Alkali-metal Ion Catalysis and Inhibition in Nucleophilic Displacement Reactions of Phosphorus-, Sulfur- and Carbon-based Esters

M. J. Pregel, E. J. Dunn, R. Nagelkerke, G. R. J. Thatcher and E. Buncel*
Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6

1 Introduction

Selectivity among alkali-metal ions is a feature of a number of important biological processes. High potassium-ion and low sodium-ion concentrations are maintained in mammalian cells by Na^+–K^+ pumps which consume one third to one half of the ATP required by the resting cells.[1,2] Selective transport of these ions across membranes by Na^+–K^+ ATPase enzymes creates ionic concentration gradients which control cell volume, allow for the excitability of nerve and muscle cells, and drive the active transport of sugars and amino acids across cell membranes.[1] Transport by the enzyme involves phosphate transfer from ATP to form a phosphoenzyme, a process that requires Na^+ and Mg^{2+} to proceed and whose reversal is catalysed by K^+.[3]

Nerve impulses are electrical signals produced by the flow of alkali-metal ions across the plasma membrane of neurons. The action potential arises from large, selective, and transient changes in the permeability of the axon membrane to Na^+ and K^+.[1] These fluxes are created by ion channels; the sodium channel selects for Na^+ by providing a negatively-charged site with a small radius. The creation of artificial ion channels that mimic this process is a subject of current interest,[4,5] as is the understanding of alkali-metal ion selectivity in chemical systems, where the same or similar underlying principles must come into play.

The importance of acyl, phosphoryl and sulfuryl group-transfer reactions in living systems is indisputable. The transfer of the acetyl group from acetyl coenzyme A, a central molecule in metabolism, is used to generate ATP by the citric acid cycle and oxidative phosphorylation.[1] The transfer of a phosphoryl group between ATP and ADP is the fundamental mechanism for energy transfer, and coupling to ATP hydrolysis is used to drive many unfavourable reactions. Phosphoryl transfer is also the fundamental process in the assembly and transcription of the genetic code. Metal-ion catalysis

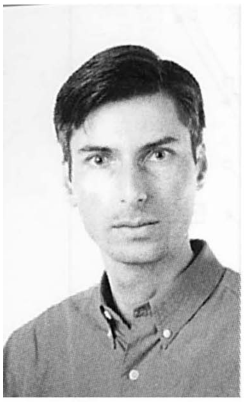
Marko Pregel completed his Ph.D. in 1990, then did postdoctoral work on artificial ion channels in the lab of Prof. Jean-Marie Lehn at the Collège de France on a NATO Science Fellowship. He is currently a Research Associate at the Biotechnology Research Institute (National Research Council, Canada) with interests in the regulation of protein tyrosine phosphatases in cellular signal transduction.

Edward Dunn obtained his Ph.D. in 1985 and became a Visiting Fellow and Defence Scientist at Defence Research Establishment Ottawa, then an Ontario Ministry of Health Fellow at McMaster University. Dr. Dunn is a certified clinical chemist who has been an Assistant Professor of Pathology at McMaster University since 1993. His current research interests are in the areas of neurochemistry and neuropsycho-pharmacology.

Ruby Nagelkerke received her Ph.D. in 1993. She is currently an NSERC Postdoctoral Fellow in the laboratory of Prof. Weston T. Borden at the University of Washington doing computational studies on homoaromatic compounds.

Greg Thatcher is a native of Brighton, England and received his first degree in Chemistry at the University of Manchester. After completing a Ph.D. with Ron Kluger at the University of Toronto, he spent a brief postdoctoral stint with Mike Blackburn at Sheffield before taking up a SERC Fellowship at Oxford with Gordon Lowe. Since 1988 he has been on faculty at Queen's conducting research, sometimes with the cooperation of his group, on the mechanistic, biological and medicinal chemistry of assorted phosphates, sulfates, nitrates, flustrates and phosphonoformates.

Erwin Buncel was born in Czechoslovakia, but educated in England. He received the B.Sc. and Ph.D. degrees from the University of London, the latter under the supervision of Professor Alwyn Davies, on organic peroxides of silicon. He then crossed the ocean for a postdoctoral year at the University of North Carolina with Joe Bunnett, where he was introduced to the fascinating world of aromatic azo ether hydrolysis. Going up North as a National Research Council of Canada postdoctoral fellow to work with Arthur Bourns at McMaster University, enlightened him to the clues that isotopic substitution held in reaction mechanisms. Buncel then returned to the United States for a brief period as a research chemist at American Cyanamid Central Reseeach Labs in Stamford, CT, where he learned much from the insight of Edwin Ullman. In 1962, opportunity arose to accept a faculty position at Queen's University, with promotions to Associate (1966) and Full Professor (1970). At Queen's, Buncel developed various career-long avenues of investigation in physical organic, bioorganic, and bioinorganic chemistry, with the devotion of 50 graduate students and numerous postdoctoral fellows, who made possible the publication of about 250 research papers, reviews and book chapters, as well as two books. Buncel was the recipient of the Syntex Award of the Canadian Society for Chemistry in 1985. Of great challenge have been his editorial activities, for the Canadian Journal of Chemistry (1981–1993) and currently for the Journal of Labelled Compounds and Radiopharmaceuticals. Buncel looks to continuing challenges that the world of chemistry holds.



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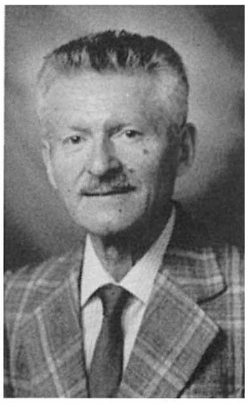


Erwin Buncel

is important in both chemical and biological group-transfer reactions and much effort has been directed at studies, particularly on the mechanism of catalysis of phosphoryl transfer.[6]

2 Alkali-metal Ion Catalysis and Inhibition

We have been involved in a systematic study of alkali-metal ion selectivity in the reaction of ethoxide ion with a series of carbon-, phosphorus- and sulfur-based esters which has revealed a number of interesting and varied selectivity patterns under a common set of experimental conditions.[7—16] It is our belief that understanding of the factors responsible for selectivity in this system will clarify the factors at play in both chemical and biological systems.

In the course of the study, a number of structural parameters were varied: diphenylphosphinate, dimethylphosphinate, methylphenylphosphinate, phenyl phosphonate, diphenyl phosphate, benzenesulfonate, methanesulfonate and benzoate esters were studied (Figure 1). Aromatic leaving groups were used in all cases, allowing leaving-group variation to give insight into transition-state structure for representative examples of each family of esters. For each ester, the rates of reaction with alkali-metal ethoxides (LiOEt, NaOEt, KOEt, CsOEt) in anhydrous ethanol at 25 °C were measured spectrophotometrically.

In all cases, the alkali-metal ethoxides had differing reactivities and curved plots of observed rate constant *vs.* total base concentration were observed (Figure 2). The reactivity of free ethoxide ion was evaluated by addition of crown-ether or cryptand complexing agents. In each case, addition of an excess of an appropriate complexing agent to LiOEt or KOEt gave identical reactivity corresponding to the reactivity of free ethoxide ion and a nearly linear plot of rate constant *vs.* base concentration. Addition of unreactive alkali-metal salts was seen to have effects opposite to addition of complexing agents. For the phosphorus-based esters, alkali-metal ions were uniformly catalytic, with reactivities following the order LiOEt > NaOEt > KOEt > CsOEt > EtO$^-$, but with magnitudes that varied from one series of esters to the next. The ordering was different for the aryl ben-

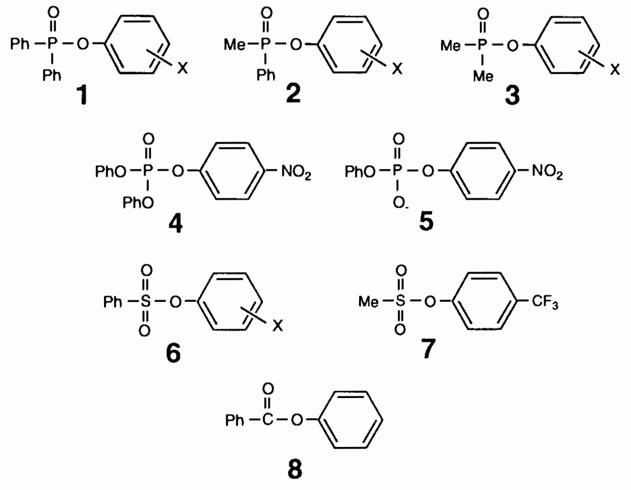


Figure 1 Esters used as substrates for reaction with alkali-metal ethoxides.

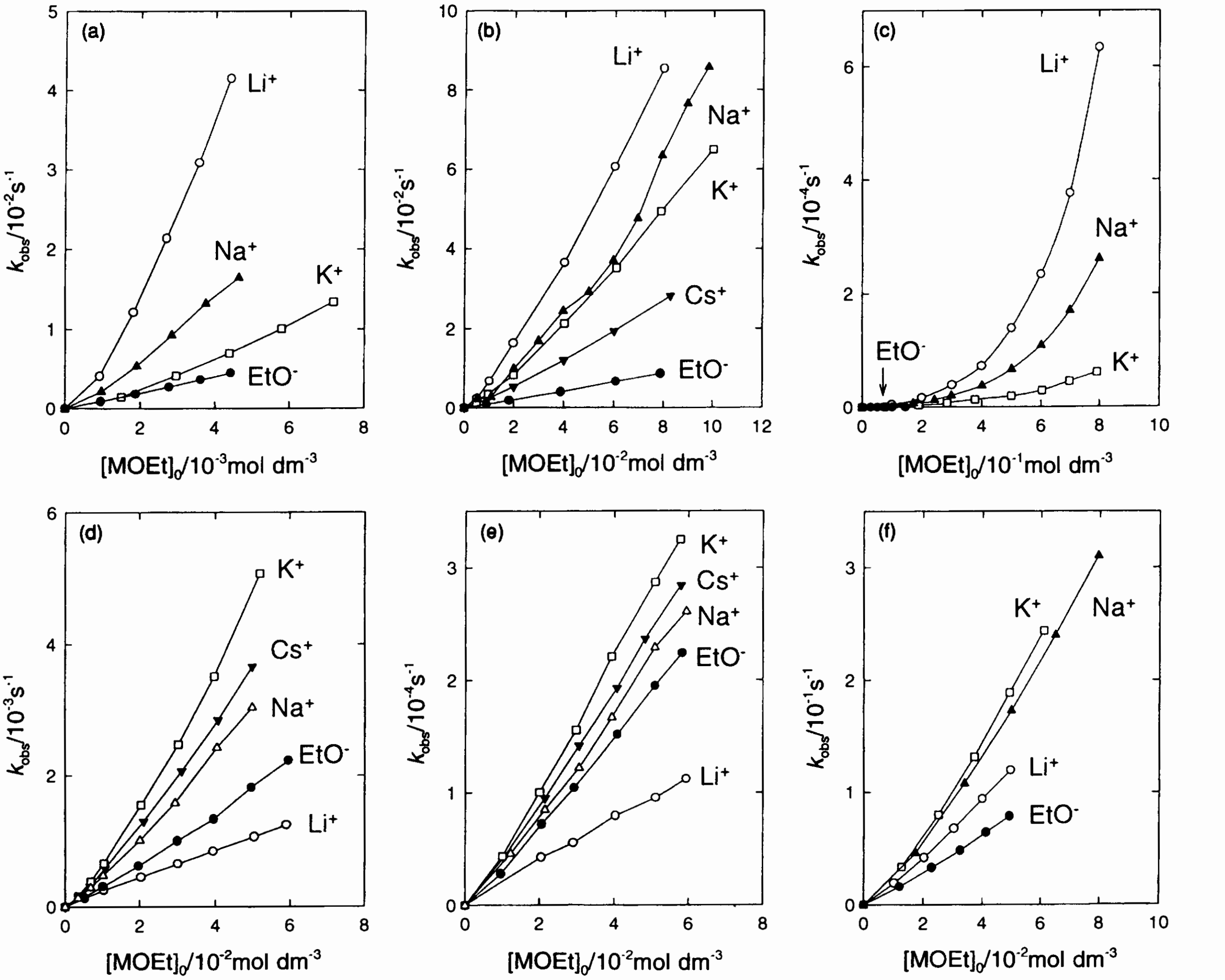


Figure 2 Plots of observed pseudo-first-order rate constant *vs.* total alkali concentration for the reaction of (*a*) **1**, (*b*) **4**, (*c*) **5**, (*d*) **6**, (*e*) **7**, and (*f*) **8** with alkali-metal ethoxides in anhydrous ethanol at 25 °C. Phosphinate esters **2** and **3** give reactivity patterns identical to that of **1**.

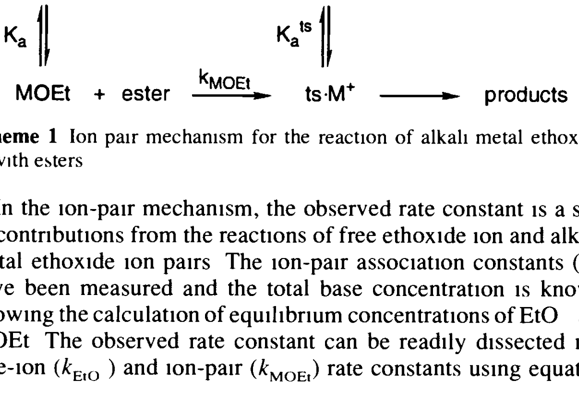
zoate esters: KOEt > NaOEt > LiOEt > EtO$^-$, with much smaller differences in reactivity. Interestingly, the sulfonate esters gave rise to a selectivity pattern which was different again: KOEt > CsOEt > NaOEt > EtO$^-$ > LiOEt. Moreover, it was seen that lithium ion, a catalyst in reactions with other families of esters, acted as an inhibitor. Thus, a spectrum of different metal-ion effects is seen as the structure of the substrate is altered. The role of lithium ion is noteworthy, as it changes from being the most effective catalyst to being an inhibitor of the reaction as the structure of the substrate is varied.

Interesting metal-ion selectivities have also been observed by Mandolini and coworkers in the reaction of hexanoate ion with the *p*-nitroaryl acetate crown ether 2-AcO-5-NO_2-18C5 where Li^+ caused strong inhibition, Na^+ had little effect and the other alkali-metal ions were catalytic in the order $K^+ > Rb^+ > Cs^+$.[17] Similarly, alkali-metal-ion catalysis has been observed in the reaction of iodide with methyl bis(3-nitrophenyl)phosphinate: LiI > NaI > KI > Bu_4NI (S_N2 reaction at carbon), the same ordering as in the reaction of aryl phosphinate esters in the present study (nucleophilic displacement at phosphorus).[18]

3 Effects of Ion Pairing on Reactivity

In polar solvents, salts exist as free ions in solution. As solvating power decreases, ion–solvent interactions become weaker. At some point, electrostatic interactions between ions compete effectively with ion–solvent interactions, leading to the formation of ion pairs. Thus, in solvents of moderate polarity, such as anhydrous ethanol used in the present study, there exists an equilibrium between free (solvated) ions and ion pairs. Further decreases in solvent polarity result in greater degrees of association, with the formation of triple ions, dimers, and higher aggregates.[19]

Alkali-metal ethoxides in ethanol exist as an equilibrium mixture of free ions and ion pairs at low total alkali concentration (10^{-2} mol dm^{-3}). We have treated the reaction of alkali-metal ethoxides with esters in terms of parallel reactions of free ions and ion pairs (Scheme 1). An alternative, kinetically-indistinguishable mechanism involving reaction of ethoxide ion with a metal-complexed ester is considered less likely in view of the demonstrated effects of ion pairing on reactivity in other systems and a lack of evidence for complexation of the esters used here.[10]



Scheme 1 Ion pair mechanism for the reaction of alkali metal ethoxides with esters

In the ion-pair mechanism, the observed rate constant is a sum of contributions from the reactions of free ethoxide ion and alkali-metal ethoxide ion pairs. The ion-pair association constants (K_a) have been measured and the total base concentration is known, allowing the calculation of equilibrium concentrations of EtO$^-$ and MOEt. The observed rate constant can be readily dissected into free-ion (k_{EtO^-}) and ion-pair (k_{MOEt}) rate constants using equation 1.

$$k_{obs} = k_{EtO^-}[EtO^-] + k_{MOEt}[MOEt] = k_{EtO^-}[EtO^-] + k_{MOEt}K_a[EtO^-]^2 \quad (1)$$

Free-ion and ion-pair rate constants were obtained by plotting $k_{obs}/[EtO^-]$ *vs.* $[EtO^-]$; they are summarized in Table 1. Values of k_{EtO^-} were in good agreement with rate constants measured in the presence of complexing agents. In cases where $k_{MOEt} > k_{EtO^-}$, addition of complexing agent caused a reduction in reaction rate and conversely addition of alkali-metal salts caused a rate increase. When $k_{MOEt} < k_{EtO^-}$, the opposite behaviour was observed. In the case of added salts, the rate constants in the presence of added salt were in good agreement with those predicted from the rate constants for free ions and ion pairs together with the ion-pair association constants of the alkali-metal ethoxide and the alkali-metal salt.[10]

Since the ion-pair association constants are all greater than unity, the proportion of ion pairs increases as the total base concentration increases and the balance between free-ion and ion-pair pathways changes in favour of the ion-pair pathway. Thus, upward curvature in plots of the observed rate constant *vs.* total base concentration reflects greater reactivity of ion pairs relative to free ions ($k_{MOEt} > k_{EtO^-}$), and the converse is also true.

Table 1 Free-ion and ion-pair rate constants (k/dm^3 mol^{-1}s^{-1}) for the reaction of alkali-metal ethoxides with esters in ethanol at 25 °C

Ester	EtO$^-$	LiOEt	NaOEt	KOEt	CsOEt
1	0.980	24.0	11.6	4.84	1.89
2	55.8	492	—	184	—
3	251	640	—	279	—
4	0.105	1.36	1.03	0.852	0.421
6	0.0287	0.0180	0.080	0.137	0.097
7	0.0030	0.0015	0.0055	0.0074	0.0060
8	0.127	0.306	0.550	0.584	0.481

The differential reactivities of ion pairs and free ions can be better understood by reference to two examples. In the reaction of sodium ethoxide with methyl iodide in 10% dioxane–ethanol, the observed second-order rate constant decreased with total alkali concentration: ion pairs were much less reactive than free ions.[20] In the ground state, metal ions can interact strongly with ethoxide ion to form ion pairs while in the transition state, the negative charge is delocalized over the ethoxide nucleophile and iodide leaving group, making the transition state a poorer ligand. Since stabilization of the ethoxide nucleophile by metal ions in the ground state outweighed stabilization of the transition state, the net result was inhibition by metal ions.

Catalysis *via* ion pairs results when the transition state for the reaction is stabilized by metal ions to a greater extent than the ground state.[19,21–23] In the reaction of alkali- metal ethoxides with *p*-nitrophenyl diphenylphosphinate, metal-ion stabilization of the nucleophile is outweighed by stabilization of the transition state in which the metal ion may be chelated by two oxygen ligands (see below). Catalysis *via* chelation of metal ions in the transition state has been previously observed.[24]

Catalysis by multiple metal ions can also be observed in cases where the transition state has multiple sites for interaction. This appears to be the case for *p*-nitrophenyl phenylphosphonate monoanion (**5**), in which the pseudo-first-order rate constant for the reaction of LiOEt, NaOEt, and KOEt showed higher-order dependencies (fourth- to sixth-order) on total alkali concentration (Figure 1) than was possible in the simple ion-pair–free-ion mechanism described above (first- and second-order dependency on $[EtO^-]$, equation 1).[16] In this case, metal-ion coordination to the anionic ester substrate as well as to ethoxide ion appears likely. Clearly, transition-state stabilization greatly outweighs ground-state stabilization. We infer from the higher-order dependencies that the transition state must contain multiple metal ions and/or ethoxide ions.

4 Mechanism of Reaction

In order to determine whether the differing metal-ion effects were related to differences in reaction mechanism, the results for leaving-group variation in series of aryl phosphinate,[7] sulfonate[13] and benzoate[7] esters were assessed (Table 2). In all cases, the reaction rate was very sensitive to nucleofugality and Hammett treatment resulted in large ρ values, indicating a large redistribution of charge onto the leaving group upon formation of the transition state. Correlations with σ^0 and σ substituent constants were much better than with σ^- substituent constants. For example, in the reaction of ethoxide ion with aryl benzenesulfonate esters, plots of log k_{EtO^-} *vs.* substituent constants gave correlation coefficients of 0.999 (σ^0), 0.996 (σ), and 0.937 (σ^-).[13] This demonstrates that resonance delocalization of negative charge onto the leaving group (which would result in a correlation with σ^- constants) was not occurring, in apparent contradiction to the conclusion from the ρ values. However, a significant increase in charge on the aryl oxygen, consistent with a large ρ value, can occur without resonance delocalization of that charge onto aryl substituents (σ/σ^0 correlation) if the aryl oxygen bears a partial positive charge in the ground state. This could arise by a π interaction between the aryl oxygen and the oxygen(s) double bonded to the central phosphorus, carbon or sulfur atom of the ester.[25]

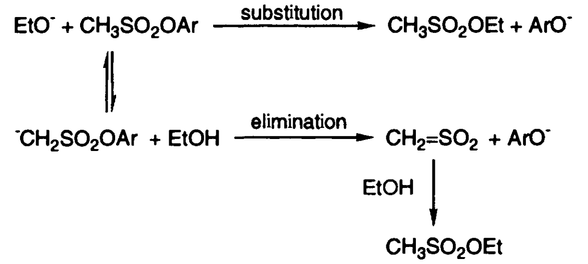
Table 2 Hammett ρ values (ρ^0 substituent constants) for leaving-group variation in the reactions of alkali-metal ethoxides with aryl esters of phosphorus-, carbon- and sulfur-based acids.

Ester	EtO^-	LiOEt	KOEt
1	2.6	2.8	2.3
2	2.8	3.1	2.6
3	3.0	3.2	2.6
6	3.4	3.1	3.0
8	2.2	2.0	1.8

In all cases, the mechanism of reaction may be characterized as associative with a transition state in which nucleophilic attack is well-advanced but leaving-group bond breakage is minimal. Comparable behaviour has been reported for the hydrolysis reactions of aryl benzenesulfonates and aryl tosylates.[26]

When Hammett plots for free ethoxide ion were compared to those for KOEt and LiOEt ion pairs, similar behaviour including large ρ values and σ/σ^0 correlations was noted for all three nucleophiles in all cases (Table 2). Thus, the important conclusion can be drawn that alkali-metal ions do not significantly perturb transition-state structure in reactions of these esters. This conclusion parallels findings related to Ca^{2+} and Mg^{2+} catalysis of transphosphorylation reactions, in which Brønsted β_{nuc} values for the metal-ion-catalysed reactions were nearly identical to that of the uncatalysed reaction.[24a]

In the case of methanesulfonate esters, a detailed analysis of the mechanism of reaction revealed a change in mechanism as nucleofugality decreased:[12] *p*-nitrophenyl methanesulfonate reacted predominantly by an *E*1*cb* elimination mechanism *via* a sulfene intermediate with nucleophilic substitution as a minor concurrent pathway (Scheme 2) and displayed unusual catalysis by a cryptand-complexed potassium ion.[16] The *m*-nitro-substituted ester reacted predominantly by substitution and the available evidence was consistent with a nucleophilic substitution at sulfur as the sole pathway for reaction of *p*-trifluoromethylphenyl methanesulfonate with alkali-metal ethoxides. Therefore, it was appropriate to compare metal-ion effects on the reaction of this ester to those on the other esters discussed here.



Scheme 2 Parallel *E*1*cb* elimination and nucleophilic substitution mechanisms observed in the reactions of alkali-metal ethoxides with *p*- and *m*-nitrophenyl methanesulfonate esters.

A number of the phosphorus-, carbon- and sulfur-based esters identical or similar to those we considered have also been studied by Williams and coworkers, who investigated reactions in aqueous solution with aryloxide ions and other weak nucleophiles. These include aryl diphenylphosphinates, aryl dimethylphosphinates, aryl diphenylphosphates, aryl *p*-nitrobenzenesulfonates, aryl toluenesulfonates and aryl acetates.[27] The extents of bond formation to the nucleophile and bond breakage to the leaving group in the transition state were measured using Brønsted β_{nuc}, β_{lg}, and β_{eq} parameters. The pK_a values of the nucleophiles were varied above and below the pK_a of the leaving group without the observation of a break in the plot of log k vs. pK_{nuc}, indicating no change in rate-determining step and that a concerted mechanism was operating.[27d] For symmetrical reactions (identical nucleophile and leaving group), the data were consistent with loose or 'exploded' transition states with well-advanced bond breakage but little bond formation.

The major difference between these studies and our own is the use of aryloxide ions as both nucleophiles and leaving groups (poor nucleophiles, good leaving groups). Our work used a strong nucleophile (ethoxide ion) and good leaving groups (aryloxide ions). The use of a nucleophile of greater basicity was predicted by Williams to shift the transition state towards a structure having bond formation further developed than bond breakage, so the differing transition-state structures observed by the two groups refer to different points on the same potential-energy surface.[27f] Our findings do not allow us to determine whether the reaction proceeds by a concerted or by a stepwise mechanism, but serve to characterize the extents of bond formation and bond breakage in the transition state.

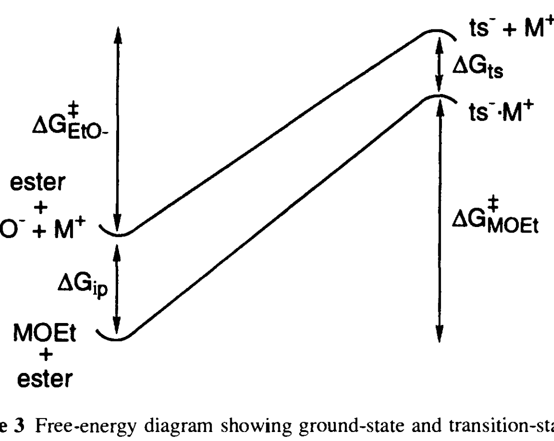
5 Stabilization of the Ground State and the Transition State

Since the different families of esters react *via* transition states in which nucleophilic attack has proceeded to a greater extent than leaving-group departure and alkali-metal ions do not significantly perturb transition-state structure, we sought to quantify the catalytic and inhibitory effects of metal ions and to compare their effects on the transition state of the reaction for the different esters. A thermodynamic cycle may be used to calculate a virtual association constant (K_a^{ts}) which governs interaction of metal ions with the transition state (Scheme 1; equation 2).[21,28,29] In free energy terms,

$$K_a^{ts} = k_{MOEt} K_a / k_{EtO} \qquad (2)$$

the stabilization of the ground state (ΔG_{ip}) and the transition state (ΔG_{ts}) by metal ions are related to the free energies of activation in the absence ($\Delta G_{EtO}{}^{\ddagger}$) and presence of metal ions ($\Delta G_{MOEt}{}^{\ddagger}$) as described in Scheme 3 and equation 3.

$$\Delta G_{EtO}{}^{\ddagger} - \Delta G_{ip} = \Delta G_{MOEt}{}^{\ddagger} - \Delta G_{ts} \qquad (3)$$



Scheme 3 Free-energy diagram showing ground-state and transition-state stabilization by metal ions in the reaction of alkali-metal ions with esters.

Since alkali-metal ethoxides are the nucleophiles in all cases and interactions between metal ions and the neutral esters are assumed to be negligible, ground-state stabilizations are identical for all families of esters. Therefore, the differing selectivity patterns must arise from differences in transition-sate stabilization by metal ions. The free energies of stabilization for ground state and transition state are compared graphically in Figure 3. In cases where transition-state stabilizations are much larger than ground-state effects, *e.g.*, phosphinate esters, trends in ΔG_{ts} values are identical to the reactivity

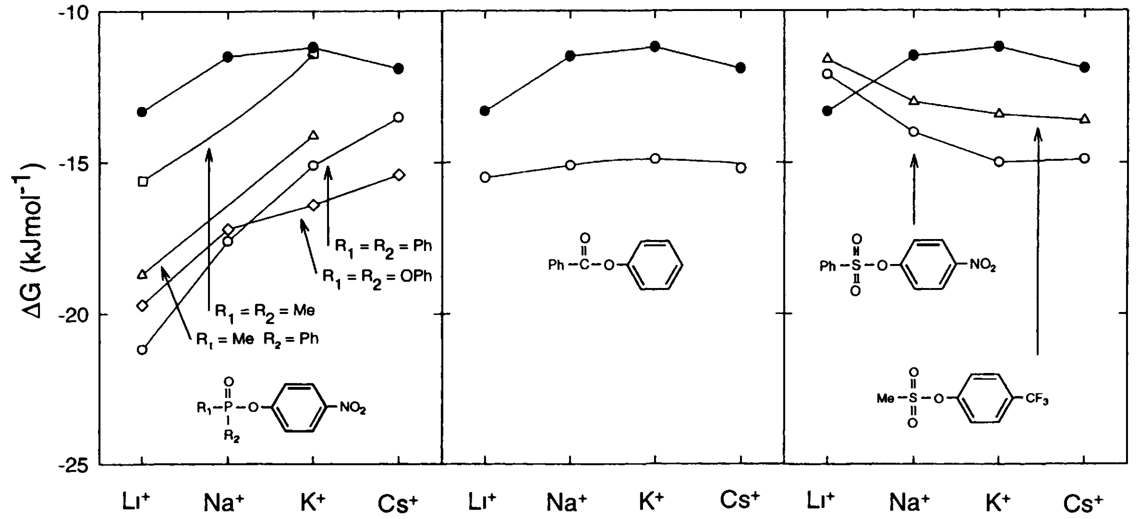


Figure 3 Graphical comparison of metal ion stabilization in the ground state (filled circles) and transition states (open circles) of reaction of alkali metal ethoxides with esters **1—4**, **6—8**

sequences of the corresponding alkali-metal ethoxides When ground-state and transition-state stabilizations are comparable in size, as in the case of the sulfonate esters, the patterns are not always identical because ground-state effects have been removed from the overall (kinetic) effects to arrive at transition-state effects (equations 2 and 3) It may be seen that the trend in the transition-state stabilizations changes from a strong preference for smaller ions for the phosphorus-based esters ($Li^+ > Na^+ > K^+ > Cs^+$), to a situation where there is little selectivity for the benzoate ester, to a preference for larger ions for the sulfonate esters ($Cs^+ > K^+ > Na^+ > Li^+$)

Mandolini and coworkers analysed their kinetic data for the reaction of hexanoate with their crown-ether substrate in a similar fashion equilibrium constants for association of M^+ with hexanoate ion in the ground state were compared to association constants for the transition state Transition-state selectivity was low but a preference for K^+ was seen in accord with the hole size of the 18-crown-6-like substrate [17]

Differing selectivity patterns for alkali-metal ions have also been observed for ion-exchange resins and glass electrodes and have been interpreted elegantly by Eisenman [30] In the Eisenman theory of ion-exchange selectivity, two opposing factors govern the strength of the interaction between a cation and a fixed ionic group the energy gained when ions of opposite charge approach one another (electrostatic interactions), and the energy expended to rearrange solvent around the ions to permit close contact (solvent rearrangement) The latter term would be closely related to the difference in the solvation energies of the ions Thus, the overall free energy change for interchange of cations 1 and 2 ($\Delta G°_{1/2}$) at a fixed anionic site is given by the differences in electrostatic interaction and solvent rearrangement terms as shown in equation 4, where e is the electronic charge, r_1 is the radius of cation 1, r_2 is the radius of cation 2, r_A is the radius of the anion, and ΔG_1 and ΔG_2 are the solvation energies of cations 1 and 2

$$\Delta G°_{1/2} = [e^2/(r_A + r_2)] - [e^2/(r_A + r_1)] - (\Delta G_2 - \Delta G_1) \quad (4)$$

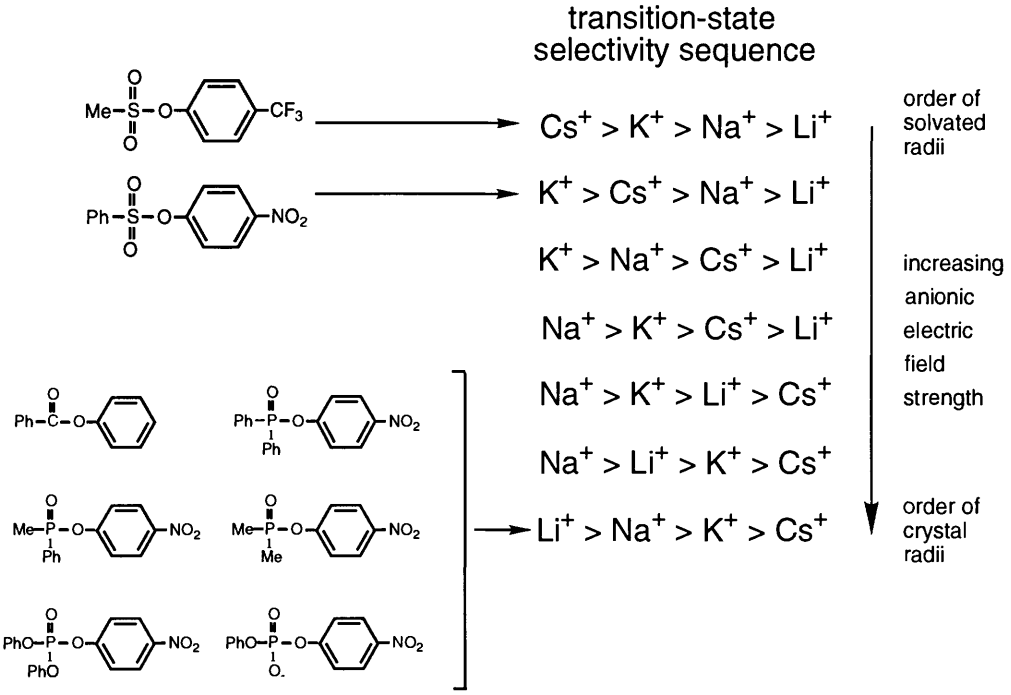
For an anionic group with a high electric-field strength (localized charge), the electrostatic term is dominant electrostatic attraction is greater than the solvation energy of the cation and the ions come into direct contact Smaller cations are bound most strongly $Li^+ > Na^+ > K^+ > Cs^+$, as predicted by Coulomb's law This selectivity pattern is observed for carboxylate ion-exchange resins and is consistent with the size and charge density of this group Such a pattern in transition-state stabilization is followed for all of the phosphorus-based esters and the relationship was seen to be essentially quantitative for *p*-nitrophenyl diphenylphosphinate, with a linear relationship between $\Delta G_{ts}(M^+)$ and the inverse of the crystal radius of M^+ [10]

For an anionic group with low electric-field strength (delocalized charge), electrostatic attraction cannot overcome the solvation of the cation The solvation term is dominant and the selectivity $Cs^+ > K^+ > Na^+ > Li^+$ is determined by the solvation energies of the cations The sulfonate group (RSO_3^-) is believed to have low electric field strength and many ion-exchange resins containing sulfonate groups have given this selectivity sequence,[30] parallelling the sequence observed for the sulfonate transition states in the present work In the case of *p*-trifluoromethylphenyl methanesulfonate, a linear relationship between $\Delta G_{ts}(M^+)$ and the inverse of the solvated (Stokes) radius of M^+ was observed [11]

The two examples above define limiting cases of charge-localized and charge-delocalized anions As the electric-field strength of the anion is varied between these extremes, intermediate selectivity sequences are observed Eisenman predicted a spectrum of seven selectivity sequences for the four cations which result from variation of the electric-field strength or charge density of the anionic group from one extreme to the other (Scheme 4) These sequences have been shown to have a wide natural occurrence many experimentally-observed selectivity sequences including those of ionophore antibiotics, crown ethers,[31] and artificial ion channels[5] are among the predicted sequences The sequences for the transition states for reaction of the phosphorus-based esters all fall at the high electric-field strength end of the spectrum, while sulfonate ester transition state selectivities are at the opposite extreme The selectivity pattern for the benzoate transition state nominally falls in the region of high electric-field strength, as might be expected by analogy to carboxylate-based ion-exchange resins (Scheme 4) However, in this case the differences in transition-state stabilization between metal ions are small enough to be comparable in size to the experimental error in the measurement, making an unambiguous assignment difficult Thus, if this theory is correct, the different alkali-metal ion effects in these systems arise from differences in the electric-field strengths of the transition states for reaction of ethoxide ion with the esters high electric-field strength transition states are produced upon reaction of the phosphinate esters and low electric-field strength transition states result from reaction of the sulfonate esters To our knowledge, this is the first application of the Eisenman theory to transition-state stabilization The simplicity of the theory, based on competing electrostatic interactions and solvent rearrangements, suggests that it could have widespread applications in the understanding of transition-state effects and metal-ion catalysis

6 Theoretical Studies of Transition-State Stabilization

As a complement to the kinetic studies, theoretical calculations were used to reveal the intrinsic properties of the transition states Gas-phase interactions between metal ions and truncated ground-



Scheme 4 Eisenman alkali-metal ion selectivity sequences as a function of anionic electric-field strength and their correspondence with observed transition-state selectivities in the reactions of alkali-metal ions with various esters.

state and transition-state models were calculated at the *ab initio* HF/3—21+G* level for the reactions of the phosphinate and sulfonate esters. The transition states were modelled by the five-coordinate intermediates resulting from attack of hydroxide ion on H_3PO_2 and H_2SO_3, and energies, geometries and charge distributions of the intermediates were calculated in the presence and absence of Li^+ and Na^+.

In the absence of metal ions, trigonal bipyramidal structures were observed with significant negative charge localized on all the oxygens (Figure 4). Studies of the interactions of metal ions with these species revealed a number of interesting similarities and differences. Metal ions were chelated by apical and equatorial oxygens of the phosphorane and by two equatorial oxygens of the sulfurane. More stable complexes were formed with the phosphorane than the sulfurane, and in both cases Li^+ formed stronger complexes than Na^+, but the difference [ΔE(Na^+ complex) − ΔE(Li^+ complex)] was smaller for the sulfurane than for the phosphorane (Figure 5).

The calculations provide a plausible explanation for how metal ions bind more strongly to the transition state than to ethoxide ion: chelation by two oxygens bearing almost full negative charges in the transition state results in greater stabilization than interaction with a single negative charge on ethoxide ion. Also, these initial results may be interpreted to support the Eisenman theory detailed above: overall, the sulfurane appears to have a lower intrinsic affinity for metal ions than the phosphorane. However, it should be noted that no significant differences in the degree of charge delocalization between the phosphorane and sulfurane (which would lead to different selectivity patterns in the Eisenman scheme) were revealed by these calculations. Further calculations examining other differences in these systems including absolute hardness and electronegativity are in progress.

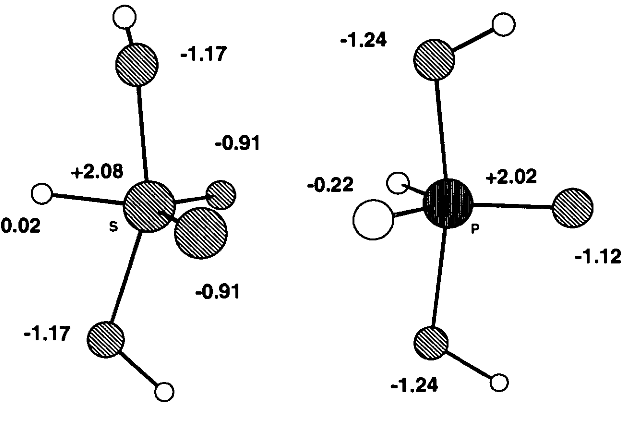


Figure 4 Structures and charge distributions of sulfurane and phosphorane intermediates from *ab initio* calculations.

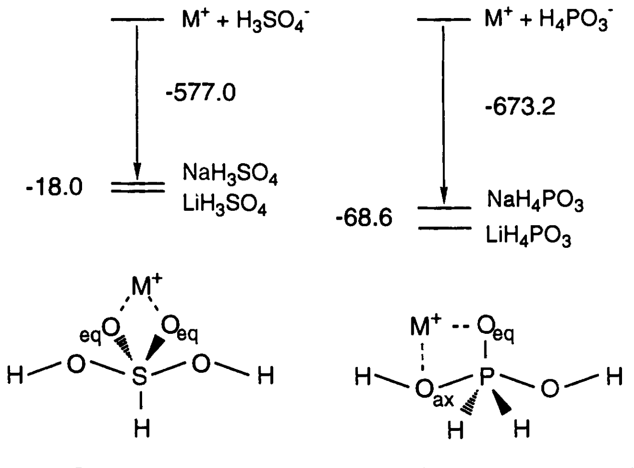


Figure 5 Free energies (kJ mol^{-1}) for the stabilization of sulfurane and phosphorane intermediates by Li^+ and Na^+ and the geometries of the complexes from *ab initio* calculations.

It is interesting that the calculations revealed differences in the geometry of metal-ion complexation between the two systems. For the phosphorane, the metal ion was in the apical–equatorial plane and complexation polarized and lengthened the $P-O_{apical}$ bond. In contrast, the metal ion was in the equatorial plane of the sulfurane and complexation compressed the equatorial O—S—O angle. Such compression would be expected to induce bond-angle-bending strain in the σ-framework in addition to increased destabilizing electrostatic and 4e$^-$ interactions between the two oxygens. Thus, in the gas phase, metal ions, especially lithium ion, cause a net stabilization of the sulfurane in which electrostatic stabilization is partially counterbalanced by destabilizing compression of the equatorial O—S—O angle. This interaction results in weaker electrostatic interactions with cations as compared to the phosphorane. Weakening of electrostatic interactions by this effect could in principle be large enough to lead to interaction with solvated rather than bare cations for the sulfonate transition state in the Eisenman scheme.

7 Concluding Remarks

Studies of the reaction of alkali-metal ethoxides with esters **1—8** revealed a spectrum of reactivity patterns under a common set of experimental conditions where the esters reacted by the same associative nucleophilic displacement mechanism. It was demonstrated that metal ions did not significantly perturb transition-state structure in these reactions. Metal-ion effects arose through parallel reactions of free ethoxide ion and alkali-metal ethoxide ion pairs and were analysed in terms of ground-state and transition-state contributions. With the exception of the phosphonate monoanion 5, ground-state stabilization of the neutral ester substrates was assumed to be negligible. Metal ions were assumed to coordinate to ethoxide ion only, so ground-state stabilizations were identical for these reactions. Consequently, differing reactivity patterns arose from different alkali-metal ion selectivities in the transition states. These patterns corresponded to those predicted by Eisenman for anionic species having low (**1—5**, **8**) or high (**6**, **7**) electric-field strength, highlighting the importance of the balance between electrostatic interactions and solvation. This is the first application of the Eisenman theory to transition-state selectivity. The possible wider applications of this theory include: (i) prediction of metal-ion selectivity in other systems, and (ii) a deeper understanding of the roles of electrostatic interactions and solvent reorganization in transition-state stabilization. Theoretical calculations of complexation of model phosphorane and sulfurane species by metal ions in the gas phase revealed differences in the energetics and mode of coordination in the two systems. These differences may be the cause of the changing balance between electrostatic interactions and solvation which gives rise to different selectivity patterns for different families of esters.

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