Chem. Soc., Chem. Commun.* **1984**, 162. (d) Dunn, E. J.; Buncel, E. *Can. J. Chem.* **1989**, *67*, 1440. (e) Buncel, E.; Pregel, M. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1566. (f) Dunn, E. J.; Moir, R. Y.; Buncel, E.; Purdon, J. G.; Bannard, R. A. B. *Can. J. Chem.* **1990**, *68*, 1837. (g) Pregel, M. J.; Dunn, E. J.; Buncel, E. *Can. J. Chem.* **1990**, *68*, 1846.

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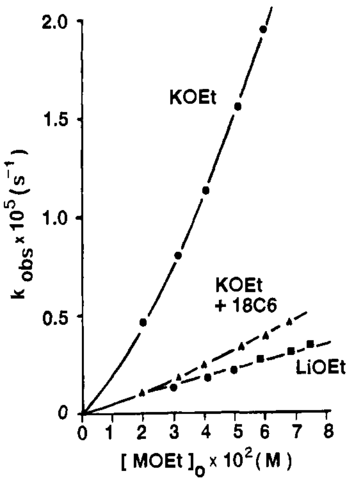

**Figure 1.** Kinetic data for the reaction of **1f** with KOEt, LiOEt, and KOEt in the presence of 18-crown-6 in EtOH at 25 °C.

and yields further information on the role of metal ions (catalysis and inhibition) in these processes.

Nucleophilic substitution reactions at sulfonyl sulfur centers could conceivably occur by three distinct routes: a concerted $S_N2(S)$ process, a stepwise addition–elimination mechanism (associative nucleophilic substitution ($S_Na$)) involving a pentacoordinate intermediate, or a stepwise $S_N1(S)$ process.[2] There is no evidence for the occurrence of an $S_N1(S)$ mechanism in the sulfonyl-transfer reactions of benzenesulfonate esters, though such a mechanism is conceivable for some compounds.[2]

In this research, linear free energy relationships are used to gain insight into the structure of the rate-determining transition state of the reaction. A correlation of leaving-group effects on rate with Hammett $\sigma^-$ constants is expected if the reaction is concerted $S_N2$ or if elimination is the rate-limiting step in an addition–elimination reaction. A negative charge builds up on the phenolate oxygen in both cases, and it is stabilized by resonance interactions with aryl substituents. A $\sigma^0$ dependence is expected if addition is rate-limiting in the addition–elimination mechanism or if leaving-group bond breakage is not well-advanced in the $S_N2$ transition state since direct resonance with negatively charged centers is not possible.

The solvolysis reactions of benzenesulfonate and tosylate esters have been studied in a number of different media,[3-6] but not in anhydrous ethanol. Ethanol is a solvent of moderate polarity in which metal ions are not as effectively solvated as in solvents of greater polarity, e.g., water. In ethanol, stabilization of metal ions through interactions with anions becomes significant and ion pairs are formed to an appreciable extent. Ion pairing of alkali-metal ethoxides is well-known and can have interesting effects on reactivity,[7-9] as demonstrated below.

## Results

We have measured the rates of reaction of aryl benzenesulfonates (**1a**–**1f**) with lithium ethoxide, potassium ethoxide, and potassium ethoxide in the presence of excess crown ether (corresponding to the reaction of free ethoxide ion) in anhydrous ethanol at 25 °C. The variation of the observed pseudo-first-order rate constant ($k_{obs}$) with the total base concentration $[\mathrm{MOEt}]_0$ for the reaction of **1f** is shown in Figure 1 (see Tables S1–S6 in the supplementary material). It is noted that the ethoxide species have different reactivities, which fall in the order LiOEt < EtO$^-$ < KOEt, and that sharp upward curvature is seen for KOEt, while the plots for KOEt + 18-crown-6 and LiOEt are essentially linear. For a given ethoxide species, the rate constant decreases in the order **1a** → **1f**.[10]

**Table I.** Summary of Second-Order Rate Constants (M$^{-1}$ s$^{-1}$) from Ion Pairing Treatment of Kinetic Data on Reactions of **1a**–**1f** with KOEt, LiOEt, and KOEt + 18-Crown-6 in EtOH at 25 °C

| compd | X | $k_{\mathrm{KOEt}}$ | $k_{\mathrm{LiOEt}}$ | $k_{\mathrm{EtO^-}}$ |
|---|---|---|---|---|
| **1a** | *p*-NO$_2$ | $1.37 \times 10^{-1}$ | $1.80 \times 10^{-2}$ | $2.87 \times 10^{-2}$ |
| **1b** | *m*-NO$_2$ | $7.8 \times 10^{-2}$ | $1.04 \times 10^{-2}$ | $1.40 \times 10^{-2}$ |
| **1c** | *p*-CF$_3$ | $1.66 \times 10^{-2}$ | $2.10 \times 10^{-3}$ | $2.69 \times 10^{-3}$ |
| **1d** | *m*-Br | $8.2 \times 10^{-3}$ | $8.5 \times 10^{-4}$ | $1.10 \times 10^{-3}$ |
| **1e** | *p*-Cl | $3.5 \times 10^{-3}$ | $3.6 \times 10^{-4}$ | $4.5 \times 10^{-4}$ |
| **1f** | H | $5.2 \times 10^{-4}$ | $5.4 \times 10^{-5}$ | $5.1 \times 10^{-5}$ |

Similar behavior was observed in a previous study of the reaction of alkali-metal ethoxides with **1a**, and the same ordering of reactivity was observed.[1e,g] Addition of cryptand to the reaction of KOEt with **1a** resulted in the rate decreasing to a minimum value corresponding to the reaction of free ethoxide. Conversely, addition of cryptand to the reaction of LiOEt resulted in the rate increasing to a maximum value that was identical with the minimum value seen in the reaction of KOEt in the presence of excess complexing agent. In complementary experiments, addition of a K$^+$ salt to the reaction of KOEt was found to increase the rate, while addition of a Li$^+$ salt to the reaction of LiOEt was found to decrease the rate.[1g] Therefore, in the present research, KOEt and LiOEt have been chosen as representative ethoxide bases (K$^+$ being a catalyst, while Li$^+$ is an inhibitor of the reaction) and used in further mechanistic studies with the reaction series **1a**–**1f**.

Following our previous treatment of the data for reactions of alkali-metal ethoxides,[1d,g] the kinetic data are analyzed in terms of the reactivity of free ethoxide ion and alkali-metal ethoxide ion pairs. An ion pair association constant ($K_a$) governs the equilibrium between free ions and ion pairs, both of which may react with the ester.

$$\mathrm{M^+ + EtO^- \rightleftharpoons MOEt} \qquad K_a = \frac{[\mathrm{MOEt}]}{[\mathrm{M^+}][\mathrm{EtO^-}]} \tag{1}$$

$$\begin{array}{l} \mathrm{M^+ + EtO^- + PhSO_2OAr} \xrightarrow{k_{\mathrm{EtO^-}}} \text{products} \\ \quad K_a \Big\updownarrow \\ \mathrm{MOEt + PhSO_2OAr} \xrightarrow{k_{\mathrm{MOEt}}} \text{products} \end{array} \tag{2}$$

$$k_{obs} = k_{\mathrm{EtO^-}}[\mathrm{EtO^-}] + k_{\mathrm{MOEt}}[\mathrm{MOEt}] \tag{3}$$

$K_a$ values for alkali-metal ethoxides in anhydrous ethanol at 25 °C have been determined,[11] and hence equilibrium concentrations of free ions and ion pairs can be calculated since the total base concentration, $[\mathrm{MOEt}]_0$, is known and $[\mathrm{M^+}] = [\mathrm{EtO^-}]$ at equilibrium. Consequently, the observed pseudo-first-order rate constant may be dissected into second-order rate constants for free ethoxide and metal–ethoxide ion pairs with use of eq 4. The second-order rate constants for the reactions of LiOEt, KOEt, and EtO$^-$ with **1a**–**1f** are summarized in Table I.

$$k_{obs}/[\mathrm{EtO^-}] = k_{\mathrm{EtO^-}} + k_{\mathrm{MOEt}}K_a[\mathrm{EtO^-}] \tag{4}$$

It is also conceivable that metal ions may be involved in the reaction by complexation of the ester in a preequilibrium step,[12,13]

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as shown in eq 5, for which the rate law is given in eq 6. Equation

$$\begin{tikzcd}
\mathrm{MOEt} + \mathrm{PhSO_2OAr} \arrow[r, "k_{\mathrm{MOEt}}"] \arrow[d, shift left, "K_a"'] & \text{products} \\
\mathrm{EtO^-} + \mathrm{M^+} + \mathrm{PhSO_2OAr} \arrow[r, "k_{\mathrm{EtO^-}}"] \arrow[u, shift left] \arrow[d, shift right, "K_c"'] & \text{products} \\
\mathrm{EtO^-} + \mathrm{PhSO_2OAr{\cdot}M^+} \arrow[r, "k_{\mathrm{M^+}}"] \arrow[u, shift right] & \text{products}
\end{tikzcd} \qquad (5)$$

$$k_{\mathrm{obs}} = k_{\mathrm{EtO^-}}[\mathrm{EtO^-}] + (k_{\mathrm{MOEt}} + (k_{\mathrm{M^+}}K_{\mathrm{C}})/K_{\mathrm{a}})[\mathrm{MOEt}] \qquad (6)$$

6 is of the same form as eq 3, so kinetic experiments cannot distinguish between these two mechanisms. However, the ion pair mechanism is preferred for the following reasons. First, there is no evidence to suggest that alkali-metal ions complex sulfonate esters in alcoholic media to an appreciable extent. Second, previous studies of reactions of alkali-metal ethoxides with alkyl halides[7,8] and carboxylate esters[9] in ethanol have provided evidence for reactive ion pairs. Finally, when the preassociation mechanism was assumed for **1a** with $k_{\mathrm{MOEt}} = 0$ and reasonable values of $K_c$, values of $k_{\mathrm{M^+}}$ were obtained that were considered unrealistically large.[18]

## Discussion

**Mechanism of Reaction.** Examination of the kinetic data in Table I reveals that the second-order rate constant for a given ethoxide species (KOEt, LiOEt, or EtO⁻) decreases along the series **1a** → **1f**, i.e., as the leaving ability of the aryloxide becomes poorer. Hammett treatment of leaving-group effects yields a correlation with $\sigma^0$ substituent constants and large $\rho$ values. Table II compares the correlations obtained using $\sigma$, $\sigma^0$, and $\sigma^-$ constants. Similar correlation coefficients are seen for $\sigma$ and $\sigma^0$ constants, with $\sigma^0$ giving a slightly better correlation, while a significantly poorer correlation coefficient is obtained when $\sigma^-$ constants are used. Hammett plots of the kinetic data for KOEt, LiOEt, and EtO⁻ with $\sigma^0$ constants are shown in Figure 2, yielding slopes ($\rho$) of 2.98 ($r = 0.9977$), KOEt; 3.14 ($r = 0.9982$), LiOEt; and 3.37 ($r = 0.9987$), EtO⁻.

These results may be compared to Hammett $\sigma$–$\rho$ treatments of leaving-group effects in the alkaline hydrolysis and nucleophilic displacement reactions of arenesulfonate esters. The rates of alkaline hydrolysis of substituted aryl esters of benzenesulfonic acid in 70% aqueous dioxane (50 °C)[14] and substituted aryl tosylates in water (75 °C),[15] 80% aqueous ethanol (27 °C),[16] and 80% aqueous DMSO (75 °C)[17] all gave good correlations with $\sigma$ and $\sigma^0$ constants and large $\rho$ values ranging from 1.61 to 2.75 but poor $\sigma^-$ correlations.

The effect of substituent variation on the arenesulfonic acid portion of aryl arenesulfonate esters has also been investigated. The rates of alkaline hydrolysis of phenyl arenesulfonates (70% aqueous dioxane, 50 °C) gave a correlation with $\sigma$ ($\rho = 2.30$).[18] A large $\rho$ value for substituents on the acid portion suggests that a significant charge transfer from the nucleophile has occurred on going from ground state to transition state; this charge may be expected to reside predominantly on the sulfonyl center. This is expected when HO–S bond formation (charge donation) has proceeded further than S–OAr bond breakage (charge removal).

Turning to other nucleophilic displacement reactions, an $S_N2(S)$ mechanism has been proposed for a number of reactions of aryl arenesulfonates. A study of the attack of substituted phenoxides on *p*-nitrophenyl *p*-toluenesulfonate in 41% ethanol–water yielded a $\beta_{\mathrm{nuc}}$ value of 0.21,[19] indicating a small degree of bond formation to the nucleophile in the transition state.

**Table II.** Comparison of the Results of Hammett Plots with Use of $\sigma$, $\sigma^0$, and $\sigma^-$ Substituent Constants for the Reactions of EtO⁻ with **1a–1f**

| compd | X | $\sigma^a$ | $\sigma^{0\,b}$ | $\sigma^{-\,c}$ | $\log k_{\mathrm{EtO^-}} + 5$ |
|---|---|---|---|---|---|
| **1a** | *p*-NO$_2$ | 0.78 | 0.82 | 1.27 | 3.548 |
| **1b** | *m*-NO$_2$ | 0.71 | 0.70 | | 3.146 |
| **1c** | *p*-CF$_3$ | 0.54 | 0.53 | 0.74 | 2.430 |
| **1d** | *m*-Br | 0.39 | 0.38 | | 2.041 |
| **1e** | *p*-Cl | 0.23 | 0.27 | | 1.653 |
| **1f** | H | 0 | 0 | | 0.708 |
| | | $\sigma$ | $\sigma^0$ | | $\sigma^-$ |
| $\sigma$ | | 3.39 | 3.37 | | 2.10 |
| $r$ | | 0.9956 | 0.9987 | | 0.9367 |

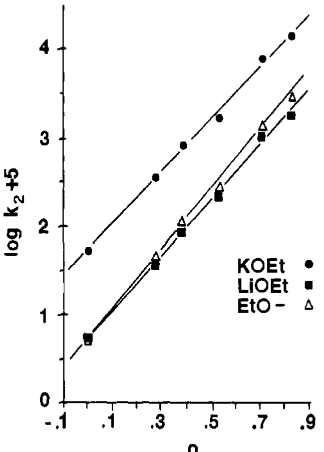

**Figure 2.** Hammett plot of the kinetic data for the reactions of **1a–1f** with KOEt, LiOEt, and EtO⁻ with use of $\sigma^0$ substituent constants.

The reaction of 4′-nitrophenyl 4-nitrobenzenesulfonate with oxygen nucleophiles has provided evidence for an $S_N2$ reaction at sulfur.[20] In a stepwise mechanism, a change in the rate-limiting step is expected when the p*K* of the nucleophile is varied about the p*K* of the leaving group. A change in the rate-limiting step should result in a break in a Bronsted plot of log rate vs p$K_{\mathrm{Nu}}$ at the p*K* of the leaving group.[20] A concerted mechanism, on the other hand, should give a linear or gently curved Bronsted plot. The Bronsted plot for the reaction of oxyanions with 4′-nitrophenyl 4-nitrobenzenesulfonate is in fact reasonably linear ($\beta_{\mathrm{nuc}} = 0.64$; $r = 0.986$), with no break at p$K_{\mathrm{lg}}$, and a concerted $S_N2(S)$ mechanism was inferred.[20] Similarly, Bronsted relationships for rate and equilibrium constants for variation of nucleophile and leaving group in reactions of phenolate ions with substituted (2-hydroxyphenyl)methanesulfonic acid sultones were found to be consistent with a concerted process having a symmetrical transition state.[21]

In summary, alkaline hydrolysis reactions of aryl arenesulfonates appear to proceed through a transition state with significant bond formation to the nucleophile and little leaving-group bond breakage. However, studies of other nucleophilic displacement reactions have provided evidence for an $S_N2(S)$ mechanism in which bond formation to the nucleophile is not well-advanced, while there is significant leaving-group bond breakage.

The substituent effect results of the present study are similar to previously reported results for alkaline hydrolysis of aryl benzenesulfonates and aryl tosylates:[14] Large $\rho$ values and $\sigma^0$ correlations are obtained. The results are consistent with a stepwise addition–elimination mechanism with addition as the

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(18) Hammett treatment of kinetic data in ref 6 was done by us.

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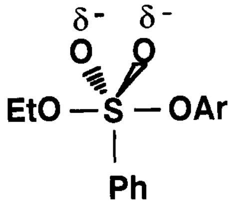
rate-limiting step or an $S_N2(S)$ mechanism in which bond formation to the nucleophile is well-advanced and bond breakage to the leaving group is minimal in the transition state. The present results do not distinguish between these two mechanistic possibilities but rather serve to characterize the rate-determining transition state as having well-advanced EtO–S bond formation, but negligible S–OAr bond breakage, as shown below.

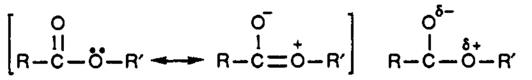


**1**

The correlation of rates with $\sigma^0$ substituent constants implies that direct resonance interactions of the aryl substituent and the reacting center are *not* occurring. Therefore, the S–OAr bond is essentially intact in the transition state, and the phenolic oxyen does not bear a significant negative charge, or else a correlation with $\sigma^-$ constants would be observed.

The large $\rho$ values (3.0–3.4) for the reactions of KOEt, LiOEt, and $EtO^-$ indicate a large charge change on the phenolic oxygen on going from ground state to transition state. For comparison, the ionization of substituted phenols in ethanol has a $\rho$ value of −3.06 ($pK_a$ vs $\sigma^0$).[22] This seems inconsistent with the correlation of rate data with $\sigma^0$ constants, which suggests that there is little S–OAr bond breakage in the transition state.

Haake et al., in a discussion of the alkaline hydrolysis of carboxylate and phosphinate esters,[23] have suggested that, in the ground state, $\pi$ interaction of the alcohol oxygen with the carbonyl or phosphinyl oxygen results in a partial positive charge on the alcoholic oxygen.



$$\left[ R-\overset{\overset{O}{\|}}{C}-\ddot{O}-R' \longleftrightarrow R-\overset{\overset{O^-}{|}}{C}=\overset{+}{O}-R' \right] \quad R-\overset{\overset{O^{\delta-}}{|}}{C}-\overset{\delta+}{O}-R'$$

This is supported by Williams' calculations of effective charge in which the phenolic oxygens of various esters were found to bear a partial positive charge.[24] Effective charges are defined on a scale having the charge on the oxygen of phenol as 0 and the charge on phenolate oxygen as −1. The results of Williams' analysis are shown below.

$$\underset{+0.7}{CH_3C(O)OAr} \qquad \underset{+0.8}{PhS(O)_2OAr}$$

It can be proposed in an analogous fashion that the phenolic oxygen of aryl benzenesulfonates may also bear a partial positive charge in the ground state due to a $\pi$ interaction between the phenolic oxygen and the sulfonyl oxygens. Therefore, the large charge change (large $\rho$ value) on going from ground state to transition state may be accounted for by the change from partial positive charge on the phenolic oxygen (ground state) to near neutral charge (transition state). A large charge change on the phenolic oxygen is not accompanied by bond breakage because the oxygen is electropositive in the ground state.

**Role of Metal Ions.** The observation of metal ion catalysis ($K^+$) and inhibition ($Li^+$) is of considerable interest in the present research. The kinetic data obtained for the reactions of KOEt, LiOEt, and $EtO^-$ with **1a–1f** may be used to gain insight into the origin of the metal ion effects and their relation to the mechanism of reaction.

**Scheme I**

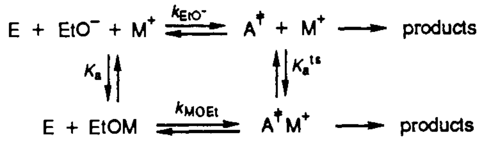
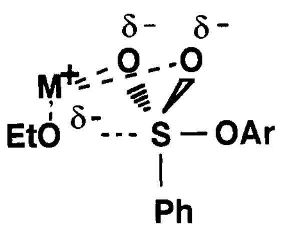


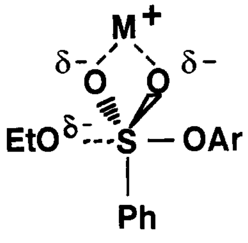
Table III. Theoretical Association Constants ($K_a^{ts}$, $M^{-1}$) for the Interaction of $K^+$ and $Li^+$ with the Transition States and Ground State ($K_a$, $M^{-1}$)[11] in the Reactions of Aryl Benzenesulfonates with Alkali-Metal Ethoxides

| | | $K_a^{ts}$ | | | | | |
|---|---|---|---|---|---|---|---|
| | $K_a$ | 1a | 1b | 1c | 1d | 1e | 1f |
| $K^+$ | 90 | 430 | 501 | 555 | 671 | 700 | 918 |
| Li | 212 | 133 | 157 | 166 | 164 | 170 | 224 |

Ion pairs may be envisioned to react via a "push-pull" interaction in which the metal ion stabilizes developing negative charges on the sulfonyl oxygens while the ethoxide ion attacks the sulfonyl sulfur, as shown below.



**2a**



**2b**

Metal ion stabilization of the transition state exceeds metal ion stabilization of ethoxide ion in the ground state (in the case of potassium ion) due to chelation of the metal ion by a number of ligand oxygens in the transition state and results in catalysis. For lithium ion, transition-state stabilization is envisioned to occur similarly, but in this case ground-state stabilization outweighs transition-state stabilization and inhibition is observed. The reasons for the difference in behavior between potassium and lithium ions is discussed below. Thus, stabilization of the transition state by metal ions is due to chelation of the metal by oxygen atoms in both the alkoxy and sulfonyl moieties. Similarly, Jencks has ascribed catalysis by $Mg^{2+}$ of the attack of acetate ion on phosphorylated $\gamma$-picoline monoanion to chelation of the metal ion by acetate- and phosphoryl-oxygen atoms in the transition state.[25]

As stated previously, the $\rho$ values in Hammett plots of rate vs $\sigma^0$ constants are 3.0 (KOEt), 3.1 (LiOEt), and 3.4 ($EtO^-$). The values of $\rho$ are similar in magnitude, implying that the three reactions have transition states that are similar with respect to the extent of S–OAr bond breakage.[26] Therefore, alkali-metal ions do not significantly alter the nature of the bond to the leaving group in the transition state, to the extent that substituent effects are sensitive to such changes. This conclusion parallels Jencks' findings regarding $Ca^{2+}$ and $Mg^{2+}$ catalysis of transphosphorylation reactions. Bronsted $\beta_{nuc}$ values for the catalyzed reactions (0.21 for $Ca^{2+}$ and 0.17 for $Mg^{2+}$) were found to be practically identical with the uncatalyzed reaction ($\beta_{nuc} = 0.18$) in studies of the attack of substituted pyridines on *p*-nitrophenyl phosphate dianion.[27] It was concluded that all three reactions have essentially the same transition-state structure with respect to the extent of bond formation to the nucleophile. Similarly, it has been found that, in the attack of aryloxides on aryl acetates in DMSO–water mixtures, the structure of the transition state is not affected by changes in solvent composition.[28]

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[22] Guanti, G.; Cevasco, G.; Thea, S.; Dell'Erba, C.; Petrillo, G. *J. Chem. Soc., Perkin Trans. 2* **1981**, 327.

[23] Cook, R. D.; Diebert, C. E.; Schwarz, W.; Turley, P. C.; Haake, P. *J. Am. Chem. Soc.* **1973**, *95*, 8088.

[24] Williams, A. *Acc. Chem. Res.* **1984**, *17*, 425.

[25] Herschlag, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1990**, *112*, 1942.

[26] Strictly speaking, $\rho/\rho_{eq}$ should be used as a measure of the extent of reaction, $\rho_{eq}$ being the Hammett $\rho$ value for substituent effects on the equilibrium constant for the reaction.

[27] Herschlag, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 4665.

[28] Buncel, E.; Um, I. H.; Hoz, S. *J. Am. Chem. Soc.* **1989**, *111*, 971.

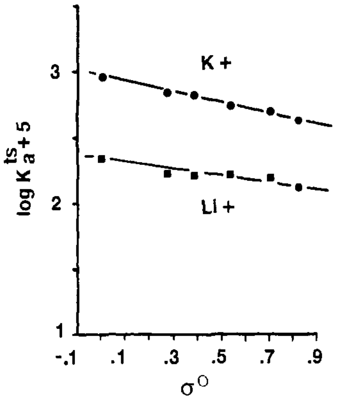

**Figure 3.** Hammett plot of theoretical association constants of $K^+$ and $Li^+$ for the transition states in the reactions of **1a–1f** with use of $\sigma^0$ substituent constants.

The kinetic data for the reactions of alkali-metal ethoxides with **1a–1f** may be analyzed with use of a thermodynamic cycle to yield theoretical association constants for the interaction of $K^+$ and $Li^+$ with the transition states ($K_a^{ts}$) for reaction of ethoxide with the various esters. The reaction mechanism is described as a set of equilibria among the various reactants (the ester E, free and ion-paired ethoxides) and transition states for free ion and ion-paired pathways (Scheme I). $K_a^{ts}$ can be calculated even though there is no direct equilibrium between the two transition states[29] and is obtained from the kinetic data by means of eq 7. $K_a^{ts}$ values

$$K_a^{ts} = \frac{k_{MOEt}K_a}{k_{EtO^-}} \tag{7}$$

for interaction of the various esters with $K^+$ and $Li^+$ were calculated and are compared with their respective $K_a$ values in Table III. Thus, for all esters, $K_a^{ts}(K^+) > K_a(KOEt)$: The potassium ion stabilizes the transition state of the reaction more than it stabilizes ethoxide ion in the ground state and acts as a catalyst. Conversely, $K_a^{ts}(Li^+) \leq K_a(LiOEt)$ for all esters:[30] Lithium ion stabilizes ethoxide ion in the ground state more than it stabilizes the transition state and acts as an inhibitor (cf. ref 31).

These results are similar to the results of our previous measurements of metal ion association to the transition state for the reaction of ethoxide with **1a** in which $K_a^{ts}$ values increased in the order $Li^+ < Na^+ < Cs^+ < K^+$.[1g] This ordering is similar to that expected for association of solvated metal ions with anions: $Li^+ < Na^+ < K^+ < Cs^+$ ($Li^+$, having the largest *solvated* radius, binds least strongly). The free energy of association of metal ions with the transition state for the reaction of ethoxide with **1a** ($\delta G_{ts}$ (where $\delta G_{ts} = -RT \ln K_a^{ts}$)) was found to decrease more or less linearly with the reciprocal of the solvated radius of the metal ion. This relationship and the ordering of $K_a^{ts}$ values was interpreted in terms of interactions of *solvated* metal ions with the transition state.[1g]

In the present study, an analogous ordering of $K_a^{ts}$ values for $Li^+$ and $K^+$ is obtained ($Li^+ < K^+$). As above, interaction of solvated metal ions with the transition state is inferred. If bare metal ions were interacting with the transition state, the ordering would be $Li^+ > K^+$ because $Li^+$, having a smaller *crystal* radius, would bind more strongly owing to its greater charge density.

For both $K^+$ and $Li^+$, association constants increase as the substituent becomes a better electron donor. This is consistent with tighter binding of the cation to a more electron rich transition state (electrostatic interaction). As before, $\sigma^0$ substituent constants give a better correlation than $\sigma$ or $\sigma^-$ constants in the Hammett plot. Plots of log $K_a^{ts}$ vs $\sigma^0$ give $\rho = -0.39$ ($r = 0.995\,39$) for $K^+$ and $\rho = -0.23$ ($r = 0.928\,89$) for $Li^+$ (Figure 3), indicating that the effect of substituents on metal ion binding to the transition state is relatively small.

An interesting deduction arises from the continuing increase of $K_a^{ts}(Li^+)$ as $\sigma^0$ decreases. It follows that, at some $\sigma^0 < 0$, $K_a^{ts}(Li^+)$ will exceed $K_a(LiOEt)$; i.e., $k_{LiOEt}$ will exceed $k_{EtO^-}$, and an inversion of reactivity will occur, with $Li^+$ changing from an inhibitor to a catalyst.

## Conclusions

The present study of the reaction of alkali-metal ethoxides with aryl benzenesulfonates has allowed us to draw a number of conclusions:

(1) The kinetic behavior of alkali-metal ethoxides with aryl benzenesulfonates is qualitatively similar for all esters, with reactivity in the order LiOEt < $EtO^-$ < KOEt. Therefore, $Li^+$ acts as an inhibitor and $K^+$ acts as a catalyst for all esters.

(2) Hammett treatment of leaving-group effects yields a best correlation with $\sigma^0$ substituent constants and $\rho$ values of 3.0 (KOEt), 3.1 (LiOEt), and 3.4 ($EtO^-$).

(3) These results imply that the transition state for the reaction of ethoxide with aryl benzenesulfonates is characterized by well-advanced EtO–S bond formation but negligible S–OAr bond breakage.

(4) While alkali-metal ions lower the energy of the transition state, they do not significantly alter the extent of S–OAr bond breakage in the transition state: KOEt and LiOEt give $\rho$ values similar to that of $EtO^-$.

(5) Association constants for interaction of $Li^+$ and $K^+$ with the transition state for the reaction of ethoxide with **1a–1f** fall in the order $Li^+ < K^+$. This is taken as evidence for interaction of *solvated* metal ions with the transition state.

(6) Hammett plots for the association of metal ions with the transition state (log $K_a^{ts}$ vs $\sigma^0$) indicate that substituent effects on metal ion binding in the transition state are small. More electron rich transition states bind $K^+$ and $Li^+$ more strongly, as expected on electrostatic grounds.

## Experimental Section

**Kinetic Methods.** Reaction rates were measured by following UV-visible absorbance changes due to the release of aryloxide ion with use of Beckman DU-8 and Perkin-Elmer Lambda 5 spectrophotometers. All reactions were carried out under pseudo-first-order conditions with the base in excess (the excess was at least 10-fold and was usually more than 20-fold). Solutions were equilibrated to 25.0 °C in the thermostated cell block of the spectrophotometer and maintained at 25.0 ± 0.1 °C during the reaction. For some long reactions (ca. 1 week), it was necessary to tolerate larger temperature changes, generally ±0.2 °C. It is estimated that the error in any particular measured rate constant is ca. ±3%.

Rate constants were calculated by one of three different methods, depending on the rate of reaction. For relatively fast reactions ($k_{obs} \geq 10^{-4}$ $s^{-1}$), at least 30 absorbance readings spanning 3 half-lives were taken. An infinity absorbance reading was taken after at least 10 half-lives. Rate constants were calculated as the slope of a plot of ln ($A_\infty - A_t$) vs time.

For slower reactions ($10^{-5} \geq k_{obs} \geq 10^{-6}$ $s^{-1}$), the Guggenheim method was used. Typically, 50 or more absorbance readings covering 4 half-lives were recorded. Rate constants were obtained from the slope of plots of ln ($A_{t+lag} - A_t$) vs time. The lag between pairs of data points was taken as half of the data set (2 half-lives), following the suggestions of Kalantar et al.,[32] Bacon and Demas,[33] and Moore and Pearson.[34]

For very slow reactions ($k_{obs} \cong 10^{-6}$ $s^{-1}$), it was not possible to measure absorbances over 4 half-lives. Rate constants were calculated from at least 30 absorbance readings collected during the first half-life. The value for the infinity absorbance was not measured but was varied iteratively until the best correlation coefficient was seen for the plot of ln ($A_\infty - A_t$) vs time. The rate constant was taken as the slope of the line that had

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[29] Kurz, J. L. *J. Am. Chem. Soc.* **1963**, *85*, 987.

[30] It is noted that the vlaue of $K_a^{ts}(Li^+)$ for **1f** is 224 $M^{-1}$, which is greater than $K_a$ for LiOEt (212 $M^{-1}$). A larger association with the transition state relative to the ground state would indicate that $Li^+$ should act as a catalyst, contrary to the observed behavior (the line for LiOEt falls below the line for $EtO^-$ in plots of $k_{obs}$ vs $[MOEt]_0$ for **1f** (Figure 1). However, error analysis shows that the numbers are actually identical within experimental error: $K_a^{ts}(Li^+) = 224 \pm 30$ ($1\sigma$), where $\sigma$ is a unit of standard deviation, and $K_a(LiOEt) = 212 \pm 12$.[11]

[31] a) Buncel, E.; Wilson, H. *J. Chem. Educ.* **1980**, *9*, 629. b) Buncel, E.; Wilson, H. *Acc. Chem. Res.* **1979**, *12*, 42.

[32] McKinnon, G.; Backhouse, C. J.; Kalantar, A. H. *Int. J. Chem. Kinet.* **1985**, *17*, 655.

[33] Bacon, J. R.; Demas, J. N. *Anal. Chem.* **1983**, *55*, 653.

[34] Moore, J. W.; Pearson, R. *Kinetics and Mechanism*, 3rd ed.; Wiley and Sons: New York, 1981.

the highest correlation coefficient. This method of fitting $A_\infty$ to data spanning 1 half-life was compared, with the use of identical data sets, to the Guggenheim method (4 half-lives) and to a method in which $A_\infty$ was calculated with the extinction coefficient of the product aryloxide for the reaction of KOEt with **1f**. Comparison of the two mean rate constants from the $A_\infty$ (fitted) and Guggenheim methods showed that they were not statistically different at the 95% confidence level. However, the scatter in the results (95% confidence level) was about 4% of the mean for the fitted $A_\infty$ method compared to 2% for the Guggenheim method. The fitting method was found to be more accurate than methods that use infinity absorbances calculated from extinction coefficients: The mean rate constant from the $A_\infty$ (calculated) method differed by 12% from the mean rate constant from the Guggenheim method.

Anhydrous ethanol, 18-crown-6, lithium ethoxide, and potassium ethoxide were prepared and/or purified as described previously.[18]

**Synthesis of Aryl Benzenesulfonates.** Six esters were prepared following the general procedure of Davy et al.[35] Benzenesulfonyl chloride (2.6 mL, 0.02 mol) was dissolved in dry ether (100 mL), and redistilled $Et_3N$[36] (5 mL, 0.07 mol) was added. Next, the substituted phenol (0.022 mol) was dissolved in dry ether (100 mL) and added to the acid chloride solution. The reaction mixture was stirred under nitrogen; progress of the reaction was monitored by TLC, the reaction time generally being about 2 days. When the reaction was complete, the reaction mixture was worked up as follows: $Et_3NHCl$ was filtered off and washed with dry ether, and then the ether solution was washed with 5% aqueous HCl solution (4 × 50 mL), 5% aqueous $Na_2CO_3$ solution (6 × 50 mL), and saturated aqueous NaCl solution (3 × 50 mL). The ether solution was dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was either repeatedly recrystallized from ethanol to a constant melting point (**1a**–**1c**, **1f**) or purified by fractional distillation under reduced pressure (**1d**; 146–155 °C at 0.35 mmHg).[37] Purified esters gave excellent $^1H$ and $^{13}C$ NMR spectra and IR spectra, as well as elemental analyses.

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**Registry No. 1a**, 3313-84-6; **1b**, 41076-06-6; **1c**, 132803-38-4; **1d**, 132803-39-5; **1e**, 80-38-6; **1f**, 4358-63-8; KOEt, 917-58-8; LiOEt, 2388-07-0; $K^+$, 24203-36-9; $Li^+$, 17341-24-1; $PhSO_2OCl$, 98-09-9; 18-crown-6, 17455-13-9.

**Supplementary Material Available:** Tables of kinetic data for the reactions of **1a**–**1f** with alkali-metal ethoxides, as well as observed and literature values of melting points of the esters (5 pages). Ordering information is given on any current masthead page.

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(35) Davy, M. B.; Douglas, K. T.; Loran, J. S. A.; Steltner, A.; Williams, A. *J. Am. Chem. Soc.* **1977**, *99*, 1196.

(36) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

(37) See the supplementary material for a comparison of observed and literature values of melting points.

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# Kinetic HH/HD/DH/DD Isotope Effects on Nondegenerate Stepwise Reversible Double Proton Transfer Reactions. NMR Study of the Tautomerism of *meso*-Tetraphenylchlorin

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**Abstract:** The tautomerism of *meso*-tetraphenylchlorin-$^{15}N_4$ (TPC) has been studied by dynamic $^1H$ NMR spectroscopy. Only two degenerate tautomers of TPC, AC and CA, are observed whose structure corresponds to 5,10,15,20-tetraphenyl-7,8-dihydroporphyrin. Thus, the IUPAC name 5,10,15,20-tetraphenyl-2,3-dihydroporphyrin proposed for TPC is incorrect. Both tautomers interconvert via a mutual proton exchange process along two different routes. The rate constants of the tautomerism are given by $k^{HH}_{AC\to CA} = 10^{11.4\pm0.2}\exp(-58.4 \pm 1.4\ \mathrm{kJ\ mol^{-1}}/RT)$, $298\ \mathrm{K} \le T \le 406\ \mathrm{K}$, $k^{HH}_{AC\to CA}(298) \approx 15\ \mathrm{s^{-1}}$, and $k^{HD}_{AC\to CA} = 10^{11.5\pm0.3}\exp(-61 \pm 2\ \mathrm{kJ\ mol^{-1}}/RT)$, $329\ \mathrm{K} \le T \le 411\ \mathrm{K}$, $k^{HD}_{AC\to CA}(298) \approx 5.8\ \mathrm{s^{-1}}$, with an unusually small kinetic HH/HD isotope effect of $k^{HH}_{AC\to CA}/k^{HD}_{AC\to CA} \approx 2.6$ at 298 K. A theory of kinetic HH/HD/DD isotope effects for nondegenerate stepwise reversible double proton transfer reactions is described that can accommodate these kinetic results. Thus evidence is obtained that the proton transfer mechanism in TPC is stepwise as in the case of porphyrins. The analysis leads to the following conclusions. Both proton exchange routes are equivalent in the case of TPC-$H_2$ but nonequivalent in the case of TPC-HD. In the HD reaction a H isotope is in flight in the rate-limiting step of route i but a D isotope is in flight in the rate-limiting step of route ii. Therefore, the D route contributes only to a minor extent to the HD reaction. The observed kinetic HH/HD isotope effect arises, therefore, not from an intrinsic kinetic isotope effect but from the circumstance that in the HH case there are two equivalent H reaction routes and in the HD case there is only one H reaction route.

## Introduction

Using dynamic NMR spectroscopy it has been possible in recent years to measure full kinetic HH/HD/DD isotope effects of degenerate intra- and intermolecular double proton transfer reactions of the type shown in Figure 1.[1–7] In all cases deviations from the so-called "rule of the geometric mean" (RGM) were observed. The latter states for the isotopic rate constants that[2,8–12]

$$k^{HD} = k^{DH} = (k^{HH}k^{DD})^{1/2}, \quad \text{i.e.,} \quad k^{HH}/k^{HD} = k^{HD}/k^{DD} \qquad (1)$$

This rule is expected to be valid in good approximation for concerted double proton transfers, not only for the degenerate case

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(1) Limbach, H. H. Dynamic NMR Spectroscopy in the Presence of Kinetic Hydrogen/Deuterium Isotope Effect. In *NMR-Basic Principles and Progress*; Springer: Heidelberg, 1991; Vol. 23, pp 63–164.

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